Cochrane for Clinicians

Putting Evidence into Practice

Medications for Treatment-Resistant Depression in Adults

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Clinical Question

Is augmentation with a second antidepressant or an atypical antipsychotic effective for treatment-resistant depression in adults?

Evidence-Based Answer

In patients with treatment-resistant depression, augmenting therapy with atypical antipsychotics can be effective. Adding quetiapine (Seroquel) to antidepressant therapy reduces symptoms below the remission threshold (number needed to treat [NNT] = 9), whereas the number of people who stop using the medicine (dropouts) increases only at the highest dosage. Augmentation with cariprazine (Vraylar) or ziprasidone (Geodon) improves the clinical response; however, the benefit is offset by increased dropouts.[1] (Strength of Recommendation: C, based on disease-oriented outcomes.)

Practice Pointers

Treatment-resistant depression is defined as failure to respond to one or more antidepressant medications at therapeutic doses and occurs in at least 12% of patients with depression.[1,2] In a large major depression trial, treatment resistance was observed in one-third of patients.[3] Only 20% of patients with treatment resistance achieve remission, even after multiple interventions.[2] Patients with treatment-resistant depression also have a 17% rate of attempted suicide and report suicidal ideation twice as often as those with treatment-responsive depression.[2]

This Cochrane review included 10 randomized controlled trials with 2,731 patients.[1] Nine studies were industry funded and conducted in the outpatient setting. One study involved switching medications, whereas the others augmented therapy with a second medication. The most common baseline antidepressant was fluoxetine (Prozac). Most studies had 12 weeks or less of follow-up, but one included follow-up at one year.

Because changes in average depression scores are difficult to interpret, studies reported more clinically oriented measures. The response rate was defined as the number of participants whose depression scores were reduced by at least 50% from baseline. The remission rate was defined as the number of participants with depression scores reduced below a threshold that demonstrates resolution of depression. Studies also reported dropout rates for any reason as a measure of treatment harm.

One small, low-quality study demonstrated that switching from fluoxetine to mianserin (a tetracyclic antidepressant not available in the United States) did not improve depression scores, response rates, or remission rates.

Two European studies evaluated the benefit of augmenting fluoxetine therapy with another antidepressant. Augmentation with mianserin at a daily dosage of 60 mg increased both response and remission rates, without increasing drop-out rates. Augmentation with mirtazapine (Remeron), 30 mg daily, failed to improve depression symptoms, response rates, or remission rates after 12, 24, or 52 weeks.

One study in which fluoxetine or citalopram (Celexa) was augmented with buspirone (Buspar), 10 to 30 mg twice daily, showed no improvement in depression scores or response rates compared with placebo.

Augmentation with atypical antipsychotics had more evidence of benefit. In three studies, augmenting tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or

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CME **This clinical content** conforms to AAFP criteria for CME. See CME Quiz on page 13.

SUMMARY TABLE

Medications That Effectively Augment Antidepressant Therapy in Treatment-Resistant Depression

Original medication	Added medication	Outcome	Difference	Evidence quality
Fluoxetine (Prozac), 20 mg daily	Mianserin (not available in the United States), 60 mg daily	Remission rate (HAM-D score < 8)	NNT = 4 (95% CI, 1.3 to 59)	Low (1 study, n = 70)
		Response rate (≥ 50% HAM-D score reduction)	NNT = 4 (95% CI, 1.5 to 91)	Moderate (1 study, n = 70)
		Drop-out rate	Not significant	Low (1 study, n = 70)
Various	Quetiapine (Seroquel), 150 to 300 mg daily	Remission rate (MADRS score < 9)	NNT = 9 (95% CI, 7 to 19)	Moderate (3 studies, n = 977)
		Response rate (≥ 50% MADRS reduction)	NNT = 9 (95% CI, 6 to 25)	Moderate (3 studies, n = 977)
		Drop-out rate	Not significant	Moderate (3 studies, n = 977)
Various	Cariprazine (Vraylar), 1 to 4.5 mg daily	Remission rate (MADRS score < 10)	Not significant	Moderate (1 study, n = 808)
		Response rate (50% MADRS reduction)	NNT = 10 (95% CI, 5 to 37)	Moderate (1 study, n = 808)
		Drop-out rate	NNH = 13 (95% CI, 6 to 53)	Moderate (1 study, n = 821)
Various	Ziprasidone (Geodon), 40 to 160 mg daily	Remission rate (clinician rated)	Not significant	Moderate (2 studies, n = 199)
		Response rate (≥ 50% reduction in MADRS/HAM-D score)	NNT = 7 (95% CI, 3 to 77)	Moderate (2 studies, n = 199)
		Drop-out rate	NNH = 8 (95% CI, 3 to 500)	Moderate (2 studies, n = 199)

Note: The evidence quality ratings represent the GRADE working group evidence ratings of whether the true effect is close to the estimated effect.

GRADE = Grading of Recommendations Assessment, Development, and Evaluation; HAM-D = Hamilton Rating Scale for Depression (range = 0 to 52); MADRS = Montgomery-Åsberg Depression Rating Scale (range = 0 to 60); NNH = number needed to harm; NNT = number needed to treat.

bupropion (Wellbutrin) with quetiapine, 150 to 300 mg daily, increased rates of clinical response (NNT = 9; 95% CI, 7 to 19) and remission (NNT = 9; 95% CI, 6 to 25). Although use of quetiapine did not affect drop-out rates overall, dosages of 300 mg daily increased dropouts, whereas lower dosages did not.

Augmenting an SSRI or SNRI with cariprazine, 1 to 4.5 mg daily, increased clinical response (NNT = 10; 95% CI, 5 to 37) in one moderate-quality study but did not increase the remission rate. Treatment with this agent increased the risk of dropout (number needed to harm [NNH] = 13; 95% CI, 6 to 53). In two studies, augmentation with ziprasidone, 40 to 160 mg daily, increased the response rate (NNT = 7; 95% CI, 3 to 77) with no effect on remission, but it also increased dropouts (NNH = 8; 95% CI, 3 to 500).

Guidelines from the Institute for Clinical Systems Improvement (ICSI) and the National Institute for Health and Care Excellence (NICE) recommend augmenting antidepressant therapy to manage treatment-resistant depression. ICSI suggests augmentation with bupropion, buspirone, mirtazapine, thyroxine, stimulants, lithium, or atypical antipsychotics.[4] NICE suggests switching antidepressant medications or augmenting with lithium, an antipsychotic, or mirtazapine if the patient is willing to tolerate increased adverse effects.[5]

The practice recommendations in this activity are available at http://www.cochrane.org/CD010557.

Editor's Note: The NNTs, NNHs, and CIs reported in this Cochrane for Clinicians were calculated by the authors based on raw data provided in the original Cochrane review. Dr. Arnold is a contributing editor for *AFP*.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy,

Department of the Air Force, Uniformed Services University of the Health Sciences, Department of Defense, or the U.S. government.

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Treatment of Distal DVT

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Clinical Question

In patients with distal (below the knee) deep venous thrombosis (DVT), do vitamin K antagonists safely reduce the risk of recurrence or progression of venous thromboembolism (VTE), and what duration of anticoagulation is best?

Evidence-Based Answer

Vitamin K antagonists reduce the recurrence of DVT and VTE (number needed to treat [NNT] = 17; 95% CI, 13 to 48) but not pulmonary embolism (PE) compared with no anticoagulation or placebo. The risk of clinically relevant nonmajor bleeding (number needed to harm [NNH] = 23; 95% CI, 6 to 1,000), but not major bleeding, is increased with anticoagulation. (Strength of Recommendation [SOR]: A, based on consistent, good-quality patient-oriented evidence.)

A treatment duration of three months or more reduces the recurrence of DVT and VTE (NNT = 13; 95% CI, 10 to 23) compared with six weeks of therapy.[1] (SOR: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

The term VTE encompasses a spectrum of disease ranging from mild calf symptoms from DVT to life-threatening cardiopulmonary collapse from PE. Isolated distal DVT is a subset of VTE with decreased risk of recurrent DVT and PE, compared with more proximal disease.[2] A strategy of close observation may be appropriate in those with isolated distal DVT given the lower risk of complications. The authors of this review searched for randomized controlled trials (RCTs) addressing the effectiveness and safety of treatments for distal DVT, as well as those comparing varying durations of anticoagulation.

This Cochrane review included data from eight RCTs and 1,239 participants.[1] Trials included patients with provoked and unprovoked DVT, although patients with cancer (five of eight studies) and prior VTE (six of eight studies) were often excluded. All but one trial were open label, raising the possibility of performance bias, although the authors deemed the reported outcomes unlikely to be affected. Six of the trials used vitamin K antagonists as the active treatment agent, and two used the low-molecular-weight heparin nadroparin (not available in the United States). Trials using vitamin K antagonists had a lead-in period with a parenteral agent during initiation, and follow-up ranged from three months to two years. Five of the trials (496 participants) compared anticoagulants of varying durations with no treatment or placebo. The other three studies (736 participants) compared patients treated with six weeks of anticoagulation vs. three months or more. Two studies of nadroparin had a treatment duration of six weeks or less, and outcomes were insufficient to draw conclusions about effectiveness. The authors did not find completed studies that reported on the use of compression therapy or direct oral anticoagulants (DOACs) specifically for distal DVT.

Patients treated with anticoagulation had decreased rates of recurrent DVT (absolute risk reduction [ARR] = 5.9%; 95% CI, 2.6% to 7.1%; NNT = 17; 95% CI, 14 to 38) and VTE (ARR = 6.0%; 95% CI, 2.1% to 7.7%; NNT = 17; 95% CI, 13 to 48) compared with placebo, but there was no difference in the risk of PE. Rates of major bleeding were not significantly different between the two groups, although rates of clinically significant nonmajor bleeding were higher in the treatment group (absolute risk increase = 4.3%; 95% CI, 0.1% to 17.1%; NNH = 23; 95% CI, 6 to 1,000).

SUMMARY TABLE

Anticoagulation Compared with No Intervention or Placebo for Distal DVT Treatment

Outcomes at 3 months	Probable outcome with placebo or no treatment	Probable outcome with anticoagulation (95% CI)	NNT or NNH (95% CI)	Participants (studies)	Evidence quality
Recurrent venous thromboembolism	91 per 1,000	31 per 1,000 (14 to 70)	17 (13 to 48)	496 (5 RCTs)	High
Major bleeding	8 per 1,000	6 per 1,000 (1 to 38)	NA	480 (4 RCTs)	Low
Recurrent DVT	79 per 1,000	20 per 1,000 (8 to 53)	17 (14 to 38)	496 (5 RCTs)	High
Pulmonary embolism	12 per 1,000	10 per 1,000 (2 to 44)	NA	480 (4 RCTs)	Low
Clinically relevant nonmajor bleeding	18 per 1,000	61 per 1,000 (19 to 190)	23 (6 to 1,000)	322 (2 RCTs)	High

DVT = deep venous thrombosis; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; RCT = randomized controlled trial.

Overall incidence of PE and major bleeding was low in both groups.

In studies comparing anticoagulation regimens, patients receiving three months or more of therapy had reduced rates of recurrent DVT (ARR = 9.8%; 95% CI, 5.2% to 12.1%; NNT = 10; 95% CI, 8 to 19) and VTE (ARR = 7.8%; 95% CI, 4.3% to 10%; NNT = 13; 95% CI, 10 to 23) and no difference in bleeding rates compared with patients receiving only six weeks of therapy. Bleeding rates were low in both groups.

The American College of Chest Physicians endorses a strategy of observation with serial ultrasonography to evaluate for clot progression in select patients with distal DVT and no risk factors. Anticoagulation is recommended in the case of severe pain or risk factors, such as an elevated D-dimer level, active cancer, and history of VTE, or for unprovoked clots. These same guidelines favor use of a DOAC over vitamin K antagonists and low-molecular-weight heparin in keeping with the more robust data available for proximal DVT.[3] DOACs are associated with similar reductions in VTE and have lower bleeding rates compared with vitamin K antagonists in proximal disease.[4] RCTs investigating the DOACs apixaban (Eliquis) and rivaroxaban (Xarelto) for distal DVT are currently underway.[1]

This review establishes that vitamin K antagonists reduce recurrent VTE after isolated distal DVT without increasing major bleeding events. It also confirms current guidelines that recommend three months of anticoagulation over shorter durations.[3]

The practice recommendations in this activity are available at http://www.cochrane.org/CD013422.

Editor's Note: The NNTs, NNHs, ARRs, and absolute risk increase reported in this Cochrane for Clinicians were calculated by the author based on raw data provided in the original Cochrane review.

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