Unipolar depression in adults: Treatment with anxiolytics

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INTRODUCTION

Unipolar major depression that includes high levels of anxiety symptoms (often called anxious depression) is common [1,2]. In a study of 2876 patients with major depression, high levels of anxiety were present in more than 50 percent [3].

Treatment of anxious depression frequently includes anxiolytic drugs [4,5]. In addition, insomnia that is part of the depressive syndrome often responds to anxiolytic (hypnotic) therapy [6].

This topic reviews the use of anxiolytics to treat unipolar major depression, including their indications, contraindications, administration, and efficacy. Choosing a medication regimen for the initial treatment of depression and for treatment resistant depression is discussed separately. (See "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

ANXIOUS DEPRESSION

Unipolar major depression that includes high levels of anxiety symptoms is often called “anxious depression” [7]. The clinical features and diagnosis of anxious depression are discussed separately. (See "Unipolar depression in adults: Clinical features", section on 'Anxious' and "Unipolar depression in adults: Assessment and diagnosis", section on 'Depressive episode subtypes (specifiers)'.)

INDICATIONS

Indications for augmenting antidepressants with anxiolytics to treat unipolar major depression include:

- Symptoms of anxiety, such as ruminative thoughts, worrying, health anxieties, excessive fears, and panic attacks. Major depression that includes high levels of anxiety is often referred to as “anxious depression,” and severe anxiety can increase the risk of suicide attempts [8].
- Moderate to severe insomnia [9].
- Psychomotor agitation (eg, pacing and handwringing) [10].
- Excessive activation (jitteriness) induced by antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and tricyclics [11].
- The need to accelerate improvement in patients with moderate to severe depression [12].
- Treatment resistant depression (eg, nonresponse to at least two separate, adequate antidepressant trials). (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

The short term goals of co-administering anxiolytics with antidepressants are rapid anxiolysis, control of insomnia and agitation, and limiting antidepressant side effects. The longer term aim is remission of the depressive syndrome.

Contraindications — In treating depressive syndromes, the following comorbidities are contraindications to augmenting antidepressants with anxiolytics, especially benzodiazepines:

- **Chronic posttraumatic stress disorder (PTSD)** – There is no compelling evidence that benzodiazepines are effective for the core PTSD symptoms in this clinical context [13]. In some patients, there is a risk of worsening PTSD symptoms such as hyperarousal and irritability.
- **Severe antisocial or borderline personality disorder** – Long term administration of benzodiazepines is likely to worsen impulsivity in these patients [14]. In addition, patients with these severe personality disorders are more prone to benzodiazepine dependence, and are more likely to engage in drug diversion.

- **Moderate to severe substance use disorders antedating onset of the depressive syndrome** – Patients whose history suggests a long-standing primary substance disorder are at higher risk for becoming dependent upon benzodiazepines [15].

- **Mild cognitive impairment or dementia** – Most anxiolytics should be used with caution in dementia patients. However, we avoid long-term administration of benzodiazepines in this context, due to their sedative and amnestic properties, and risk of exacerbating cognitive impairments [16].

- **General medical conditions such as severe myopathic disorders (eg, myasthenia gravis) and chronic respiratory diseases (eg, severe chronic obstructive pulmonary disease)** – The muscle relaxant properties of anxiolytics, especially benzodiazepines, are likely to exacerbate these diseases [17,18].

GENERAL PRINCIPLES

Patient assessment — The initial clinical evaluation of patients with a possible diagnosis of unipolar major depression with anxiety includes a psychiatric history and mental status examination, with emphasis upon depressive and anxiety symptoms [19-22]. The clinician should also obtain a general medical history, physical examination, and laboratory tests that are guided by the history and examination. Unipolar major depression is generally diagnosed according to the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition (DSM-5) (table 1) [23].

Assessment of major depression can be facilitated by using the Patient Health Questionnaire - Nine Item (PHQ-9) (table 2), which is a nine-item self-report instrument that screens for episodes of major depression, has good psychometric properties, is in the public domain, and can be filled out by patients prior to the appointment [24]. An alternative is the two item Patient Health Questionnaire, which screens for depression but does not provide a diagnosis; patients who screen positive must be interviewed by the clinician to establish the diagnosis of major depression [25]. Additional information about diagnosing major depression and the PHQ-9 is discussed separately. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Unipolar major depression' and "Using scales to monitor symptoms and treat depression (measurement based care)", section on 'Patient Health Questionnaire - Nine Item'.)

The initial assessment of anxiety symptoms (eg, excessive fears and worrying) can be facilitated with the seven item self-report scale for generalized anxiety disorder (GAD-7) (table 3), which is in the public domain [26]. An alternative self-report questionnaire is the Beck Anxiety

Inventory, which consists of 21 items and focuses upon somatic symptoms, but is copyrighted and must be purchased [27,28]. In addition, the 14 item Hamilton Anxiety Rating Scale assesses global anxiety, including psychic (cognitive) and somatic symptoms, and is in the public domain; however, this is a clinician administered instrument [29,30].

Following the initial evaluation, the effectiveness of treatment can be monitored with the PHQ-9 and GAD-7. A reasonable alternative is to use self-report visual analog scales; as an example, one Likert response item for level of depression and another for level of anxiety, each ranging from 0 (none) to 10 (extreme).

When to start the anxiolytic — In treating unipolar major depression with an adjunctive anxiolytic, the point at which the drug is added depends upon the severity of the depressive syndrome:

- **Severe** – For severe depression that includes anxiety and/or insomnia, we typically start the anxiolytic at the same time as the antidepressant or soon thereafter (eg, within one to two weeks).

- **Mild to moderate** – For mild to moderate depression, we typically use a stepped care approach and start the anxiolytic later [31]. The antidepressant is titrated up and then administered for a sufficient period (eg, four to eight weeks) to evaluate its efficacy as monotherapy. If anxiety and/or insomnia persist, we then add the anxiolytic.

Duration of treatment — Based upon randomized trials, we suggest that clinicians co-administer the anxiolytic and the antidepressant for four to six weeks [4,12,32,33]. There is little evidence that longer treatment is beneficial. When treatment with the anxiolytic is completed, the drug is tapered for two to four weeks prior to discontinuation. Information about discontinuing benzodiazepines is discussed elsewhere in this topic (see 'Benzodiazepines' below).

SPECIFIC DRUGS

Specific anxiolytic drugs include:

- Benzodiazepines (eg, clonazepam and lorazepam)
- Nonbenzodiazepine hypnotics (eg, zolpidem and eszopiclone)
- Second-generation antipsychotics (eg, quetiapine and aripiprazole)
- Pindolol
- Buspirone

- Other agents (doxepin and riluzole)

Benzodiazepines — For patients with unipolar major depression, adding a benzodiazepine to an antidepressant can improve anxiety, insomnia and other symptoms of depression, and treatment adherence [12,34-36]. A meta-analysis of 10 randomized trials that compared adjunctive benzodiazepines with placebo in 731 depressed patients who received antidepressants found that at four weeks [4]:

- Severity of depression was less with a benzodiazepine plus an antidepressant than antidepressant monotherapy; heterogeneity across trials was moderate to large. (The difference in depressive symptoms between the two treatment groups was greatest after one week and not demonstrable beyond six to eight weeks.)

- Response (improvement from baseline on the depression rating scale ≥50 percent) occurred in more patients who received combination treatment than monotherapy (50 versus 38 percent); heterogeneity was small to moderate.

- Discontinuation of treatment due to adverse effects occurred in fewer patients who received adjunctive benzodiazepines than placebo (7 versus 13 percent); there was little to no heterogeneity across studies.

However, the benefits of adding a benzodiazepine must be balanced against potential harms that include tolerance (diminished effect over time), physiologic dependence, sedation, amnestic effects, impaired psychomotor speed, and increased accidents [4,16,37]. Benzodiazepines should be used cautiously or avoided in patients with a history of alcohol or substance abuse, or a history of problematic adherence to antidepressants; both groups may want to stop the antidepressant and continue only the benzodiazepine due to the benzodiazepine's more rapid clinical effect.

If a benzodiazepine is indicated during treatment of unipolar major depression with an antidepressant, we generally start clonazepam at a dose of 0.5 mg at bedtime and titrate up over one to two weeks to a maximum dose of 2 mg per day, given at bedtime or divided in two daily doses. Although each of the benzodiazepines can be prescribed adjunctively with an antidepressant to treat unipolar depression, we prefer high potency, intermediate half-life agents (eg, clonazepam or lorazepam). Compared with low potency, longer half-life drugs (eg, chlordiazepoxide or diazepam), high potency, intermediate half-life agents generally have simpler metabolisms with fewer active metabolites, and may thus have a lower risk of sedation and psychomotor problems such as falls [38]. In addition, clonazepam has been frequently studied for augmentation of antidepressants [12,34,35]. Information about the pharmacology

of benzodiazepines, including doses, comparative potency, metabolism, and half-life is presented in the table (table 4).

Based upon our clinical experience, patients should avoid using benzodiazepines on an as needed basis (PRN administration) because this approach is often not effective; fluctuating serum concentrations, especially with short acting drugs (eg, alprazolam), can increase the risk of minor withdrawal reactions and reinforce psychological dependence. In addition, as needed dosing may interfere with cognitive-behavioral therapy (CBT), by promoting rescue medication as a coping strategy that competes with the coping skills taught in CBT [39].

Benzodiazepines should be tapered over two to four weeks prior to discontinuation; tapering over a period less than two weeks may lead to rebound symptoms of depression and anxiety [34,40], and abrupt discontinuation can cause seizures. For patients who have been on a benzodiazepine for more than six months, we typically decrease the total daily dose by 10 percent every week until discontinuation. The benzodiazepine withdrawal syndrome is discussed separately. (See "Benzodiazepine poisoning and withdrawal", section on 'Benzodiazepine Withdrawal'.)

Alprazolam monotherapy — Although there is strong evidence that alprazolam monotherapy is efficacious for treating unipolar depression, we rarely use this approach because of problems with abuse and dependency, particularly at higher doses (eg, >2 mg per day).

A systematic review of randomized trials that compared alprazolam with placebo in patients with unipolar major depression reported the following results [41]:

- A meta-analysis of seven heterogeneous trials compared alprazolam with placebo in 771 patients who were treated for six weeks; the mean daily doses of alprazolam ranged from 2.1 to 3.7 mg and maximum daily doses ranged from 4.5 to 6 mg. Improvement of depressive symptoms was significantly greater with alprazolam than placebo.

- A separate analysis of three homogeneous trials (312 patients) found that response (improvement from baseline on the depression rating scale ≥50 percent) occurred in more patients who received alprazolam than placebo (53 versus 22 percent).

- A third analysis of 17 trials (1636 patients) compared alprazolam with tricyclic antidepressants and found that improvement of symptoms was comparable; heterogeneity across studies was moderate to high. Alprazolam has not been directly compared with selective serotonin reuptake inhibitors (SSRIs).

Nonbenzodiazepine hypnotics — For patients with unipolar major depression that includes insomnia, adding eszopiclone or zolpidem to an antidepressant is efficacious for treating insomnia, but it is not clear if these adjunctive drugs help resolve other core depressive symptoms. Evidence for the efficacy of these nonbenzodiazepine sedatives includes the following studies:

- An eight-week randomized trial compared adjunctive zolpidem extended release (12.5 mg at bedtime) with placebo in 380 patients with unipolar major depression that included insomnia; all patients received escitalopram (10 mg per day) [42]. Improvement of insomnia was greater in patients who received zolpidem than placebo; however, improvement of other depressive symptoms was comparable for both groups. Discontinuation of treatment due to adverse effects occurred in more patients who received adjunctive zolpidem than placebo (8 versus 4 percent). It is important to note that the United States Food and Drug Administration issued a Drug Safety Communication warning that zolpidem can impair driving and other activities that require alertness the next day [43]. The recommended starting dose in females for extended release formulations is 6.25 mg, and for immediate release is 5 mg. The same doses are suggested for males as well.

- An eight-week randomized trial compared adjunctive eszopiclone (3 mg at bedtime) with placebo in 545 patients with unipolar major depression that included insomnia; all patients received fluoxetine 20 to 40 mg per day [6]. Insomnia improved more with eszopiclone than placebo, and improvement of other depressive symptoms was superior with eszopiclone. Discontinuation of treatment due to adverse effects was comparable in patients who received adjunctive eszopiclone or placebo (6 and 8 percent). Among the subgroup of patients with anxious depression (major depression that includes high levels of anxiety), insomnia and other depressive symptoms improved more with adjunctive eszopiclone than placebo [44]. It is important to note that the United States Food and Drug Administration issued a Drug Safety Communication warning that 3 mg of eszopiclone can impair driving, memory, and coordination the next day [45]. The recommended starting dose for males and females is 1 mg, which may be increased to 2 mg or 3 mg as needed.

Abrupt discontinuation of the hypnotics in these two trials did not result in appreciable rebound insomnia, which is a significant advantage over benzodiazepines.

Second-generation antipsychotics — Aripiprazole, brexpiprazole, and quetiapine and are each beneficial for anxious depression (major depression that includes high levels of anxiety). Evidence for the efficacy of these “major tranquilizers” includes the following studies [46]:

- A pooled analysis of two six-week randomized trials compared the efficacy of adjunctive aripiprazole (2 to 20 mg/day) with placebo in patients with unipolar major depression who were unresponsive to antidepressant monotherapy [32]. In the subgroup of 435 patients with anxious depression, remission occurred in more patients who received aripiprazole than placebo (25 versus 16 percent). This was consistent with the finding that adjunctive aripiprazole was superior to placebo in nonanxious depression. Side effects associated with aripiprazole in patients with anxious depression included akathisia, fatigue insomnia, blurred vision, and constipation.

- A pooled analysis of two randomized trials that each lasted six weeks compared adjunctive brexpiprazole (2 or 3 mg/day) with placebo in patients with major depression who did not respond to open-label treatment with antidepressant monotherapy [47]. In the subgroup of patients with anxious distress (n = 431), improvement of depression was greater with adjunctive brexpiprazole than placebo. This was consistent with the finding that adjunctive brexpiprazole was superior to placebo in nonanxious depression. Side effects associated with brexpiprazole in patients with anxious depression included akathisia, fatigue, restlessness, somnolence, and weight increase.

- A pooled analysis of two eight-week randomized trials compared the efficacy of quetiapine extended release monotherapy with placebo in patients with unipolar major depression [33]. In the subgroup of 403 patients with anxious depression, response (improvement from baseline on the depression rating scale ≥50 percent) occurred in more patients who received quetiapine 150 mg or 300 mg/day than placebo (50 and 47 versus 32 percent). This was consistent with the finding that quetiapine was superior to placebo in nonanxious depression. Side effects of quetiapine include dry mouth, sedation, and weight gain.

Additional information about adjunctive treatment with second-generation antipsychotics in patients with unipolar major depression who do not respond to antidepressant monotherapy is discussed separately. (See "Unipolar depression in adults: Treatment with second-generation antipsychotics".)

Pindolol — For patients with unipolar major depression, adding the beta blocker pindolol (eg, 5 mg three times per day) to a selective serotonin reuptake inhibitor (SSRI) can improve depressive symptoms and may accelerate clinical response via blockade of the 5-HT1A autoreceptor. A meta-analysis of 12 randomized trials compared pindolol plus an SSRI with placebo plus an SSRI in 889 patients with unipolar major depression and no history of treatment resistance. Response (improvement from baseline on the depression rating scale ≥50 percent) at two weeks occurred in more patients who received adjunctive pindolol than placebo

(37 versus 21 percent); however, heterogeneity across trials was high [48]. In a second analysis, response at four to six weeks occurred in more patients who received adjunctive pindolol than placebo (74 versus 67 percent), and there was little to no heterogeneity.

Buspirone — Augmentation with buspirone does not appear to help patients with anxious depression (major depression that includes high levels of anxiety). The effectiveness of buspirone was evaluated in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which compared buspirone (mean dose 41 mg per day) plus citalopram with bupropion sustained release (mean dose 268 mg per day) plus citalopram in 565 patients with unipolar major depression who were initially unresponsive to citalopram monotherapy [49]. Treatment was randomly assigned and administered on an open label basis, assessment of outcome was blinded, and concomitant use of trazodone and benzodiazepines was permitted. Among patients with anxious depression who received adjunctive buspirone, remission occurred in only 9 percent, compared to 39 percent of patients with nonanxious depression [3].

Other agents

- **Doxepin** – Randomized trials have demonstrated that the tricyclic antidepressant doxepin (3 or 6 mg at bedtime) is efficacious for insomnia in patients who are not depressed (see "Pharmacotherapy for insomnia in adults", section on 'Antidepressants'). The drug may also be useful for insomnia associated with depression, but this has not been studied in a randomized trial.

- **Riluzole** – A prospective observational study of 10 patients with unipolar major depression and anxiety found that augmentation of the antidepressant regimen with riluzole (used to treat amyotrophic lateral sclerosis) reduced symptoms of depression and anxiety [50].

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: Benzodiazepine use disorder and withdrawal".)

SUMMARY

- Unipolar major depression often includes symptoms of anxiety such as worrying or rumination, and is referred to as anxious depression. Anxiety symptoms that are part of a depressive syndrome are distinguished from anxiety disorders that are comorbid with

depressive disorders. (See 'Anxious depression' above and "Comorbid anxiety and depression in adults: Epidemiology, clinical manifestations, and diagnosis".)

- Acute treatment of unipolar major depression with antidepressants is less effective in patients with higher levels of baseline anxiety than patients with lower levels. However, adjunctive anxiolytics can improve outcomes in anxious depression. Indications for augmenting antidepressants with anxiolytics to treat unipolar major depression include symptoms of anxiety, moderate to severe insomnia, psychomotor agitation, excessive activation induced by antidepressants, the need to accelerate improvement in patients with moderate to severe depression, and treatment resistant depression. (See 'Anxious depression' above and 'Indications' above and "Unipolar depression in adults: Choosing treatment for resistant depression".)

- Contraindications to augmenting antidepressants with anxiolytics (especially benzodiazepines) to treat depression include several comorbidities, such as chronic posttraumatic stress disorder, severe antisocial or borderline personality disorder, moderate to severe substance use disorders antedating onset of the depressive syndrome, mild cognitive impairment or dementia, and general medical conditions such as severe myopathic disorders and chronic respiratory disease. (See 'Contraindications' above.)

- Depressive symptoms can be assessed with the self-report Patient Health Questionnaire - 9 Item (PHQ-9) (table 2), and anxiety symptoms with the self-report scale for generalized anxiety disorder (GAD-7). A reasonable alternative is to use self-report visual analog scales. (See 'Patient assessment' above and "Using scales to monitor symptoms and treat depression (measurement based care)", section on 'Patient Health Questionnaire - Nine Item'.)

- In using an adjunctive anxiolytic to treat severe unipolar major depression that includes anxiety and/or insomnia, we typically start the anxiolytic at the same time as the antidepressant. For mild to moderate depression, we generally use a stepped care approach, in which the antidepressant is titrated up and administered for a sufficient period to evaluate its efficacy as monotherapy; if anxiety and/or insomnia persist, we then add the anxiolytic. (See 'When to start the anxiolytic' above.)

- We generally co-administer the anxiolytic and the antidepressant for four to six weeks, and then taper the anxiolytic for two to four weeks prior to discontinuation. However, longer taper schedules may be necessary for benzodiazepines. (See 'Duration of treatment' above and 'Benzodiazepines' above.)

- For patients with unipolar major depression, prescribing a benzodiazepine (eg, clonazepam 0.5 to 2 mg/day at bedtime or divided in two daily doses) plus an antidepressant can improve symptoms of anxiety and depression, and also improve treatment adherence. However, the potential harms of adding a benzodiazepine include tolerance (diminished effect over time), physiologic dependence, sedation, amnestic effects, impaired psychomotor speed, and increased accidents. (See 'Benzodiazepines' above.)

- For unipolar major depression that includes insomnia, adding eszopiclone (3 mg at bedtime) or zolpidem extended release (females 6.25 mg/males 6.25 or 12.5 mg at bedtime) to an antidepressant is efficacious for treating insomnia. However, it is not clear if these adjunctive drugs help resolve other core depressive symptoms. Abrupt discontinuation of these nonbenzodiazepine hypnotics does not result in appreciable rebound insomnia, which is a significant advantage over benzodiazepines. (See 'Nonbenzodiazepine hypnotics' above.)

- Aripiprazole (2 to 20 mg/day), brexpiprazole (2 or 3 mg/day), and quetiapine (150 mg or 300 mg/day)are each beneficial for anxious depression (major depression that includes high levels of anxiety). (See 'Second-generation antipsychotics' above.)

- For patients with unipolar major depression who are treated with an antidepressant, adding pindolol (eg, 5 mg three times/day) can accelerate or improve response to the antidepressant. (See 'Pindolol' above.)

- Augmentation with buspirone does not appear to help patients with anxious depression. (See 'Buspirone' above.)

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