ONLINE EXCLUSIVE

Q/ Are antipsychotics effective adjunctive Tx for patients with moderate-to-severe depression?

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EVIDENCE-BASED ANSWER

A/ **YES.** Augmentation with second-generation antipsychotics, especially aripiprazole and quetiapine, appears to be effective in patients with moderate-to-severe depression who have had a suboptimal response to a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor (strength of recommendation [SOR]: **A**, based on a systematic review of randomized controlled trials [RCTs] and an individual RCT). Augmenting antidepressant therapy with cariprazine, ziprasidone, or olanzapine also appears to improve depressive symptoms over the short term. All antipsychotics studied carried an increased likelihood of adverse effects that could lead to discontinuation (SOR: **A**, based on a systematic review of RCTs).

Evidence summary

Depression symptoms improved with any of 4 antipsychotics

A 2021 systematic review of 16 RCTs (N = 3649) assessed data from trials that used an atypical antipsychotic—either aripiprazole, quetiapine, olanzapine, or risperidone—as augmentation therapy to an antidepressant vs placebo.[1] Study participants included adults ages 18 to 65 who experienced an episode of depression and did not respond adequately to at least 1 optimally dosed antidepressant. In most studies, treatment-resistant depression (TRD) was defined as the failure of at least 1 major class of antidepressants. Trial lengths ranged from 4 to 12 weeks.

Six RCTs evaluated the effectiveness of augmentation with aripiprazole (2-20 mg/d) in patients with unipolar depression, with 5 trials demonstrating greater improvement in clinical symptoms with aripiprazole compared to placebo. Augmentation with quetiapine (150-300 mg/d) was evaluated in 5 trials, with all trials showing improvement in depression symptoms; however, in 1 trial the difference in remission rates was not significant, and in another trial significant improvement was seen only at a quetiapine dose of 300 mg/d. Two trials examining olanzapine found that patients receiving fluoxetine plus olanzapine augmentation demonstrated greater improvement in depression symptoms than did those receiving either agent alone. Three trials examined augmentation with risperidone (0.5-3 mg/d); in all 3, risperidone demonstrated significant improvement in depression symptoms and remission rates compared to placebo.[1]

This systematic review was limited by small sample size and heterogeneity of antipsychotic dosages in the RCTs included, as well as the lack of a standardized and globally accepted definition of TRD.

Augmentation reduced symptom severity, but dropout rates were high

A 2019 Cochrane review of 10 RCTs (N = 2731) compared 5 strategies, including augmenting treatment with an antipsychotic vs continuing antidepressant monotherapy.[2] Participants were adults ages 18 to 74 with unipolar

Adjunctive antipsychotic medications more effectively treat resistant depression than increasing antidepressant dosage, switching to a different antidepressant, or adding another antidepressant.

depression who had not responded to a minimum of 4 weeks of antidepressant treatment at a recommended dose. The primary outcome was depressive symptom severity, as measured by the Montgomery-Asberg Depression Rating Scale (MADRS; range of 0-60) or the Hamilton Depression Rating Scale (HAM-D; range, 0-52).

Compared with continued antidepressant monotherapy, symptom severity was reduced when current treatment was augmented with cariprazine 1-4.5 mg/d (1 trial; N = 808; mean difference [MD] on MADRS = –1.5; 95% CI, –2.7 to –0.25; high-quality evidence); quetiapine 150-300 mg/d (3 trials; N = 977; standardized MD = –0.32; 95% CI, –0.46 to –0.18; high-quality evidence); ziprasidone 40-160 mg/d (2 trials; N = 199; MD on HAM-D = –2.7; 95% CI, –4.5 to –0.93; moderate-quality evidence); or olanzapine 5-20 mg/d (1 trial; N = 20; MD on MADRS = –12; 95% CI, –22 to –2.4; low-quality evidence). One trial did not show a significant difference on the HAM-D for olanzapine (1 trial; N = 20; MD = –7.9; 95% CI, –17 to 0.96; low-quality evidence).[2]

Dropout rates, which were most commonly secondary to adverse effects, ranged from 10% to 39% in the groups augmented with an antipsychotic and from 12% to 23% in the comparison groups.[2] This systematic review was limited by the small number of studies included in the various comparisons.

Antipsychotic augmentation was effective but came with adverse effects

A 2017 RCT (N = 1522) examined the effectiveness of augmenting an antidepressant with aripiprazole in patients with TRD.[3] Participants were adults (mean age, 54.4 years; 85% men) at 35 US Veterans Health Administration (VA) medical centers who had a diagnosis of nonpsychotic major depressive disorder that was unresponsive to at least 1 antidepressant course meeting minimal standards for treatment dose and duration.

Patients were randomly assigned to 1 of 3 different treatment groups, which included switching to a different antidepressant (bupropion sustained release 150-500 mg/d); augmenting current treatment with bupropion; or augmenting with an atypical antipsychotic (aripiprazole 2-15 mg/d) for 12 to 36 weeks. The primary outcome was remission rate at 12 weeks, which was defined as a score ≤ 5 on the Quick Inventory of Depressive Symptomatology–Clinician Rated (QIDS-C; range, 0-27) at 2 consecutive visits. The secondary outcome, symptom response to treatment, was defined as ≥ 50% reduction on QIDS-C score.

The augment-aripiprazole group (N = 146) exceeded the switch group (N = 114) in remission rate (absolute remission rates = 28.9% vs 22.3%; relative risk [RR] = 1.3; 95% CI, 1.1-1.6; number needed to treat [NNT] = 15), but had similar remission rates to the augment-bupropion group (N = 136; absolute remission rate = 26.9%; RR = 1.1; 95% CI, 0.88-1.3). Symptom response in the augment-aripiprazole group (74.3%) was higher than in either the switch group (62.4%; RR = 1.19; 95% CI, 1.09-1.29; NNT = 8) or the augment-bupropion group (65.6%; RR = 1.13; 95% CI, 1.0-1.2; NNT = 11). There was no difference noted in response rate between the switch group and the augment-bupropion group (RR = 1.05; 95% CI, 0.96-1.15).[3]

The adverse events that occurred more often in the augment-aripiprazole group than in the other groups included weight gain ≥ 7% (25% at 36 weeks) and extrapyramidal symptoms (19%).[3] Limitations of the study included the evaluation of only 1 antipsychotic and 1 antidepressant, the dropout rate (only 75% of patients completed the 12-week follow-up), and the homogeneity of the patient population (older, male, veterans), all of which may limit the effect size.

Editor's takeaway

Multiple trials show that adjunctive antipsychotic medications such as aripiprazole and quetiapine more effectively treat resistant depression than adding a placebo, increasing antidepressant dosage, switching to a different antidepressant, or adding another antidepressant. However, while primary care physicians should be comfortable with this option, the magnitude of difference between these options was modest, and adverse effects were common. All options can still be reasonably considered. JFP

References

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