Combining Bupropion SR With Venlafaxine, Paroxetine, or Fluoxetine: A Preliminary Report on Pharmacokinetic, Therapeutic, and Sexual Dysfunction Effects

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Background: This study was designed to evaluate the effect of combining bupropion sustained release (SR) with venlafaxine, paroxetine, or fluoxetine in patients who reported unacceptable sexual dysfunction when treated with monotherapy with the latter 3 agents.

Method: Following a minimum of 6 weeks of antidepressant treatment with a selective serotonin reuptake inhibitor (SSRI) or venlafaxine (a serotonin-norepinephrine reuptake inhibitor), eligible subjects received a further 8 weeks of monitored combination therapy with bupropion SR at a dose of 150 mg/day with no alterations to index antidepressant dosing.

Results: There was a clinically significant benefit in 14 (78%) of 18 partial responders or nonresponders, and 33% (N = 6) achieved a full response ($\chi^2 = 8.06$, df = 2, p = .017). Sexual dysfunction, particularly a decrease in orgasmic delay, was also significantly improved with combination therapy (men: paired t = –2.1, df = 6, p = .08; women: paired t = –3.0, df = 7, p = .02). Plasma monitoring of drugs and their metabolites revealed a statistically significant increase in venlafaxine levels (F = 6.89, df = 4,24; p = .001) accompanied by a decrease in *O*-desmethylvenlafaxine (F = 14.26; df = 4,24; p < .0005) during combined treatment with bupropion SR. There were no statistically significant changes in plasma levels of SSRIs (paroxetine and fluoxetine) during the trial.

Conclusion: Bupropion had an effect on the pharmacokinetics of venlafaxine but not those of the SSRIs. Further investigation of combination treatments under randomized, double-blind conditions is recommended.

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Despite the demonstrated therapeutic benefits of monotherapy with selective serotonin reuptake inhibitor (SSRI) antidepressants such as paroxetine and fluoxetine[1,2] and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine,[3] the use of polypharmacy has been steadily increasing in the management of major depression.[4]

Bupropion, a dopamine and norepinephrine modulator[5,6] with antidepressant effects comparable to those of SSRIs,[7] represents an alternative first-line treatment for major depression,[8] with evidence of enhanced sexual function or minimal sexual dysfunction.[9] Because of the distinct mode of action and favorable sexual side effect profile of bupropion, there have been reports of the beneficial effects of combining bupropion with SSRI antidepressants.[10,11] However, the potential for pharmacokinetic interactions with this combination has not been systematically examined.

The potential benefits of this combination therapy need to be balanced against the possible hazards of adverse drug interactions. In addition to their inhibitory effects on several of the major cytochrome P450 (CYP) isoenzymes

(paroxetine and fluoxetine are potent inhibitors of CYP2D6), these SSRIs (paroxetine and fluoxetine) and SNRI (venlafaxine) antidepressants are themselves substrates for CYP2D6.[12,13] Although bupropion is primarily metabolized to hydroxybupropion by CYP2B6,[14,15] its potential to interact with CYP2D6-metabolized drugs has been described.[16,17] Pollock and colleagues[18] provided equivocal evidence that bupropion metabolism is not affected by CYP2D6. Although plasma level/dose ratios for bupropion, and its metabolites erythrohydrobupropion and threohydrobupropion, were not associated with debrisoquin metabolic status, statistically significant elevations in hydroxybupropion plasma level/dose ratios were reported in poor debrisoquin metabolizers. If replicated, this finding would have clear implications for the combination of bupropion with antidepressants such as fluoxetine, paroxetine, or venlafaxine that inhibit CYP2D6 to varying degrees. The primary objective of this study was to evaluate the pharmacokinetic effects of adding bupropion sustained release (SR) to fluoxetine, paroxetine, or venlafaxine. We also evaluated the therapeutic and adverse effects of this combination, with specific emphasis on sexual dysfunction.

METHOD

Participants

The study was conducted at the Depression Clinic of the Centre for Addiction and Mental Health (CAMH), University of Toronto, with approval by the Research Ethics Board, and subjects were enrolled after providing written informed consent. Inclusion criteria included the presence of a major depressive episode, diagnosed according to DSM-IV criteria derived from clinical interview and confirmed with the Structured Clinical Interview for DSM-IV (SCID).[19] Following at least 6 weeks of paroxetine, fluoxetine, or venlafaxine extended release (XR) monotherapy, subjects were required to have documented evidence of sexual dysfunction (based on a measured reduction of desire, arousal, or orgasm). The presence of unstable medical conditions (e.g., endocrine, cardiovascular, neurologic, renal, or respiratory disorders) or a positive drug screen were exclusion criteria. Subjects were also excluded if they met DSM-IV criteria for bipolar disorder, psychotic disorders, or substance abuse or dependence.

Measures

The Sexual Function Questionnaire-Version 2 (Sex-FX) is a self-report instrument that assesses sexual functioning across 3 domains (desire, arousal, and orgasm). This scale is modified from Healy.[20] The drive/desire scale is identical for both men and women and consists of 4 items. The arousal and orgasm scales consist of appropriately modified items for men and women. Four additional items are included to assess enjoyment and overall satisfaction with sexual activity as well as frequency of sexual activity and orgasm. (For additional information on this scale, see Kennedy and colleagues.[21,22])

Respondents are asked to rate on a 5-point Likert scale whether each item was experienced never, rarely, sometimes, often, or very often in the past 2 weeks. Mean scores (scores range from 1 to 5; higher scores indicate better levels of functioning) for each domain were calculated (by summing up individual items and dividing by the total number of items) to allow for direct comparison of scores in men and women. In addition, mean scores across all 3 domains were obtained to provide a global assessment of sexual functioning. The 17-item Hamilton Rating Scale for Depression (HAM-D)[23] and the Clinical Global Impressions scale (CGI)[24] were also administered.

Procedures

The SCID, HAM-D, and CGI were completed by a trained clinical rater at baseline. Prior to initiating combination therapy with bupropion SR, subjects completed the Sex-FX and provided urine for drug screening. Blood samples were also drawn at 23 to 24 hours after last dose to obtain baseline trough plasma SSRI or SNRI levels. Bupropion SR, 150 mg/day, was then added. The study was prospective and naturalistic in design, with clinicians providing standard clinical management, although they were requested to not alter SSRI/SNRI dosing. Blood samples were obtained every 2 weeks at 23 to 24 hours after last dose of SSRI/SNRI to assess trough plasma levels, at which times the HAM-D and Sex-FX were administered and side effect reports were obtained.

Clinicians elicited side effects using a standardized verbal probe and asked the following question before initiating combination treatment and every 2 weeks thereafter: "Have you experienced any unpleasant effects from your medications since you were last seen at the clinic?" These side effects were then rated for each subject as either mild (no impairment in usual activity), moderate (some impairment in usual activity), or severe (interference with usual activity).

Assay Methodology

Fluoxetine and its *N*-demethylated metabolite, norfluoxetine, were analyzed using a modification of the procedure of Rotzinger and colleagues.[25] This involved reaction with pentafluorobenzoyl chloride under aqueous conditions followed by analysis using gas chromatography with electron-capture detection (Hewlett-Packard HP 5890; Agilent, Palo Alto, Calif.). Paroxetine was analyzed using the procedure of Lai and colleagues.[26] This procedure involved extraction under basic aqueous conditions, reaction with heptafluorobutyric anhydride under anhydrous conditions, and quantification using gas chromatography with electron capture detection (Hewlett-Packard HP 5890; Agilent, Palo Alto, Calif.). Venlafaxine and its demethylated metabolite were measured using a

Table 1. Patient and Drug Characteristics According to Primary Antidepressant[a]

Characteristic	Venlafaxine XR	Fluoxetine	Paroxetine
Subjects, N			
Total	8	5	6
Men	3	1	3
Women	5	4	3
Age, y	38.5 ± 13.1	46.2 ± 5.6	37.5 ± 15.9
HAM-D score	15.1 ± 4.8	17.0 ± 6.8	13.7 ± 6.4
Dose, mg/d	243.8 ± 77.6	44.0 ± 8.9	45.0 ± 25.1
Dose range, mg/d	150.0–375.0	40.0–60.0	20.0–80.0

[a]All values shown as mean ± SD unless noted otherwise.
Abbreviation: XR = extended release.

high-pressure liquid chromatography (HPLC) method (C. T. Lai, Ph.D.; A. N. Bateson, Ph.D.; G.B.B., manuscript submitted, 2002). Plasma samples, to which internal standard (desipramine) had been added, were basified and extracted with ethyl acetate. After the samples were dried under a stream of nitrogen, the residues were reconstituted in methanol and injected into an HPLC apparatus (WISP 710B and model 510 pump; Waters, Milford, Mass.) equipped with a guard column, a phenosphere CN column, and a UV detector (model 2487; Waters, Milford, Mass.) set at a wavelength of 224 nm.

Statistical Methods

Categorical data were analyzed using chi-square or Fisher exact tests. Differences in continuous data among groups were analyzed using 1-way analysis of variance (ANOVA). The Sex-FX data were analyzed using paired t tests to identify differences between baseline assessment (week 0) and endpoint (week 8). Data were analyzed on an intent-to-treat basis using the last-observation-carried-forward method for measures of clinical response and sexual functioning. Plasma levels were assessed using repeated-measures ANOVA to compare differences at weeks 0, 2, 4, 6, and 8.

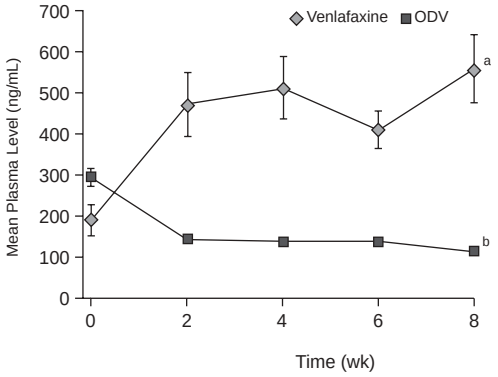
RESULTS

Demographic and Clinical Characteristics

Between February and October 1999, a total of 19 consecutive subjects (7 men and 12 women) met criteria for inclusion. Eighteen subjects were white, and 1 was East Indian. The mean ± SD age of the sample was 40.2 ± 12.5 years. For men, the mean age in years was 35.1 ± 11.8; for women, it was 43.2 ± 12.5. There were no statistically significant differences between men and women in terms of age ($t = -1.4$, $df = 17$, $p = .19$). Thirty-seven percent of the sample (7/19) were single/never married, 16% (3/19) were married/cohabiting, 42% (8/19) were separated/divorced, and 5% (1/19) were widowed.

Ninety-five percent (18/19) had recurrent depression, and 5% (1/19) had a single episode. The mean ± SD baseline 17-item HAM-D score was 15.2 ± 5.7 (men, 15.6 ± 6.0; women, 14.9 ± 5.7; $t = 0.24$, $df = 17$, $p = .82$). Table 1 shows the patient and drug characteristics across the 4 drug groups.

Figure 1. Venlafaxine and *O*-desmethylvenlafaxine (ODV) Trough Plasma Levels (mean ± SEM) During Combination Treatment (N = 7)



[a]$F = 6.89$, $df = 4,24$; $p = .001$ for change in mean venlafaxine levels over time.
[b]$F = 14.26$, $df = 4,24$; $p < .0005$ for change in mean ODV levels over time.

Plasma Levels of Primary Antidepressants During Bupropion SR Combination

Of the 8 subjects who were treated with venlafaxine, 1 subject discontinued after 2 weeks of combined bupropion SR treatment. Plasma levels of venlafaxine and its major metabolite, *O*-desmethylvenlafaxine (ODV), after bupropion SR addition for the remaining 7 subjects are shown in Figure 1. There was a significant increase in mean venlafaxine levels ($F = 6.89$, $df = 4,24$; $p = .001$) and a corresponding significant decrease in levels of ODV ($F = 14.26$, $df = 4,24$; $p < .0005$).

Assay-detectable plasma paroxetine levels were available for only 4 of the 6 subjects and were not statistically different during the trial ($F = 1.83$, $df = 4,12$; $p = .19$). Similarly, fluoxetine ($F = 0.44$, $df = 4,16$; $p = .78$) and norfluoxetine ($F = 0.41$, $df = 4,16$; $p = .80$) levels were not significantly altered in 5 subjects throughout the trial (see Table 2 for fluoxetine, norfluoxetine, and paroxetine levels).

Clinical Efficacy and Tolerability

For the 18 partial responders (response defined as a 17-item HAM-D score ≥ 8 and ≤ 15) or nonresponders (nonresponse defined as a 17-item HAM-D score ≥ 16) at baseline, there was a clinically and statistically significant effect ($\chi^2 = 8.06$, $df = 2$, $p = .017$) following 8 weeks of combination therapy with bupropion. Six of 9 nonresponders improved (1 became a full responder and 5 became partial responders). Of the 9 subjects who were initially partial responders, 5 became full responders and 4 remained partial responders. This was also reflected in

Table 2. SSRI/SNRI Plasma Levels (mean ± SD ng/mL) During Combination Treatment With Bupropion SR[a]

Parent Drug or Metabolite	Week 0	Week 2	Week 4	Week 6	Week 8
Paroxetine	326.5 ± 231.0	273.4 ± 172.2	234.6 ± 121.2	233.8 ± 142.5	249.4 ± 161.5
Venlafaxine	192.1 ± 205.4	475.5 ± 445.7	516.6 ± 426.6	415.6 ± 254.8	567.1 ± 467.1
O-desmethylvenlafaxine	295.4 ± 127.8	145.7 ± 87.9	144.1 ± 93.5	143.7 ± 82.2	124.4 ± 75.0
Fluoxetine	281.0 ± 130.4	311.8 ± 150.8	300.6 ± 146.7	298.6 ± 147.4	320.5 ± 118.8
Norfluoxetine	232.8 ± 133.1	242.0 ± 128.6	223.0 ± 118.7	202.7 ± 96.1	221.0 ± 75.2

[a]Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SR = sustained release, SSRI = selective serotonin reuptake inhibitor.

Table 3. Clinical Response According to Primary Antidepressant During Bupropion SR Combination[a]

Variable	Venlafaxine XR	Fluoxetine	Paroxetine	Total
Subjects, N	8	5	5	18
Baseline HAM-D score, mean ± SD	15.1 ± 4.8	19.8 ± 3.3	15.0 ± 6.2	16.2 ± 5.1
Week 8 HAM-D score, mean ± SD[b]	12.0 ± 5.7	14.8 ± 6.0	7.4 ± 4.2	11.3 ± 5.8[c]

[a]Baseline full responders not included. Abbreviations: HAM-D = Hamilton Rating Scale for Depression, SR = sustained release, XR = extended release.
[b]Comparison of mean baseline HAM-D scores for venlafaxine XR, fluoxetine, and paroxetine: F = 1.35, df = 2,14; p = .29.
[c]Difference between baseline and week 8 total mean HAM-D scores: t = 4.1, df = 16, p = .001.

Table 4. Sexual Functioning (as measured using the Sex-FX) During Bupropion SR Combination Therapy[a]

Domain	Week 0	Week 8
Desire		
Men	2.3 ± 0.6	2.6 ± 0.4
Women	2.1 ± 0.9	2.0 ± 1.1
Arousal		
Men	2.8 ± 0.6	3.0 ± 0.8
Women	3.3 ± 1.1	3.6 ± 0.7
Orgasm		
Men	2.6 ± 1.2[b]	3.2 ± 0.8
Women	2.4 ± 0.7[c]	3.1 ± 0.4
Global[d]		
Men	2.6 ± 0.2[e]	2.9 ± 0.3
Women	2.6 ± 0.5	2.9 ± 0.5

[a]All values shown as mean ± SD Sex-FX scores. Abbreviations: Sex-FX = Sexual Functioning Questionnaire-Version 2, SR = sustained release.
[b]Paired t = –2.1, df = 6, p = .08 for male mean orgasm score differences after bupropion SR treatment.
[c]Paired t = –3.0, df = 7, p = .02 for female mean orgasm score differences after bupropion SR treatment.
[d]Global score is calculated as mean of desire + arousal + orgasm scores.
[e]Paired t = –2.7, df = 6, p = .04 for male mean global sexual function score differences after bupropion SR treatment.

the significant reduction in mean ± SD HAM-D scores between baseline (16.2 ± 5.1) and week 8 (11.3 ± 5.8) (t = 4.1, df = 16, p = .001). There were no significant differences across SSRIs or venlafaxine in baseline HAM-D scores (Table 3).

Prior to starting combination therapy, 5 side effects were reported by 10% or more subjects: gastrointestinal discomfort (9/19, 47%), dry mouth (11/19, 58%), sweating (7/19, 37%), headache (11/19, 58%), and tremor (2/19, 11%). After 8 weeks of combination treatment with bupropion, 3 of these side effects were reported less frequently: gastrointestinal discomfort (5/18, 28%), dry mouth (5/18, 28%), and headache (7/18, 39%), while sweating remained unchanged (7/18, 39%) and tremor increased (4/18, 22%). Insomnia, which had not been reported at baseline, was reported with a frequency of 22% (4/18) at 8 weeks. Myoclonus accompanied tremor in 1 of the 8 subjects who received venlafaxine, and a second patient in the venlafaxine group who had a prior history of SSRI-induced lactation also reported lactation during the combination trial. Overall, there were no changes in blood pressure during bupropion SR treatment, although 1 individual with a past history of hypertension, who received venlafaxine XR, experienced a 10-point increase in diastolic blood pressure.

Change in Sexual Dysfunction During Bupropion SR Combination

All 19 subjects had reported deterioration in some aspect of sexual function during index antidepressant treatment, and there were no significant differences across drug groups with respect to baseline levels of sexual dysfunction. There were no statistically significant differences between men and women in terms of their baseline scores across the desire, arousal, and orgasm domains, nor were there differences in measures of global sexual functioning and enjoyment. Although numerical improvement in all 3 domains of sexual function (desire, arousal, and orgasm) occurred after 8 weeks of combination treatment, these differences were statistically significant only for orgasm in women and for global sexual functioning in men; a trend was noted for improvement in orgasm score in men (Table 4). There was also no significant change in frequency of sexual activity or orgasm after combination treatment.

DISCUSSION

The primary objective of this study was to evaluate pharmacokinetic effects of adding bupropion SR to existing SSRI or SNRI therapy. We report an almost 3-fold increase in plasma levels of venlafaxine associated with a greater than 50% reduction in levels of the principal metabolite, ODV. To our knowledge, this is the first study to specifically demonstrate a pharmacokinetic interaction between bupropion and venlafaxine. The most likely explanation is an inhibitory effect by bupropion and/or one of

its metabolites on CYP2D6, which is required for the conversion of venlafaxine to ODV. Although Pollock and colleagues[18] "inferred that bupropion is neither metabolized by nor inhibits CYP2D6,"(p581) they did indeed observe an association between plasma levels of hydroxybupropion and CYP2D6 phenotype in 12 healthy subjects. Specifically, they demonstrated that hydroxybupropion plasma level/dose ratios were significantly higher in poor CYP2D6 metabolizers versus extensive CYP2D6 metabolizers as determined by correlation with debrisoquin metabolic status. This finding suggests that hydroxybupropion, but not bupropion (i.e., the same effect was not observed for this parent drug), is a substrate for CYP2D6. It may therefore be inferred that the accumulation of hydroxybupropion substantially inhibited the CYP2D6-mediated metabolism of venlafaxine to ODV in our sample. Indeed plasma hydroxybupropion levels are typically higher than those of bupropion, and this has been suggested to be accountable for toxicity.[27] Our finding is also consistent with information in the *Physicians' Desk Reference*[16] that up to 5-fold increases in desipramine levels may occur when bupropion is added, and with a case report[17] involving combination therapy with imipramine and bupropion in which repeated plasma levels of imipramine and desipramine demonstrated a reduced clearance of desipramine following the addition of bupropion. Desipramine is known to be metabolized by CYP2D6.

How does one account for our findings with regard to plasma levels of fluoxetine/norfluoxetine and paroxetine after treatment with bupropion? Although fluoxetine and paroxetine are metabolized by CYP2D6 and are potent inhibitors of this isoenzyme,[12,13,28] the absence of any change in plasma levels of fluoxetine or paroxetine when bupropion was added may be related to the fact that these SSRIs have very high affinity for and thus easily saturate CYP2D6. It would therefore require a competitive inhibitor of at least equal (i.e., high) potency to displace these antidepressants from the substrate-binding site of CYP2D6. Conversely, venlafaxine has been shown to be a weak inhibitor of CYP2D6 in vitro[29,30] and thus has a low affinity for this isozyme. It would therefore be expected that a weak inhibitor of CYP2D6, potentially hydroxybupropion, might cause venlafaxine to be displaced from the substrate-binding site of this cytochrome P450 isozyme. This hypothesis is supported by a recent study[15] which demonstrated that both bupropion and hydroxybupropion have relatively low inhibitory potentials of CYP2D6 in vitro. Additionally, in vitro and in vivo enzyme-kinetic studies examining the displacement of venlafaxine from CYP2D6 are required to confirm our preliminary finding and to replicate the work of Hesse and colleagues.[15]

What are the clinical implications of significant elevations in venlafaxine levels? It is notable that in our study, all subjects had a reduction in depressive symptoms after bupropion augmentation, independent of initial antidepressant therapy (see Table 2). Our result can be explained by the fact that both venlafaxine and ODV are pharmacologically active and inhibit the serotonin transporter with similar potency.[28] Preskorn[30] speculated that there is a low potential for clinically relevant changes in efficacy of venlafaxine even in the context of a significant pharmacokinetic interaction, given that ODV has similar pharmacodynamic properties to its parent compound, venlafaxine.

A second preliminary conclusion is that the combined treatment enhanced antidepressant response. Since we did not have a "bupropion-only" treatment group, we cannot rule out the possibility that bupropion alone would have been as effective as the combination. In general, however, clinicians are reluctant to discontinue treatments that are partially or fully effective and often prefer to use combination or augmentation strategies.

The therapeutic benefit of bupropion in combination with SSRIs has previously been reported.[31–34] Bodkin and colleagues[34] retrospectively reviewed the effects of SSRI and bupropion combination therapy after failure of either monotherapy; 70% of the case series showed significant clinical improvement, while 15% discontinued due to adverse effects. Spier[33] reported clinical improvement in 12 of 15 partial responders to SSRI therapy when bupropion was added, but only 2 of 10 showed an improvement in side effects with combination therapy. Similarly, in a single case report, bupropion added to venlafaxine XR resulted in a full remission and no adverse effects after multiple previous failures to respond.[35] These results are comparable to our findings, in which 14 (78%) of 18 partial responders or nonresponders to SSRI/SNRI monotherapies showed improvement and 33% achieved a full response. This study also supports previous reports that bupropion can enhance sexual function when added to SSRI or SNRI antidepressants.[11,36] Bupropion on a regular or as-needed basis reversed a variety of sexual dysfunctions caused by SSRIs in 66% of 47 patients[11]; Labbate and colleagues[36] reported marked improvement in sexual dysfunction among 4 of 8 patients following the addition of bupropion (75 mg/day) to SSRI therapy. Of related interest is the recent report of enhanced orgasmic function in nondepressed women and men following treatment with bupropion.[37]

To our knowledge, this is the first study that employed a rating instrument of sexual functioning, the Sex-FX (for which validity and reliability data had been previously documented[21,22]), to examine whether the addition of bupropion SR to SSRI or SNRI monotherapy has a positive impact on antidepressant-induced sexual dysfunction. We demonstrated that bupropion significantly enhances orgasmic function in women. This finding suggests that the Sex-FX is a responsive scale that can be used to measure changes in levels of sexual functioning. Future studies are warranted to determine the clinical relevance of such changes in Sex-FX scores and should significantly contribute to the continued refinement of this rating instrument.

With the obvious limitations of unblinded open-label design and small sample size, these findings contribute to the limited data on safety and effectiveness of combined antidepressant therapy, and in the case of venlafaxine provide evidence of pharmacokinetic effects when bupropion SR is coprescribed. Although our small sample size precludes a detailed analysis of side effects, the combinations were generally well tolerated. Myoclonus, lactation (in a patient with a past history of SSRI-induced lactation), and an isolated rise in diastolic blood pressure occurred individually in 3 venlafaxine-treated subjects after coadministration of bupropion SR. These may represent adverse effects developing secondarily from the observed pharmacokinetic interaction between venlafaxine and bupropion SR, although larger randomized controlled trials are required to confirm these preliminary findings.

In conclusion, preliminary results in a small clinical sample demonstrate an effect of bupropion on the pharmacokinetics of venlafaxine, but not of paroxetine and fluoxetine. Because of alterations in venlafaxine metabolism, clinicians should exercise caution when bupropion SR and venlafaxine XR are combined. Given the inherent limitations of small sample size and nonrandomized design, we believe a larger randomized trial is warranted to examine the benefits and risks of this and other forms of combination antidepressant therapies.

Drug names: bupropion (Wellbutrin and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), paroxetine (Paxil), venlafaxine (Effexor).

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