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USE OF BUPROPION WITH SRIs AND VENLAFAXINE

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Because of reported efficacy of combining classes of antidepressants, 25 patients were treated with bupropion in combination with SRI's and venlafaxine. Fifteen patients inadequately responsive to monotherapy received combination treatment; ten patients without residual symptoms received adjunctive bupropion to treat SRI- or venlafaxine-induced side effects. Fourteen subjects (56%) responded, 11 (44%) did not. Twelve of 15 subjects receiving combination treatment to boost the effects of monotherapy responded, while only 2 of 10 subjects receiving combination treatment for side effects responded. Combination therapy was well tolerated even by geriatric and "medically frail" patients. Depression and Anxiety 7:73–75, 1998. *© 1998 Wiley-Liss, Inc.*

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INTRODUCTION

Treatment-resistant depression has been reported to respond to combinations of antidepressants from different classes, notably monoamine oxidase inhibitors with tricyclics (White and Simpson, 1981), and serotonin reuptake inhibitors (SRIs) with heterocyclics (2,3). Although several reports have reported toxicity or questioned the safety of combining bupropion with SRIs (Young, 1996; Zubieta and Demitrack, 1991; Van Putten and Shaffer, 1990; Preskhorn, 1991), a growing literature supports the value of such a combination treatment (Boyer and Feighner, 1993; Labbate and Pollack, 1994; Marshall et al., 1995; Marshall and Liebowitz, 1996; Bodhin et al., 1997). SRIs are efficacious in depression and anxiety disorders, but may induce sexual dysfunction (Balon et al., 1993) and a syndrome of apathy and indifference (Hoehn-Saric et al., 1990). Bupropion's mechanisms of action is unclear, but it may parallel the "nonadrenergic boost" of tricyclics added to SRIs, and/or the stimulatory effects of increasing dopaminergic transmission (Ferris and Cooper, 1993; Golden et al., 1988).

Because of the apparent utility of combining classes of antidepressants, bupropion was added to SRIs and venlafaxine beginning in 1993. It was initially hypothesized that bupropion would be more useful for treating serotonin-related side effects than treating residual symptoms of depression.

METHODS

Subjects were the first 25 patients treated with bupropion in combination with an SRI or venlafaxine, recruited from the private practice of the author, a practice skewed toward treatment-resistant and medically ill patients. Diagnoses were made clinically, by DSM III R or DSM IV criteria. Combination treatment was employed in 3 clinical scenarios (see Table 1):

1. Inadequate response to SRIs or venlafaxine. Usually low-dose bupropion was added after previous upward titration of the initial agent has been unsuccessful. Prior to adding bupropion, doses were increased to these target ranges as tolerated: fluoxetine 60 mg, sertraline 200 mg, paroxetine 60 mg, venlafaxine 375 mg. Maximum tolerated dose of SRI or venlafaxine was continued for at least 6 weeks for all patients before bupropion was added. "Inadequate response" was defined as incomplete resolution of presenting depressive symptoms, to the extent that a new medication regimen was to be considered or recommended.
2. Inadequate response to bupropion monotherapy. Low-dose SRIs were added in patients incompletely responsive to bupropion. Maximally tolerated dose of bupropion was maintained for at least six weeks prior to adding an SRI.
3. Intolerance of SRI side effects despite positive response to SRI monotherapy. Bupropion was added in ten patients responsive to SRIs without residual symptoms to counteract side effects. Side effects were apathy and anergy, sexual dysfunction, and one case of unremitting nausea at therapeutic doses of sertraline. Most patients with sexual dysfunction and several with apathy and anergy had also undergone trials with yohimbine, amantadine, and/or stimulants.

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Subjects were rated at each visit on the Clinical Global Impression Scale (Guy, 1976), a seven-point scale ranging from "normal" [1] to "among the most ill patients I have treated" [7]. Ratings are reported prior to the addition of the second agent, and after response to the second agent had stabilized. Responders for categories I and II were defined as those subjects who had improved by at least two levels on the CGI and maintained their improvement for at least 3 months. For category III, response was defined as resolution of side effects and maintenance of antidepressant effect.

Patients over 65 years were termed "geriatric." Those patients with multiple medical problems with resultant disability, whose death within 2 years would not be unexpected, were defined as "medically frail."

Patients were not selected randomly. Bupropion, the only antidepressant shown in a double-blind placebo-controlled study to be ineffective for panic disorder (Sheehan et al., 1983), was generally employed for relatively anergic and/or retarded patients, not those with uncontrolled panic attacks or significant levels of anxiety.

RESULTS

Sixteen women (64%) and nine men (36%) were treated. Mean age was 49.4 (range 28–88) years. Five (20%) were geriatric. Twenty-four subjects had a current primary diagnosis of major depression: nineteen (76%) had recurrent unipolar depression, five (20%) had bipolar II disorder. One subject who received bupropion for SRI-induced side effects had obsessive compulsive disorder.

Regarding secondary diagnoses, seven (28%) had alcohol abuse or dependence in remission, two (8%) had dementia, two (8%) OCD, three (12%) panic disorder, one (4%) social phobia, and one (4%) PTSD. Five (20%) were "medically frail," and one had a history of complex partial seizures controlled with carbamazepine.

Eleven (44%) subjects fell into category I, four (16%) into II, and ten (40%) into III. Of the ten patients in category III (i.e., effectively treated with SRIs but intolerant of side effects) five (20%) had marked apathy and/or anergy. Three of these five also had sexual dysfunction (impaired libido or orgasm) in conjunction with their anergy and apathy. Four others (16%) in category III had sexual dysfunction alone. One (4%) had persistent intolerable nausea on therapeutic doses of sertraline, and repeated relapses of depressive symptoms when dosage of sertraline was reduced on three different occasions to levels where nausea resolved.

Overall, 14 (56%) of 25 patients responded (see Table 1). Of the eleven patients receiving adjunctive bupropion for inadequate response, nine (82%) responded. Of the four patients who received adjunctive SRI to boost response to bupropion, three (75%) responded.

In category III, where bupropion was added to treat side effects, only two of ten (20%) responded. Only one of the five apathetic patients on SRIs responded, and none of four patients who had sexual dysfunction alone responded when adjunctive bupropion was initiated. The one patient with persistent nausea on sertraline was able to decrease her dose of sertraline to acceptable levels but still maintain euthymia via the addition of bupropion. Depressive symptoms recurred on bupropion alone without sertraline.

Average initial CGI of responders was 5.2 (4–7), and final CGI was 2.2 (1–4). Dosages in each category are listed in Table 2. Average time of follow-up of responders on combined treatment was 21.3 months (range 3–41 months). Medication regimen was changed in four patients despite positive response because of pregnancy, hypomania, and unassociated medical illnesses in two patients (metastatic CNS lesion and renal failure requiring dialysis). The patient who developed hypomania 4 weeks after bupropion was added to venlafaxine had a history of mild hypomanias, which were never problematic until the addition of bupropion. She subsequently did well with discontinuation of venlafaxine and addition of lithium.

Side effects leading to nonresponse when bupropion was added occurred in three patients, and included headache, nausea, diaphoresis, decreased concentration, and irritability. Two responders developed tremor or insomnia managed by decreasing the dose of bupropion.

DISCUSSION

These preliminary results suggest that the addition of low to moderate doses of buproprion to SRIs or venlafaxine, or low doses of SRIs to bupropion, is generally well tolerated and may be effective for patients unresponsive to monotherapy. This combination may

TABLE 1. Response to combination treatment by clinical scenario

Category		Total	Responders	Nonresponders
I.	Inadequate response to SSRI or venlafaxine	11	9 (82%)	2
II.	Inadequate response to bupropion alone	4	3 (75%)	1
III.	Responsive to SRI but intolerable side effects	10	2 (20%)	8
	5 apathy and anergy		1	4
	4 sexual dysfunction		0	4
	1 nausea		1	0
Total		25	14 (56%)	10

TABLE 2. Average doses of medications in each clinical scenario

	Doses mean (range) mg/d				
Category	Bupropion	Fluoxetine	Sertraline	Paroxetine	Venlafaxine
I.	N = 11 241 (75–450)	N = 7 22.9 (10–40)	N = 1 25	N = 2 25 (10–40)	N = 1 225
II.	N = 4 413 (300–450)		N = 3 41.7 (25–50)		N = 1 37.5
III.	N = 10 145 (75–300)	N = 4 13.8 (5–20)	N = 6 66.7 (25–125)		
Total	N = 25 230 (75–450)	N = 11 19.5 (5–40)	N = 10 55 (25–125)	N = 2 25 (10–40)	N = 2 131 (37.5–225)

be effective because it combines synergistically SRI's serotonergic effects with bupropion's nonadrenergic or dopaminergic effects, which might be useful in treatment resistance. Alternatively, each drug might be preferentially treating different target symptoms. Bodkin et al. (12) noted in their series that SRIs were particularly helpful for mood and anxiety, and bupropion was particularly helpful for interest and energy levels.

The initial hypothesis, that combination treatment with bupropion would be most useful by treating serotonin-related side effects, was not supported, given the poor response rate in group III. It is striking that bupropion, despite its activating profile and lack of sexual side effects, appeared unsuccessful in "overriding" SRI-induced side effects of apathy, anergy, and sexual dysfunction. Therefore, clinicians must be vigilant in differentiating these side effects, often best treated by dosage reduction, from recurrence of depressive symptoms.

Combination treatment appeared safe, even in geriatric and medically ill patients. All subjects were treated with immediate release bupropion, and sustained release bupropion may provide even greater margins of tolerability and safety (Wellburtin, 1996). However, it should be noted that doses in this sample were generally low, and preliminary reports suggest that SRIs might raise blood levels of bupropion (9, 12).

This series is retrospective, nonrandom, and uncontrolled, and so is subject to concerns of observer bias and patient selection. Any observations gleaned from it can be considered only tentative, but should be added to other preliminary reports suggesting efficacy and safety of combining bupropion with newer generation antidepressants. Future double-blinded, randomized studies should evaluate the utility of combined SRI and bupropion therapy vs. a standard adjunct such as lithium.

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