

# Editorials

## Comparing Clinical Guidelines for the Management of Major Depressive Disorder

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**Major depressive disorder** is a leading cause of disability in the United States.<sup>1</sup> The lifetime prevalence is as high as 16.2% among veterans and U.S. military members.<sup>2</sup>

Clinical practice guidelines from the U.S. Department of Veterans Affairs and Department of Defense (VA/DoD), updated in 2022; American Psychological Association (APA), published in 2019; and American College of Physicians (ACP), published in 2016, are widely used for the management of major depressive disorder.<sup>3-5</sup> All of these guidelines recommend treatment with pharmacotherapy or psychotherapy. Treatment recommendations are similar among guidelines, with only select differences in patient populations, specific treatments, and strength of recommendations. This editorial highlights the similarities and differences that are most relevant to family physicians and other clinicians treating patients with major depressive disorder.

### Patient Population

The APA guidelines provide recommendations for three age cohorts: children and adolescents, adults, and older adults. The ACP and VA/DoD guidelines do not address children and adolescents, focusing mainly on adults; the VA/DoD guidelines provide some specific recommendations for older adults. The ACP and APA guidelines focus on the effectiveness of psychotherapy and the comparative effectiveness of psychotherapy vs. pharmacotherapy, whereas the VA/DoD guidelines additionally examine a broader range of interventions (e.g., electroconvulsive therapy) and settings (e.g., telemental health).

### Initial Treatment Recommendations

All three guidelines recommend initial treatment with evidence-based psychotherapy or pharmacotherapy. Notably, the VA/DoD guidelines provide the strongest level of recommendation for the use of psychotherapy or pharmacotherapy but a weaker level of recommendation for specific treatment options. This reflects changes in the literature—recent, larger pharmacotherapy trials demonstrate smaller

effect sizes than older, smaller trials.<sup>6</sup> It also reflects more stringent application of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, with evidence that was previously rated as higher quality now rated lower.<sup>6</sup>

According to the VA/DoD and APA guidelines, the best available evidence is unable to establish superiority among bupropion, mirtazapine, serotonin-norepinephrine reuptake inhibitors, trazodone, vilazodone (Viibryd), vortioxetine (Trintellix), or selective serotonin reuptake inhibitors.<sup>3,4,6</sup> The only clear and consistent finding is each antidepressant's superior effectiveness compared with placebo for the treatment of major depressive disorder in adults.

Despite theoretical benefit, pharmacogenetic testing has not been shown to improve patient-oriented outcomes and is not recommended to assist in drug choice.<sup>7</sup> Because no antidepressant is clearly superior, it is reasonable to prescribe a medication based on anticipated adverse effects and patient preference. The VA/DoD guidelines are the first in the United States to clearly recommend a treatment duration of at least six months once a medication is prescribed.

### Combining Therapies

There is a lack of evidence showing a significant benefit from combining psychotherapy and pharmacotherapy in most patients with major depressive disorder. The VA/DoD guidelines recommend combining psychotherapy and pharmacotherapy only in patients with depression that is severe, persistent (more than two years), or recurrent (two or more episodes). If psychotherapy and pharmacotherapy are combined, the APA recommends cognitive behavior therapy or interpersonal psychotherapy plus a second-generation antidepressant.

### Complementary and Alternative Therapies

For patients who prefer alternative treatments to pharmacotherapy and are unwilling or unable to participate in psychotherapy, the VA/DoD, ACP, and APA recommend exercise or St. John's wort for major depressive disorder, based on low-quality evidence. The benefit of exercise was consistent across

various exercise types. Although St. John's wort is not approved by the U.S. Food and Drug Administration for depression, the most studied extracts were hypericin 0.1% to 0.3% and hyperforin 1% to 6% at a daily dose of 500 to 1,800 mg.<sup>3,8</sup> Based on a recent systematic review, the VA/DoD guidelines provide a weak recommendation for the use of light therapy, regardless of seasonal pattern diagnosis.<sup>3,9</sup>

The APA concludes that there is insufficient evidence to make a recommendation about omega-3 fatty acids, whereas the VA/DoD recommends against omega-3 fatty acids. Docosahexaenoic acid does not affect depressive symptoms. Eicosapentaenoic acid demonstrates a potentially small benefit in methodologically flawed studies, which cannot not be used to justify prescribing this therapy over other clinically validated treatments.

### Telemedicine

The VA/DoD found insufficient evidence to determine whether telemedicine is inferior or superior to in-person treatment. Telemedicine may have many positive downstream effects, including improved health care equality and expanded mental health accessibility. However, further research is needed to determine the effectiveness of different modalities, including audio-only telemedicine.

### Summary

For major depressive disorder, it is reassuring that different guideline processes arrived at generally similar conclusions. However, it is important for physicians to understand the guidelines' differences to effectively apply these tools to patient care.

**Editor's Note:** Dr. Buelt served as a member of the work group that developed the VA/DoD guidelines. Dr. McQuaid served as a cochampion for the VA/DoD revision and chair of the panel that developed the APA guidelines.

The views expressed in this article are those of the authors and do not reflect the position of the U.S. Department of the Navy, Uniformed Services University of the Health Sciences, U.S. Department of Defense, U.S. Department of Veterans Affairs, or U.S. government.

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