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How should we treat major depression combined with anxiety?

Evidence-based answer

One approach is to use antidepressants alone, which reduce symptoms for patients with major depression plus symptoms of anxiety or major depression plus generalized anxiety disorder. Selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCAs), bupropion, mirtazapine, nefazodone, and venlafaxine are equally effective for combined symptom relief (strength of recommendation [SOR]: **A**, based on systematic review of randomized controlled trials [RCTs]).

Another approach is to add a

benzodiazepine to the antidepressant.

This reduces anxiety symptoms (more in the short term) and decreases patient dropout, but it also has possible harms, including development of dependence and accident proneness (SOR: **A**, based on systematic review of RCTs).

Psychotherapy, particularly cognitive behavioral therapy, produces and maintains reductions in symptoms of anxiety and depression that are comparable with the reductions seen with medication (SOR: **A**, based on systematic review of RCTs).

Clinical commentary

Talk to the patient about risks and benefits of drug therapy, and the need to closely monitor him in the first few weeks

Such discussions are essential, in light of the Food and Drug Administration's mandate that all classes of antidepressant carry a black box warning label about increased suicidality (suicidal thinking and behavior) among patients taking these medications.¹

Benzodiazepine medications are effective in mitigating symptoms of anxiety

but have additional risks such as altered cognition, tolerance, and abuse potential. In addition, benzodiazepine can be lethal in overdose with alcohol. Therefore, using a benzodiazepine alone for a patient who has both anxiety and depression is unwise. Even when used in combination with an antidepressant, benzodiazepine therapy should be brief.

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Evidence summary Antidepressants have similar positive effects

A systematic review of 28 randomized trials comparing various antidepressant

medications found no significant differences in reduction of symptoms of depression and anxiety for patients who had both.² Patients in these trials met *DSM (Diagnostic and Statistical Man-*

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Explain why close monitoring is a necessity for the first few weeks

ual of Mental Health) criteria for major depression, with symptom severity as measured by a standardized scale, the Hamilton Rating Scale for Depression (HAM-D). They also had moderate to severe levels of anxiety symptoms as measured by standardized scales (Hamilton Rating Scale for Anxiety [HAM-A], Covi Anxiety Rating Scale, or the anxiety/somatization factors on the HAM-D).

Trials ranged from 6 to 24 weeks long, with outcomes including reductions in depression and anxiety symptom scores as measured by standardized scales. Study quality was variable; only 8 trials used a placebo control, and many were sponsored by pharmaceutical manufacturers.

Although some individual studies found differences in outcomes between medications, no significant differences in efficacy were seen in combined data from each comparison group. Medication was more efficacious than placebo in most studies that used a placebo control. Side-effect profiles were not described.

Patients with major depression and high anxiety levels relapsed more often than those with low anxiety levels with discontinuation of fluoxetine compared with placebo in a double-blind placebo-controlled parallel trial with 596 patients.³

Three trials evaluated antidepressant medication for patients who met diagnostic criteria for both major depression and generalized anxiety disorder. A manufacturer-sponsored RCT (N=90) found no differences in HAM-A or HAM-D score reduction among fluoxetine, venlafaxine, and placebo (except at 12 weeks, when venlafaxine significantly differed from placebo).⁴ Two open-label cohort trials (N=153) found that fluoxetine and fluvoxamine (Luvox, an older SSRI) reduced both depression and anxiety by about half.^{5,6}

Adding benzodiazepines is not a long-term solution

A Cochrane systematic review (10 RCTs, N=731) compared antidepressants alone

vs combinations with benzodiazepines for patients with major depression and a 35% to 85% estimated prevalence of anxiety symptoms. Three studies used standardized scales to measure anxiety symptom severity.

Antidepressants in combination with benzodiazepines were more likely than antidepressants alone to reduce depression scores by 50% or more (for 50% depression improvement at 1 week, number needed to treat [NNT]=12; at 4 weeks, NNT=8). The combination group also had fewer dropouts (relative risk [RR]=0.63, 95% confidence interval [CI], 0.49–0.81). The authors concluded that potential benefits of adding a benzodiazepine to an antidepressant must be balanced against possible harms, such as the development of dependence.⁷

Psychotherapy appears likely to help

A review of 13 controlled clinical trials⁸ evaluated standardized depression and anxiety score reductions for patients with generalized anxiety disorder receiving cognitive behavioral therapy compared with various control treatments (waiting list, pill placebo, or alternative therapy—such as supportive listening psychotherapy). Approximately half of the patients were also taking medication (not specified).

After an average of 10 sessions, cognitive behavioral therapy reduced anxiety and depression symptom scores more than control treatments (difference in effect size were 0.71 and 0.66, respectively). At 6- to 12-month follow-up, cognitive behavioral therapy gains were maintained (difference in effect size=0.30 for anxiety scores and 0.21 for depression scores). (An effect size of 0.2 is usually considered small, 0.5 moderate, and 0.8 is large.)

Another trial assigned primary care patients (N=464) with depression or mixed depression and anxiety to 1 of 2 psychological therapy groups (cognitive behavioral therapy or non-

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Relapse was more likely with high anxiety levels than with low anxiety levels, when fluoxetine was discontinued

directive counseling for 12 sessions) vs usual general practitioner care. At 4 months, both psychological therapy groups had lower Beck Depression Index scores (by 4–5 points) than the usual general practitioner care group, but by 12 months there were no significant differences among all groups.⁹

Recommendations from others

The National Collaborating Centre for Mental Health guidelines state: “when depressive symptoms are accompanied by anxious symptoms, the first priority should usually be to treat the depression. Psychological treatment for depression often reduces anxiety, and many antidepressants also have sedative/anxiolytic effects.”¹⁰

The Brigham and Women’s Hospital guideline recommends adjunctive therapy with anxiolytics—such as lorazepam (Ativan) and clonazepam (Klonopin)—for some patients with depression and mild to moderate anxiety, to help control symptoms such as sleeplessness and restlessness.¹¹ ■

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10 psychotherapy sessions led to lower depression and anxiety scores, which were maintained after a year

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PRACTICE ALERT

Medicare Update: What the changes will mean for you

The big news in Medicare last year was the start of the prescription drug program—Medicare Part D—and changes in physician payments beginning in January 2007. The latter includes revisions to the relative value unit scale, the elimination of the scheduled decrease in the physician fee schedule, and the beginnings of pay-for-performance. This article spells out the details of how these changes may impact your practice.