

Augmentation of Venlafaxine With Bupropion: Risks Associated With a Triple Monoamine Reuptake Inhibition Approach to Partially Responsive Depression

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Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to JCP readers in psychiatric and general medical settings.

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Clinical Problem

Mr B is a 52-year-old man with recurrent major depressive disorder. He has had 3 episodes of major depressive illness during the past 20 years; the third episode (ie, the current one), began about 4 months ago. There was no improvement with citalopram (20 mg/d) and only partial improvement with extended-release venlafaxine after 6 weeks of treatment, with the dose held at 225 mg/d during the last 4 weeks. Bupropion was added to venlafaxine in order to enhance antidepressant response through pharmacodynamic synergy. However, rapid deterioration occurred rather than improvement: within days, Mr B became increasingly anxious, agitated, and restless; suicidal ideation emerged; and his blood pressure increased from 130/90 mm Hg before bupropion to 160/100 mm Hg a week after the initiation of combination treatment. What could be the explanation for this turn of events?

Triple Monoamine Reuptake Inhibition

At low doses, venlafaxine inhibits the reuptake of serotonin. At higher doses, it inhibits the reuptake of norepinephrine, as well.¹ Thus, venlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI). If a patient responds inadequately to an adequate trial of an SNRI, it could make pharmacologic sense to add an antidepressant drug that belongs to a different pharmacodynamic category. Bupropion, which inhibits the reuptake of dopamine and norepinephrine,² is one such drug.

Why augment with bupropion instead of switch to bupropion? Some clinicians might argue that the continuation of venlafaxine carries the expectation that the benefits accrued with venlafaxine are not lost; after all, there is no assurance that bupropion will be effective in this patient. The addition of bupropion carries the expectation that a different antidepressant mechanism will add to the benefits brought about by venlafaxine.

The venlafaxine-bupropion combination will result in reuptake inhibition of serotonin, norepinephrine, and dopamine, that is, all 3 of the important monoamine neurotransmitters that are classically implicated in depression. This combination has received some support in the literature.^{3,4}

Effects of Bupropion on the Pharmacokinetics of Venlafaxine

There may be a favorable pharmacodynamic interaction between bupropion and venlafaxine in patients who do not respond sufficiently to venlafaxine alone.^{3,4} However, bupropion may also interact adversely with venlafaxine. Bupropion inhibits cytochrome P450 (CYP) 2D6,⁵ which is the enzyme that converts venlafaxine into an active metabolite, desvenlafaxine (also an approved antidepressant).⁶ Desvenlafaxine is not a substrate of CYP2D6; about 45% of the drug is excreted unchanged in urine, about 20% is glucuronidated and excreted in urine, and about 5% is metabolized by CYP3A4.⁷ Therefore, when CYP2D6 is inhibited, venlafaxine levels rise at the expense of desvenlafaxine. Because the

- In patients with partial response to venlafaxine, augmentation with bupropion may be considered, with the goal being “triple reuptake inhibition” of serotonin, norepinephrine, and dopamine.
- Because bupropion inhibits CYP2D6, the enzyme responsible for metabolizing venlafaxine, it can raise venlafaxine levels. In some patients, adverse effects may result, ranging from anxiety and restlessness to increased blood pressure.
- Should such adverse effects arise, treatment strategies include temporary withdrawal of venlafaxine or down-titration of the dose, using serum venlafaxine/desvenlafaxine levels as a guide in down-titration.

renal excretion of venlafaxine is small, the consequence is increased dose-dependent venlafaxine-related adverse effects.

Initial signs and symptoms of an adverse bupropion-venlafaxine pharmacokinetic interaction could include features of serotonergic overstimulation, including anxiety, restlessness, and agitation. These symptoms may be associated with suicidal ideation in vulnerable patients. Headache may develop and blood pressure may rise as a result of noradrenergic overstimulation. Other adverse events associated with venlafaxine may also increase in frequency or severity when bupropion is combined with the drug.

Bupropion inhibition of CYP2D6 will develop immediately after initiation of the drug. As a result, adverse events can occur within days, that is, within a few half-lives or dosage intervals of venlafaxine. Importantly, as evident from the data presented later in this article, not all persons will experience adverse events related to the interaction. This is because venlafaxine will gradually rise to new steady-state levels and because individuals will suffer adverse effects only if the new peak blood levels or new steady-state levels cross the threshold of tolerability. Levels of venlafaxine and thresholds of tolerability will vary widely across patients, and thresholds of tolerability will vary for different adverse effects. Therefore, the risk of adverse pharmacokinetic effects would correspondingly vary widely.

Evidence for Adverse Interactions Between Venlafaxine and Bupropion

Examples have been reported of adverse interactions when bupropion was used to augment venlafaxine treatment.^{3,4,8} In a prospective study⁸ of 8 depressed patients receiving venlafaxine (mean dose = 244 mg/d), augmentation with low-dose bupropion (150 mg/d) was associated with treatment dropout in 1 patient after 2 weeks of combination therapy (reason for dropout not specified). In the remaining 7 patients, venlafaxine levels increased 2- to 3-fold in serial assessments across 8 weeks of combination treatment; in contrast, desvenlafaxine levels dropped by about half. The levels of venlafaxine and desvenlafaxine combined were

consistently higher (by about a third) during the course of combination treatment. Adverse events reported included myoclonus and tremor in 1 patient, a 10-point increase in diastolic blood pressure in a patient with a previous history of hypertension, and recurrence of lactation in a patient with a previous history of selective serotonin reuptake inhibitor-associated lactation.

In a prospective case series³ of 8 difficult-to-treat bipolar depressed patients, bupropion (modal dose = 300 mg/d) augmentation of venlafaxine (225–500 mg/d) resulted in remission in 5 patients. One patient did not respond, 1 patient dropped out after 3 weeks because of tachycardia, and 1 patient opted out of the study after 3 weeks for unstated reasons.

In a small, prospective case series, Paslakis et al⁴ described 3 depressed patients who had insufficiently responded to venlafaxine alone. One patient was a CYP2D6 extensive metabolizer; she remitted uneventfully with bupropion (150 mg/d) augmentation of venlafaxine (375 mg/d). Another patient was a CYP2D6 poor metabolizer in whom the addition of bupropion (300 mg/d) to venlafaxine (150 mg/d) resulted in an increase in blood venlafaxine levels; this patient reported increased inner tension as a manifestation of the drug interaction and later remitted uneventfully after the dose of venlafaxine was reduced to 75 mg/d. A third patient, who was a CYP2D6 normal metabolizer, received bupropion (300 mg/d) in addition to ongoing treatment with venlafaxine (375 mg/d). Venlafaxine levels increased to more than 5 times the baseline level, and desvenlafaxine levels also increased (by about a third). The patient developed tension, agitation, headache, and insomnia. The adverse effects diminished after bupropion was withdrawn and the dose of venlafaxine was reduced to 225 mg/d.

Other Data Suggesting a Possible Interaction

In a postmortem study of 123 cases of fatal venlafaxine poisoning, Launiainen et al⁹ reported that an interacting drug may have contributed to the poisoning in 46% of cases; 1 of these patients was identified to have received bupropion.

Risk of the Interaction in CYP2D6 Poor Metabolizers

About 0%–14% of the population, depending on geographical origin,¹⁰ is made up of CYP2D6 poor metabolizers, and these patients may have high levels of venlafaxine even before starting bupropion treatment.¹¹ On the one hand, bupropion could be expected to raise venlafaxine levels to a lesser extent in such patients because venlafaxine levels are already high and because there is less of the CYP2D6 enzyme to inhibit. On the other hand, the interaction could push the already high venlafaxine levels to new levels that are above the threshold of tolerability, resulting in an adverse pharmacokinetic interaction. Thus, there is no room for complacency; yet, there is no need for special concern, either, when bupropion is used to augment venlafaxine in CYP2D6 poor metabolizers.

Dealing With the Adverse Interaction

Clinicians who attempt bupropion augmentation of venlafaxine should be aware that this drug can raise venlafaxine levels. They should know that patients may develop signs and symptoms of serotonergic and noradrenergic overstimulation within days of initiation of bupropion augmentation. They should therefore monitor patients for such adverse events during the initial week or weeks of the combination treatment.

Should clinical features of serotonergic or noradrenergic overstimulation arise, the dose of venlafaxine will need to be down-titrated, or venlafaxine may need to be temporarily withdrawn and later reintroduced at a lower dose. These decisions are best assisted, wherever available, by an assessment of venlafaxine and desvenlafaxine drug levels. Ideally, these levels should be obtained before bupropion augmentation so that a baseline is available, should it be necessary for comparison with later levels. Baseline values could be especially useful in patients who are CYP2D6 poor metabolizers.

Effects of Venlafaxine on the Pharmacokinetics of Bupropion

Venlafaxine and desvenlafaxine mildly inhibit CYP2D6; the former, perhaps through the latter.^{12,13} Venlafaxine and desvenlafaxine do not affect CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and P-glycoprotein activity.¹⁴ Bupropion is principally metabolized by CYP2B6,^{15,16} but other CYP enzymes such as 2E1,¹⁵ 3A4,¹⁷ and 3A5¹⁸ and non-CYP pathways¹⁶ also play a (small) role in its breakdown. Bupropion is not metabolized by CYP2D6. Thus, venlafaxine and desvenlafaxine will not affect bupropion levels. This is reassuring because increased bupropion levels could be associated with serious adverse effects. For example, bupropion doses of 450 mg/d and higher have been associated with an increased risk of seizures.^{2,19}

Conclusions

Clinicians who augment venlafaxine with bupropion should know that bupropion can raise blood levels of venlafaxine. This can result in signs and symptoms of serotonergic and noradrenergic overstimulation in some patients.

Here is a parting note: A systematic review suggested that an antidepressant combination strategy may be a suboptimal approach to major depression in incomplete responders²⁰; augmentation with an atypical antipsychotic may be a better approach.²¹

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