

## Naltrexone/Bupropion (Contrave) for Weight Loss

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STEPS new drug reviews cover Safety, Tolerability, Effectiveness, Price, and Simplicity. Each independent review is provided by authors who have no financial association with the drug manufacturer.

This series is coordinated by Allen F. Shaughnessy, PharmD, MMedEd, Contributing Editor.

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Naltrexone/bupropion (Contrave) combines an opioid receptor antagonist (naltrexone) with a dopamine and norepinephrine reuptake inhibitor (bupropion) in an extended-release tablet. It is labeled as an adjunct to increased physical activity and a reduced-calorie diet for chronic weight management in adults who have a body mass index (BMI) of at least 30 kg per m<sup>2</sup> or who have a BMI of at least 27 kg per m<sup>2</sup> with one or more weight-related comorbidities such as type 2 diabetes mellitus, hyperlipidemia, or hypertension.

Drug	Dosage	Dose form	Cost*
Naltrexone/bupropion (Contrave)	8/90 mg per day, increasing over four weeks to 16/180 mg twice daily	8/90-mg extended-release tablet	\$212 for four tablets per day

\*—Estimated retail price of one month's treatment based on information obtained at <http://www.goodrx.com> (accessed February 23, 2015).

### SAFETY

Safety concerns with bupropion include depression, hypertension, and risk of seizures, whereas acute opioid withdrawal and opioid overuse have been associated with naltrexone.<sup>1</sup> Naltrexone/bupropion is labeled as increasing the risk of depression and suicidal behavior, based on studies of bupropion alone that showed an increase in the incidence of these events. However, clinical trials of the combination compared with placebo found no increase in depression and no increase in suicidality.<sup>2-4</sup> Naltrexone/bupropion should not be given to children or adolescents. Because it may raise blood pressure and heart rate, it should not be used in patients with uncontrolled high blood pressure. It also should not be prescribed to patients with a known seizure disorder or those already taking opioids. The total daily dosage of naltrexone/bupropion should not exceed two tablets twice a day.<sup>1</sup>

Although one of the goals of weight loss is to decrease the risk of cardiovascular outcomes, patients with active cardiovascular disease, including significant heart failure, history of myocardial infarction, angina, or stroke, were

excluded from premarketing studies. A large cardiovascular outcomes study that includes these patients is now ongoing. Bupropion is metabolized in the liver and its use may increase serum levels of some antidepressants, antipsychotics, beta blockers, and antiarrhythmics. Lower doses of these medications may be needed with concomitant use.<sup>1</sup>

Naltrexone/bupropion is pregnancy category X. Both components are excreted in breast milk and the medication should not be taken by breastfeeding mothers.<sup>1</sup>

### TOLERABILITY

Gastrointestinal symptoms are common with naltrexone/bupropion. Up to one in three patients will report nausea and 19% will experience constipation, especially early in treatment. Headache, dizziness, and sleep disorders are also common.<sup>1</sup> In premarketing studies, about 20% of patients discontinued treatment because of adverse effects.<sup>2-5</sup>

### EFFECTIVENESS

Naltrexone/bupropion has been evaluated in three studies that enrolled more than 4,000 ►

overweight or obese patients with hyperlipidemia or hypertension, and in one study of 505 patients with diabetes. In all studies, naltrexone/bupropion combined with a diet and exercise program for one year resulted in greater weight loss than placebo combined with a diet and exercise program.<sup>2-5</sup> About four patients need to be treated with naltrexone/bupropion instead of placebo for one additional patient to achieve at least a 5% weight loss (number needed to treat = 4).<sup>2-4</sup> Clinically significant weight loss was also achieved with placebo plus an intensive program of behavior modification, which supports the implementation of intensive interventions when these resources exist.<sup>4</sup> In settings where these resources are not available, naltrexone/bupropion combined with less intensive lifestyle interventions may also achieve clinically significant weight loss for obese patients.<sup>2,3</sup>

Naltrexone/bupropion has not been compared with other pharmacologic approaches. It is unknown if weight gain occurs after stopping the medication, and patient-oriented outcomes such as the development of osteoarthritis, diabetes, hypertension, cardiovascular disease, and mortality have not been studied.

#### PRICE

Naltrexone/bupropion costs approximately \$212 for a one-month supply.

#### SIMPLICITY

The dosing of naltrexone/bupropion must be titrated. In week 1, patients should take one 8/90-mg tablet once a day in the morning with a low-fat meal. In week 2, they should increase the daily dosage to one tablet in the morning and one tablet in the evening. During week 3, patients should increase the daily dosage to two tablets in the morning and one tablet in the evening, and in week 4 patients will reach the maximum recommended dosage of two tablets twice a day.<sup>1</sup> Patients with moderate to severe renal impairment should be limited to one tablet twice daily, and patients with moderate hepatic impairment should be limited to one tablet daily.<sup>1</sup> If patients do not lose 5% of their baseline body

weight after 12 weeks, further treatment is unlikely to be beneficial and therapy should be discontinued.<sup>1</sup> If patients achieve clinically significant weight loss after 12 weeks, therapy should be continued for up to one year. Naltrexone/bupropion has not been studied beyond 56 weeks.<sup>2-5</sup>

#### Bottom Line

Naltrexone/bupropion produces clinically significant weight loss when combined with a diet and exercise program. It decreases body weight in patients with diabetes, but its effect on diabetic outcomes is not known. A significant proportion of patients will experience adverse effects. It should not be prescribed for patients with preexisting heart disease until the effects are known. If prescribed, naltrexone/bupropion should be used with a diet and exercise program and should be discontinued if at least a 5% weight loss is not achieved within three months.

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