

Find Your Perfect Fit with **AAFP CareerLink**

START
NOW

AFP Community Blog

Advertisement

**Expand Your CME
Activity Reach with
AAFP Accreditation**

Accredit your CME activities with AAFP.
aafp.org/creditsystem



Meet the newest antidepressant: dextromethorphan/bupropion (Auvelity)

[< Previous](#) | [Next >](#)

Jennifer Middleton, MD, MPH

Posted on October 24, 2022

Dextromethorphan/bupropion (Auvelity), was [recently approved](#) by the United States (US) Food and Drug Administration (FDA) for the treatment of depression. Until now, [dextromethorphan](#) has been best known as a cough suppressant, and [bupropion](#) is currently FDA approved to treat major depressive disorder and to facilitate tobacco cessation. While the combination of the two may seem surprising, it turns out that [dextromethorphan affects NMDA, glutamate-1, and sigma-1 receptors in the brain, all of which have been implicated in the pathophysiology of depression, while bupropion's cytochrome P450 inhibition boosts dextromethorphan's blood levels](#) to allow for once daily dosing. Auvelity was approved based on promising data from its phase 2 trial, [ASCEND](#), and its phase 3 trial, [GEMINI](#); time will tell whether longer trials affirm these benefits.

The [FDA's investigational new drug process](#) consists of 4 phases. After appropriate studies in the lab and in animal models, the FDA grants permission to begin

phase 1 studies in a small number of healthy volunteers to determine safety and dosing. In phase 2, the new drug is studied in a few hundred persons with the target health condition to determine efficacy and side effects. In phase 3, the new drug's efficacy is further studied in up to 3,000 more people along with more attention to adverse side effects. Sufficient data regarding efficacy and data from phase 2 and phase 3 trials are typically required for FDA approval. Then, in the post-approval phase 4, the drug continues to be studied to confirm its safety and efficacy.

Auvelity's phase 2 trial, [ASCEND, enrolled participants between the ages of 18-65 years with moderate or severe major depressive disorder without psychotic features](#). Persons with additional and/or other psychiatric diagnoses (bipolar disorder, obsessive compulsive disorder, panic disorder) as well as persons with "treatment-resistant depression," defined as "[having had at least two failed adequate antidepressant treatments in the current major depressive episode](#)," were excluded. 80 participants were randomized to dextromethorphan/bupropion (45 mg/105 mg) or bupropion (105 mg) once daily for the first 3 days and then twice daily thereafter. Participants completed a four week "[washout](#)" of any recent antidepressant medications prior to beginning the trial. The primary outcome was change in baseline score on the [Montgomery-Asberg Depression Rating Scale](#) (MADRS) assessed weekly for 6 weeks. [The average change in MADRS scores after six weeks was greater with dextromethorphan/bupropion than with bupropion \(-13.7 points vs -8.8 points, 95% confidence interval \[CI\] = -3.1, -6.8\), and remission rates were statistically significantly higher with dextromethorphan/bupropion beginning in week 2.](#)

Auvelity's phase 3 trial, [GEMINI, had identical enrollment criteria to ASCEND: adults between the ages of 18-65 years with moderate or severe major depressive disorder without psychotic features](#); their exclusion criteria also mirrored ASCEND. 327 participants were randomized to either dextromethorphan/bupropion or bupropion (same dosing as ASCEND), and outcomes were also measured weekly using the MADRS score:

Remission was achieved by 39.5% of patients with dextromethorphan-bupropion versus 17.3% with placebo (treatment difference, 22.2; 95% CI, 11.7 to 32.7; $P < .001$), and clinical response by 54.0% versus 34.0%, respectively (treatment difference, 20.0%; 95% CI, 8.4%, 31.6%; $P < .001$), at week 6. Results for most secondary endpoints were significantly better with dextromethorphan-bupropion than with placebo at almost all time points.

These trials were both quite brief (participants were only followed for 7 weeks), and GEMINI's enrollment was relatively small for a phase 3 trial. Regardless, the newly approved Auvelity is expected to be available on the US market [by the end of 2022](#), likely with a [hefty price tag](#). Auvelity's rates of side effects are similar to currently available antidepressants, though the side effects themselves are somewhat different. In GEMINI, Auvelity's most common side effects were dizziness, nausea, headache, somnolence, and dry mouth, and "[\[t\]he percentage of patients in whom adverse events occurred during the treatment period was 61.7% in the dextromethorphan-bupropion group and 45.1% in the placebo \[bupropion\] group.](#)" That 61.7% is similar to second generation antidepressants (SSRIs, SNRIs, and TCAs), as [about 2/3 of patients on those medications also note side effects](#). Participants in GEMINI's Auvelity

group, however, [did not report more sexual dysfunction or weight gain than placebo](#), which may appeal to some patients if longer term studies confirm these findings.

While we await Auvelity's arrival, be sure to check out the [AFP By Topic on Depression and Bipolar Disorder](#) for helpful articles about about other treatment options for depression, both pharmacologic and non-pharmacologic.

[◀ Previous](#) | [Next ▶](#)

0 comments

 [Log In](#) to comment

	Topics	Other Blogs
Get <i>AFP</i> content delivered straight to your inbox.	• Alcohol Abuse	• Getting Paid <i>FPM</i> journal
	• Anxiety Disorders	• Quick Tips <i>FPM</i> journal
	• Back pain	• FPs on the Front Lines
	• COVID	• Fresh Perspectives
	• Diabetes	• In the Trenches
	• Family Planning	• Leader Voices
	• Heart Failure	
	• Immunizations	
	• Musculoskeletal care	
	• Obesity	
Sign up to receive twice monthly emails from <i>AFP</i> . You'll	Feed	

get the AFP Clinical Answers newsletter around the first of the month and the table of contents mid-month, shortly before each new issue of the print journal is published.

- [Signs and Symptoms](#)
- [See all topics](#)
- [RSS \(About RSS\)](#)

SIGN UP NOW

Disclaimer

The opinions expressed here are those of the authors and do not necessarily reflect the opinions of the [American Academy of Family Physicians](#) or its journals. This service is not intended to provide medical, financial, or legal

advice. All comments are moderated and will be removed if they violate our [Terms of Use](#).