# Combining Serotonin Reuptake Inhibitors and Bupropion in Partial Responders to Antidepressant Monotherapy

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***Background:*** Many patients with affective illness show partial or otherwise unsatisfactory responses to standard treatments, encouraging trials of combinations of pharmacologically dissimilar antidepressants.

***Method:*** Records of consecutive outpatients with affective disorders only partially responsive to treatment with a serotonin reuptake inhibitor (SRI) or bupropion, alone, were reviewed for changes in specific symptoms and risks of adverse events when an SRI and bupropion were combined.

***Results:*** Greater symptomatic improvement was found in 19 (70%) of 27 subjects during a mean ± SD of 11 ± 14 months of combined daily use of bupropion (243 ± 99 mg) with an SRI (31 ± 16 mg fluoxetine-equivalents) than with either agent alone. Adverse effect risks were similar to those associated with each monotherapy, with a > 10% incidence of sexual dysfunction (N = 11, 41%), insomnia (N = 6, 22%), anergy (N = 4, 15%), and tremor (N = 3, 11%) during combined therapy; there were no seizures.

***Conclusion:*** With conservative dosing and close monitoring, combinations of SRIs with bupropion in this uncontrolled clinical series appeared to be safe and often more effective than monotherapy.

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In placebo-controlled trials in major depression, panic disorder, and other syndromes for which antidepressants are commonly used, response to a trial of an antidepressant is often quite limited. The proportion of depressed patients showing at least 50% improvement within 4 to 8 weeks in controlled trials has ranged from 55% to 70%; target symptoms and overall clinical ratings typically have improved by 50% to 75%, and the proportion of patients experiencing *full* clinical resolution of symptoms may be a third to a half.[1–3] Many affective disorder patients remain measurably symptomatic and dysfunctional, even if considered treatment-responsive in short-term trials.[4] Moreover, a substantial proportion of depressed or anxious patients may fail to achieve a formally defined treatment response but still gain clinically significant benefits during treatment. Such extensive experience indicates that an undetermined, but evidently large, proportion of patients, including some who may be considered antidepressant "responsive," achieve only partial remission of symptoms and fail to return fully to their best premorbid functional status.[1–4] In addition, antidepressants sometimes appear to improve some but not all symptoms of depressive and anxiety disorders, or may produce new or exacerbated symptoms as side effects.

We propose that these various presentations can be conceptualized as manifestations of *partial antidepressant treatment response.* Partial treatment response is distinguished from less common treatment-resistance or nonresponsiveness. Despite the abundant, largely industrially sponsored research on antidepressant efficacy, such limitations of short- or long-term antidepressant effectiveness have been little studied, even though they are a very common and challenging problem in clinical practice.

Plausible and commonly clinically employed alternatives for treating affectively ill patients who are partially responsive include (1) increasing the dose of a current medication, (2) continuing treatment for a longer time, (3) switching to another drug, (4) adding adjunctive agents, or (5) emphasizing nonpharmacologic forms of treatment. Research to demonstrate and quantify the possible benefits, risks, and costs of each of these approaches

in partially responsive patients is virtually nonexistent. Nevertheless, empirical clinical use of combinations of a growing variety of antidepressants appears to be increasingly common.

Antidepressants introduced into clinical use in the United States over the past decade include the serotonin reuptake inhibitors (SRIs; currently including fluoxetine, fluvoxamine, paroxetine, and sertraline) and the stimulant-like, possibly catecholaminergic agent bupropion.[3,5] Although these drugs have not shown superior efficacy to older antidepressants, they have come to dominate contemporary clinical practice due to their relative tolerability and virtual lack of fatal risk in acute overdoses.

Although the many currently available antidepressants have similar average levels of overall efficacy, they may differ in their impact on particular symptoms and vary in efficacy in syndromes other than acute major depression,[1,3] perhaps in part due to their selective pharmacodynamic actions. For example, the SRIs are at least partially effective in severe anxiety syndromes, including panic disorder [6] and obsessive-compulsive disorder (OCD),[7] but bupropion probably is not.[8] Conversely, bupropion as well as tricyclic antidepressants may be superior to the SRIs in the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adults.[9–11] Differential efficacy of SRIs and bupropion in some depressed patients has been suggested.[12] These agents also differ in their adverse effects. For example, SRIs are associated with relatively high rates of anorgasmia and other sexual dysfunctions, whereas bupropion lacks such effects, but can induce epileptic seizures at high doses.[13–16]

Their dissimilar pharmacology and apparent differences in efficacy in various disorders and their relative safety and acceptability, as well as their dissimilar adverse effect profiles, encourage combinations of SRIs with bupropion, particularly in affectively ill patients who are incompletely responsive to more conservative treatment. Several case reports suggest that SRIs can be combined safely and usefully with bupropion.[17–20] This background led to our systematic review of 27 cases treated clinically with combinations of SRIs and bupropion.

## METHOD

With authorization of the McLean Hospital Institutional Review Board, we reviewed medical records of consecutive psychiatric outpatients treated by three of the authors (J.A.B, R.A.L., J.D.W.) with the combination of an SRI and bupropion between February 1991 and April 1996. Subjects (N = 27) were observed during treatment with either an SRI or bupropion alone for a mean ± SD 19.3 ± 16.7 months, before the second agent was added, and during their combined use for 11.1 ± 14.3 months. Cases (N = 7) with inadequate information for the present analysis were excluded. Diagnoses were made with semistructured interviews and reconsidered according to DSM-IV criteria. In cases involving comorbidity, the primary diagnosis was considered the most prominently symptomatic or most prevalent during long-term follow-up.

Eight symptom categories were established as clinically relevant and sufficiently documented for analysis. They were (1) mood, (2) energy level, (3) anxiety or panic, (4) obsessive-compulsive symptoms, (5) sleep disturbance, (6) motivation, (7) cognitive function, and (8) sexual dysfunction. Each item was rated as a consensus clinical rating by at least two investigators (one of them the treating psychiatrist) as present versus absent and improved, unchanged, or worse during monotherapy compared with baseline and during combined treatment compared with the best state achieved during monotherapy; an additional global consensus rating scored the combination trial in each subject as an overall clinical "success" or "failure," to differentiate responders and nonresponders to the combination therapy.

Daily doses of SRIs were converted to approximate fluoxetine-equivalents as follows: 20 mg of fluoxetine = 20 mg of paroxetine = 150 mg of fluvoxamine = 75 mg of sertraline. Our estimate of fluoxetine-equivalents was based on 1992 World Health Organization figures,[21] which are supported by our shared clinical experience. Data are means ± SD unless stated otherwise. Dosing data were compared by one-way analysis of variance (ANOVA) with defined degrees of freedom (df). Clinical responses and adverse effects were tabulated and compared, when appropriate, in contingency tables (to compute chi-square or Fisher's exact p when cell size was < 10 subjects, with 1 df). Statistical comparisons were considered significant at two-tailed $p < .05$; nonsignificance (N.S.) reflects $p > .10$.

## RESULTS

The mean age of the 27 subjects was 43.4 ± 13.8 years (range, 20–83) when combination therapy began; 16 (59.3%) were women. Most (N = 23, 85.2%) suffered from a primary mood disorder: unipolar major depression (N = 9), dysthymic disorder (N = 6), or bipolar disorder type II (N = 5) or type I (N = 3); of the remaining 4 cases, 3 had attention-deficit/hyperactivity disorder (ADHD) as a primary diagnosis, with associated unipolar major depression, obsessive-compulsive disorder (OCD), or panic disorder (N = 1 each), and 1 other had generalized anxiety disorder (GAD) with OCD (Table 1). Of the total series, 20 (74.1%) had at least one additional comorbid psychiatric condition (4 subjects had two secondary diagnoses), including panic disorder (N = 8), OCD (N = 6), GAD (N = 2), and 1 case each with social phobia, binge eating disorder, or Gilles de la Tourette's syndrome, and 3 had a

**Table 1. Patients Treated With Bupropion and a Serotonin Reuptake Inhibitor (SRI)***

| Case | Age/Sex | Diagnoses | SRI/(mg/d)[a] | Bupropion (mg/d)[a] | Combined Rx (mo) | Adverse Effects With Combinations | Other Treatments (mg/d) |
|---|---|---|---|---|---|---|---|
| Combination treatment successful | | | | | | | |
| SRI first | | | | | | | |
| 1 | 25/F | Dysthymic disorder, Pan, OCD | Fluoxetine/40 | 150 | 6.0 | Weight gain | Clonazepam/1 |
| 2 | 32/M | BP-II, substance abuse by history[b] | Sertraline/200 | 450 | 6.0 | … | Lithium carbonate/1200 |
| 3 | 33/M | Unipolar MDD, substance abuse by history[b] | Fluoxetine/60 | 225 | 5.0 | Sexual functioning | … |
| 4 | 34/M | Unipolar MDD | Sertraline/150 | 300 | 26.0 | … | … |
| 5 | 35/F | Unipolar MDD, OCD | Fluoxetine/40 | 100 | 6.0 | … | … |
| 6 | 35/M | Dysthymic disorder, eating disorder | Fluoxetine/20 | 200 | 36.0 | Sleep, sexual functioning, memory | … |
| 7 | 41/F | BP-I, Pan, OCD | Fluvoxamine/50 | 225 | 15.0 | Sleep | Estazolam/2 |
| 8 | 42/M | BP-II, complex partial seizures, TS | Fluoxetine/20 | 400 | 61.0 | Tics | Carbamazepine/800, Lithium carbonate/900 |
| 9 | 43/F | Unipolar MDD, Pan | Fluoxetine/20 | 225 | 3.0 | … | … |
| 10 | 47/M | ADHD, Pan, substance abuse by history[b] | Fluoxetine/20 | 300 | 25.0 | Tremor | Propranolol/60, lorazepam/1 |
| 11 | 50/F | BP-II, Pan | Fluoxetine/40 | 150 | 10.0 | Sexual functioning | Lithium/600, divalproex sodium/750, clonazepam/0.5 |
| 12 | 50/M | ADHD, OCD | Fluoxetine/20 | 300 | 5.0 | Energy | … |
| 13 | 54/F | ADHD, unipolar MDD | Fluoxetine/20 | 300 | 6.0 | … | … |
| 14 | 55/F | Dysthymic disorder, unipolar MDD | Fluoxetine/40 | 300 | 7.0 | Tremor | Alprazolam/1.5 |
| 15 | 55/F | Unipolar MDD, Pan | Fluoxetine/60 | 150 | 37.0 | Sexual functioning, sleep | Lorazepam/1 |
| 16 | 83/F | Unipolar MDD with psychotic features | Sertraline/200 | 400 | 7.0 | … | Thioridazine/30 |
| Bupropion first | | | | | | | |
| 17 | 30/F | BP-I | Sertraline/150 | 375 | 2.0 | Tremor, headaches | Divalproex sodium/1000, clonazepam/1.5 |
| 18 | 39/F | Unipolar MDD | Fluoxetine/10 | 300 | 3.0 | Energy | Clonazepam/0.5 |
| 19 | 50/F | BP-II (seasonal) | Fluoxetine/20 | 225 | 14.0 | Energy | Lithium carbonate/600, lorazepam/1.5, high-intensity phototherapy |
| Combination treatment unsuccessful | | | | | | | |
| SRI first | | | | | | | |
| 20 | 20/M | Dysthymic disorder, social phobia | Fluoxetine/40 | 200 | 4.0 | Cog | … |
| 21 | 40/M | GAD, OCD | Fluoxetine/10 | 150 | 1.0 | Appetite increase | … |
| 22 | 45/M | Dysthymic disorder | Fluoxetine/20 | 225 | 0.5 | Sexual functioning, Cog | Clonazepam/1 |
| 23 | 50/F | BP-II, Pan | Fluoxetine/20 | 200 | 2.0 | Sexual functioning | Clonazepam/1 |
| 24 | 64/F | Dysthymic disorder, GAD | Sertraline/100 | 150 | 5.0 | Energy | Divalproex sodium/750 |
| Bupropion first | | | | | | | |
| 25 | 20/M | Unipolar MDD, OCD, Pan | Fluvoxamine/100 | 100 | 1.0 | Anxiety symptoms, disorder, or panic; energy | Risperidone/1.5, clonazepam/1.5 |
| 26 | 40/F | Unipolar MDD | Sertraline/75 | 200 | 0.5 | Sleep | … |
| 27 | 60/F | BP-I, GAD | Sertraline/150 | 400 | 7.5 | Mood, tremor | Buspirone/15, clonazepam/1, divalproex sodium/1500 |

**Clinical Terms:* ADHD = attention-deficit/hyperactivity disorder; Anx = anxiety symptoms, disorder or panic; BP = bipolar disorder, type I (with mania) or II (with hypomania); Cog = cognition, concentration; GAD = generalized anxiety disorder; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; Pan = panic symptoms or disorder; TS = Gilles de la Tourette's syndrome.
[a]*Doses* (mg/day) are the final doses of an SRI and bupropion during combined treatment.
[b]Alcohol and cannabis in Case 2; alcohol and cocaine in Cases 3 and 10. All three patients have been sober for the past year.

past history of substance abuse but had been sober for at least 1 year (Table 1).

In 7 potential subjects excluded because of inadequate clinical information for symptom ratings, global impressions of the efficacy of combined treatment were similar to those for the reported sample, and no serious adverse effects were encountered.

The 27 subjects had all experienced partial benefit, but incomplete recovery, with either an SRI or bupropion alone, justifying use of a second agent (Tables 1 and 2). Combination therapy was preferred to switching drugs by both patients and their psychiatrists, to avoid giving up clinical benefits gained from the initial monotherapy. In only 1 case had the second agent been tried previously

**Table 2. Clinical Effects of SRIs and Bupropion Alone and Combined***

| Effect | N | SRI Alone | | | SRI + Bupropion[a] | | |
|---|---|---|---|---|---|---|---|
| | | Better | Same | Worse | Better | Same | Worse |
| SRI given first | | | | | | | |
| Mood | 21 | 19 | 2 | 0 | 15 | 6 | 0 |
| Energy | 21 | 3 | 8 | 10 | 12 | 9 | 0 |
| Anxiety/Panic | 20 | 18 | 2 | 0 | 1 | 17 | 2 |
| Sleep | 17 | 6 | 5 | 6 | 4 | 9 | 4 |
| Motivation | 21 | 11 | 6 | 4 | 12 | 9 | 0 |
| Cognitive functions | 14 | 1 | 12 | 1 | 6 | 6 | 2 |
| Obsessions[b] | 9 | 7 | 2 | 0 | 1 | 8 | 0 |
| Sexual dysfunction | 13 | 0 | 4 | 9 | 3 | 9 | 1 |
| Global impression | 21 | 21 | 0 | 0 | 15 | 3 | 3 |
| | | Bupropion Alone | | | Bupropion + SRI[a] | | |
| Effect | N | Better | Same | Worse | Better | Same | Worse |
| Bupropion given first | | | | | | | |
| Mood | 6 | 6 | 0 | 0 | 3 | 2 | 1 |
| Energy | 6 | 5 | 1 | 0 | 0 | 2 | 4 |
| Anxiety/Panic | 6 | 0 | 5 | 1 | 4 | 1 | 1 |
| Sleep | 6 | 2 | 2 | 2 | 0 | 4 | 2 |
| Motivation | 6 | 5 | 1 | 0 | 0 | 4 | 1 |
| Cognitive functions | 4 | 3 | 1 | 0 | 1 | 4 | 0 |
| Obsessions[b] | 3 | 0 | 3 | 0 | 2 | 1 | 0 |
| Sexual dysfunction | 2 | 1 | 0 | 1 | 0 | 2 | 0 |
| Global impression | 6 | 5 | 1 | 0 | 3 | 0 | 3 |

*N = patients reporting symptoms listed; SRI = serotonin reuptake inhibitor.
[a]On combined therapy, symptom severity was rated as a change compared to final status on monotherapy.
[b]Obsessions = obsessions, ruminations, or compulsions.



and found ineffective by itself, and it proved ineffective in combination treatment. In 12 cases, a subsidiary reason for adding a second agent was to counteract apparent adverse effects encountered with the first antidepressant, such as anergy or anorgasmia with an SRI, or increased anxiety with bupropion. However, in all 27 subjects, the combination treatment was tried primarily as a result of an inadequate or partial response to monotherapy.

Table 1 summarizes salient clinical characteristics of the 27 subjects, dividing them according to the drug given first and into groups of clinical responders and nonresponders to combination treatment, based on overall consensus judgment. A high proportion of the sample (19/27, 70.4%) were considered to have benefited from the combination therapy compared to their best status during prior treatment with either bupropion or an SRI alone in a presumably adequate dose and duration. Except in 2 patients whose poor tolerance required early discontinuation, the combined treatment persisted for a minimum of 1 month before its impact was rated. When results were encouraging, combination treatment was continued for more than 6 months of follow-up (Table 1), averaging $14.7 \pm 15.6$ months for the 19 responders, $2.69 \pm 2.56$ months for the 8 nonresponders ($F = 4.60$, $df = 1,25$; $p = .042$), and $11.1 \pm 14.3$ months, overall. The 5.46-fold difference reflected early discontinuation when clinical benefits were not forthcoming within at least 4 weeks or the combination treatment was associated with intolerable adverse effects. Three subjects classified as treatment failures continued for several months on combination therapy owing to modest early benefits eventually considered unsatisfactory.

During combination therapy, the mean overall final daily dose of SRIs was $31 \pm 16$ mg (range, 7–60) (fluoxetine-equivalents), and bupropion was $243 \pm 98$ mg (range, 100–450). Drug doses did not differ between responders and nonresponders to combination therapy: respectively, the mean final daily fluoxetine-equivalent dose of SRI was $33 \pm 17$ vs. $25 \pm 14$ mg ($F = 1.93$, $df = 1,25$; N.S.), and the mean dose of bupropion was $259 \pm 100$ vs. $203 \pm 89$ mg ($F = 1.89$, $df = 1,25$; N.S.). The daily dose of bupropion was 51.9% higher when given with sertraline than with any other SRI ($325 \pm 113$ vs. $214 \pm 77$ mg; $F = 8.52$, $df = 1,25$; $p = .007$).

The two types of antidepressants appeared to exert dissimilar effects on some specific symptoms (Table 2). Not all subjects reported all symptoms, and each symptom was rated only for those reporting it, with the number of patients reporting each symptom listed under N (Table 2). Notably, bupropion given alone was associated with improved energy in 5 (83.3%) of 6 subjects and worsening in none, while SRIs alone had this apparent benefit in only 3 (14.3%) of 21 cases with worsening of energy in 10 (47.6%) of 21; (Fisher's exact $p = .004$). Similarly, bupropion monotherapy was associated with subjectively improved concentration and cognition in 3 (75.0%) of 4 patients and only 1 (7.1%) of 14 during SRI monotherapy (Fisher's exact $p = .02$). In contrast, SRIs proved greatly superior for anxiety or panic symptoms, with 18 (90.0%) of 20 subjects improving with an SRI

alone, versus none of 6 with bupropion alone (Fisher's exact $p < .0001$); when an SRI was added to bupropion 4 (66.7%) of 6 patients with anxiety symptoms improved, but only 1 (5.0%) of 20 responded when bupropion was added to an SRI (Fisher's exact $p = .0047$). If both monotherapy and combined treatment data are pooled regarding anxiety or panic symptoms, there is a highly significant difference favoring the presence of an SRI in the regimen (22 [84.6%] of 26 responding with an SRI alone or added vs. only 5 [18.5%] of 27 with bupropion alone or added; Fisher's exact $p < .0001$). In addition, several patients reported ruminative or OCD-like symptoms; these also tended to improve selectively with the use of an SRI alone (7/9 cases vs. 0/3 given bupropion alone; Fisher's exact $p = .046$), or when an SRI was added to bupropion (2/3 cases vs. 1/9 when bupropion was added to an SRI; N.S.), and when both conditions were pooled (9 [75.0%] of 12 vs. 1 [8.3%] of 12 responding, Fisher's exact $p = .003$).

Adverse effects found in at least 10% of subjects during combined treatment with an SRI and bupropion (Tables 1 and 2) were sexual dysfunction (40.7% [11/27]), insomnia (22.2% [6/27]), reduced energy level (14.8% [4/27]), and tremor (11.1% [3/27]). These risks are similar to those encountered with bupropion or SRIs alone. For example, sexual disturbances were found in 14 (51.9%) of 27 subjects during monotherapy (not statistically different from the 40.7% [11/27] risk in combined treatment). Sexual side effects tended to be more common during SRI versus bupropion monotherapy (42.9% [9/21] vs. 16.7% [1/6], but this difference was nonsignificant). Four (14.8%) of the 27 patients given bupropion with an SRI experienced sufficiently severe adverse effects to justify early discontinuation of the combination treatment.

## Illustrative Cases

The following representative case vignettes illustrate potential benefits and problems associated with the combination of SRIs and bupropion.

***Case 1.*** Mr. A is a 34-year-old married man with yearly episodes of anergic, hypersomnic, pessimistic depression with fluctuating levels of anxiety since childhood, alternating with quick-wit, high energy, and success; he was never suicidal or hospitalized. In two fluoxetine trials (20–40 mg/day) for depression, anxiety initially worsened and later abated, but overall recovery was not clearly faster than it had been without medication. Sertraline (50 mg/day) also was associated with initially worsened and later improved anxiety, with little effect on lethargy and impaired concentration.

Bupropion was added (up to 300 mg/day for 8 weeks) to sertraline (increased to 100 mg/day), with rapid improvement in energy and cognition, and much more rapid attainment of full recovery than in any previous episodes. However, he complained of tremulousness and feeling overstimulated. These symptoms disappeared at a lower daily dose of bupropion (225 mg/day) and remission was sustained for 2 years.

To evaluate continued needs for medication, sertraline was gradually discontinued. Within several weeks, he became irritable, anxious, and obsessively preoccupied with business problems, and he experienced loss of appetite and weight, sleep, and libido but without the lethargy; poor concentration; and loss of self-esteem characteristic of his earlier untreated depressive episodes. After 8 weeks, sertraline was restarted and increased to 100 mg/day over a week, with bupropion continued at 225 mg, and 0.75 mg of alprazolam daily for 1 week. Within 3 weeks, he recovered fully and remained well on only sertraline and bupropion, continuing at the same doses for 6 months.

***Case 2.*** Mr. B is a 47-year-old divorced man with occasional panic attacks and a history of ADHD treated with methylphenidate in childhood. As an adult, he continued to be distractible and inefficient. He used cocaine in a controlled manner for several years with somewhat improved cognition. In his early 30s, recurring attacks of anxiety and rage led to psychiatric hospitalization; his EEG was mildly abnormal.

Brief trials of phenytoin and lithium carbonate were unsuccessful. He stopped treatment, but worsening panic and irritability led to a return to treatment: trazodone was ineffective; fluoxetine (20 mg/day) was fully effective in treating his anger and anxiety but without effect on persistent attentional impairment during 3 years of treatment. Standard stimulants were avoided due to his past abuse of cocaine, but he tolerated and did not abuse bupropion (up to 300 mg/day), added to fluoxetine. Within 5 weeks, he reported less distraction and much greater efficiency at work. Headache emerged but resolved spontaneously, and mild tremor was controlled by adding propranolol (40–60 mg/day). He remained well and was increasingly successful at work.

After 1.5 years, to evaluate its necessity, fluoxetine was discontinued as bupropion continued at 300 mg/day. Within 6 weeks, he again became irritable; fluoxetine was restarted at Week 8, with rapid improvement that has been sustained for 6 months.

***Case 3.*** Ms. C is a 54-year-old divorced woman who developed anhedonia, dysphoria, insomnia, and functional decline at age 48, after prolonged dysthymia and a history of impaired concentration and dyslexia in childhood, and a recent diagnosis of ADHD. She abused alcohol briefly after two divorces, then lived independently and worked, but pursued several unstable relationships.

When Ms. C was 50 years old, sertraline 50 mg/day for several weeks was ineffective for depressed mood, nightmares, diminished energy, and passive suicidality. Psychotherapy did not alter her depressive symptoms, and bupropion was started. With 375 mg of bupropion

daily for 2 months, concentration, memory, and energy improved, but Ms. C had no relief from depressed mood, anhedonia, or suicidal ideation. After the change was made to fluoxetine (20 mg/day), depressive symptoms improved within 4 weeks, but 40 mg given for 2 weeks was associated with intolerable agitation, leading to a return to 20 mg, as cognition declined to its impaired pre-bupropion status. Cognitive benefits quickly returned after adding bupropion (300 mg daily) to fluoxetine (20 mg daily), with improvements in mood and vocational skills that have been sustained for nearly a year.

***Case 4.*** Ms. D is a 55-year-old housewife, first treated for acute major depression after 2 years of prolonged grief following the death of a son and at least 30 years of mild agoraphobia, but no other psychiatric illness. A trial of nortriptyline led to intolerable autonomic effects. Soon after starting fluoxetine alone (5 mg/day), she was hospitalized in a ruminative melancholic state with nearly daily new panic attacks and intense suicidality. She improved in 2 weeks while taking tranylcypromine but became hypertensive. She attained remission after eight electroconvulsive treatments. Maintained on fluoxetine treatment alone for 3 years, she led a limited and joyless life; reemergence of depressive and ruminative symptoms led to gradual increases in fluoxetine doses to 60 mg/day. Addition of lithium carbonate caused lethargy, and major depression recurred after 7 months.

Bupropion (up to 300 mg/day) replaced lithium, with marked improvement over 6 weeks but new adverse effects (tremor, night sweats, restless sleep with violent dreams). Several dosage modifications were made over 9 months, but finally both agents were discontinued because of continuing side effects, despite a sustained antidepressant response. A trial of venlafaxine 150 mg/day failed, with rapid reemergence of panic and hypersomnia. Fluoxetine alone in subsequent months was associated with lethargy, anergy, hypersomnia, loss of libido, and some depression, as well as reemergence of anxiety at doses under 40 mg/day.

Readdition of bupropion (gradually to 225 mg/day) effectively restored her energy, but with disturbed sleep and tremor. A daily regimen of fluoxetine (40 mg) with bupropion (225 mg) has proved tolerable and effective against the depressive, obsessive, and anxiety symptoms for more than a year.

***Case 5.*** Ms. E, an 83-year-old divorced, childless woman, had led an active and independent life, with many friends. She had no psychiatric history until the late onset of severe depression, with paranoid and somatic delusions following a fall and hip fracture at age 79 in the setting of osteoporosis, mild dementia, and heart failure. Declining ability to care for herself led to nursing home placement a year later despite improvement in psychotic depressive symptoms with a combination of low daily doses of fluoxetine and thioridazine (both, 10 mg). A year later, worsening delusional somatic complaints prompted an increase in thioridazine to 30 mg/day with little improvement and increasing isolation and dependence.

Lack of response to more fluoxetine (20 mg/day), with 150 mg of trazodone at bedtime led to psychiatric hospitalization 6 months later. There, thioridazine was continued at 30 mg/day, and the SRI was changed to sertraline 75 mg daily, with initial improvement; on return to the nursing home, she rapidly decompensated, with increasing isolation, somatic and persecutory delusions, poor cooperation, and a wish to be dead. Increasing thioridazine to 75 mg induced delirium that reversed after this drug was withdrawn. Increasing sertraline to 100 mg/day led to mild improvement of mood, and 30 mg/day of thioridazine was again tolerated. Despite gradual increases of the daily dose of sertraline to 200 mg, isolation and dependence persisted. However, within 3 days of the addition of bupropion 75 mg, her affect brightened, and she became sociable and energetic.

Bupropion was gradually increased over several months to a daily maximum of 375 mg, with sustained improvement in mood and self-care. Attempts to lower the dose of sertraline twice led to rapid return of depressive withdrawal. At stable, divided daily doses of bupropion (375 mg) with sertraline (200 mg), she has remained improved for a year.

## DISCUSSION

In the present series of 27 clinically treated and evaluated effectively ill patients, SRIs were combined safely with bupropion, with 70% of the cases showing apparently greater benefits than with partially effective treatment with one of the agents alone. Side effects encountered were those commonly associated with either agent alone (Table 2), although in 4 (14.8%) of 27, adverse effects were severe enough to warrant discontinuing combined treatment early. Similar dropout rates due to intolerable side effects have been reported with antidepressant monotherapies in controlled trials (12.7%) and in as many as 7.3% of depressed research subjects given a placebo.[16] There was no instance of an epileptic seizure, even though 3 patients had a past history of abnormal EEG or grand mal seizures (2 cases, one who also had chronic complex partial seizures). The apparent safety of SRI/bupropion combinations in the present series may reflect conservative dosing with both classes of drugs and low power to detect uncommon adverse effects in a small case series.

High doses of bupropion (> 450 mg/day) may induce seizures,[22] but the present dose averaged only 243 ± 99 mg/day. However, SRIs may increase circulating levels of bupropion to levels otherwise associated with doses above 450 mg/day,[23] calling for cautious dosing when bupropion is added. In this series, sertraline was associated

with higher doses of bupropion. This empirical choice reflects evidence that sertraline, at moderate doses, may have a lesser risk of elevating blood concentrations of some drugs (references 23–25 and Baldessarini RJ, Flood J, Campbell A. Manuscript submitted).

The combination of clomipramine with bupropion was avoided after seizures occurred in a patient not in the present series, who had been given up to 225 mg/day of bupropion with clomipramine (200 mg/day) (Bodkin JA. 1994. Unpublished data). Despite the apparent safety of SRI/bupropion combinations in the present small series, we emphasize that special caution is required with such treatment pending clarification of the potential hazards involved and guidelines for the rational selection of specific agents and doses.

The present findings are consistent with the pharmacologic and substantial clinical dissimilarities between SRIs and bupropion reviewed above. Both types of agents may be similarly effective as antidepressants, in general,[26] but they have dissimilar side effects and possibly differential effects on specific symptoms in mood disorders and selective benefits in other syndromes. SRIs are probably superior in anxiety disorders including panic and OCD, while bupropion is more stimulant-like and may be more effective in ADHD, as well as limiting anergy sometimes associated with SRIs.[3,27–29] Such dissimilarities in target symptoms are consistent with observations in the cases reported (Table 2).

The initial antidepressants used in these cases were associated with some improvement in mood in all 27 subjects studied, including 21 initially treated with an SRI alone and 6 first given bupropion alone (Table 2), without full recovery. Incomplete recovery allowed for additional improvements found with combination therapy in 19 (70.4%) of the 27 subjects (Table 2). Since symptoms and their changes were rated from clinical notes, some symptoms may have been missed in some subjects. The reported ratings reflect what the patients and clinicians were specifically attending to in each case, on the basis of clinical considerations. Specific improvements included elevation of mood in 66.7% of patients, and reductions of anergy in 44.4%; low motivation in 44.4%; obsessive, ruminative, or compulsive symptoms in 25.0%; and generalized anxiety symptoms or panic attacks in 19.2%. These gains are not likely due to mere passage of time or spontaneous mood cycling, and clinical worsening occurred in several cases after elective discontinuation of one agent after months of stability (see vignettes). There may be specific untoward psychobiological effects due to drug discontinuation itself,[30] but reemergence of specific symptoms after removing one drug suggests a need for both agents to obtain maximal therapeutic benefits. Future studies might compare such combinations against increased doses of each agent alone to test for synergy.

Despite their similar overall benefits in depression, there were clear dissimilarities between drug types in specific target symptoms (Table 2). Notably, *energy* levels were improved with bupropion monotherapy in 83% of subjects and did not worsen in anyone given bupropion, whereas SRI monotherapy yielded such improvement in only 14% of cases, with worsening in 48%. When bupropion was added to an SRI, energy level improved in 57% of patients, and worsened in none. In addition, when bupropion was added to an SRI, *motivation* appeared to improve in 57% and never worsened with this stimulant-like agent. Conversely, when an SRI was added to bupropion monotherapy, energy level never improved, and indeed worsened in 67% of cases.

Anergic effects of SRIs have been described variously as asthenia, apathy, or excessive sedation, in as many as 22% to 25% of patients treated with fluoxetine or paroxetine versus only 12% of cases given a placebo, and even fewer given imipramine.[27,28,31] This effect of SRIs has been found even after controlling for fatigue associated with depression.[29] Such SRI treatment-emergent symptoms may represent a variety of effects on arousal, attention, concentration, motivation, and libido. The neuropsychological and physiologic bases of such effects remain unclear, but contributions of central serotonergic neurotransmission are plausible. The contrasting activating effects of bupropion, including increased arousal, concentration, sometimes decreased appetite and sleep, and occasionally irritable overstimulation, are well known and may reflect its potentiating actions on central catecholamine neurotransmission.[3,5,32]

The arousal-inducing or stimulant-like properties of bupropion probably contribute to its recently reported beneficial cognitive and behavioral effects in pediatric and adult ADHD.[9–11] In contrast, there is little published evidence that SRIs have beneficial effect in ADHD, and they may induce intolerable sedative effects in such patients.[33] Three of the present subjects meeting diagnostic criteria for ADHD experienced no change in cognitive functioning with an SRI alone, but improved when bupropion was added. Moreover, 75% of the 4 subjects with cognitive impairment given bupropion alone experienced improved attention and concentration and none experienced worsening. In contrast, with an SRI alone, only 7% reported improved cognitive functioning (another 7% seemed worse), but 43% of these improved when bupropion was added.

Another differential effect of bupropion and SRIs is their impact on sexual functions, including libido and orgasm in men and women.[13,15] Rates of sexual dysfunction during SRI treatment as high as 30% have been found, and may be even higher due to underreporting.[34] Bupropion carries a low risk of sexual problems and has even been proposed as a treatment for SRI-associated dysfunction.[13,14] In the present series, bupropion monotherapy had

minor and inconsistent effects on sexual dysfunction, but in patients given an SRI alone, worsening sexual function was reported by 43%, and none improved (Table 2). Addition of bupropion led to reported improvement in 23% of patients with sexual dysfunction during SRI monotherapy, no change in 69%, and worsening in only one case. These observations provide further evidence that bupropion lacks prominent adverse sexual effects, but its ability to reverse those of SRIs may be quite limited.

Other target symptoms may be preferentially benefited by the SRIs. These include anxiety or anxiety-related disorders, including panic attacks,[6,35] OCD,[7,36] and perhaps ruminative or compulsive symptoms of some depressed patients. However, the onset of antianxiety effects of these and other antidepressants is often delayed and may be preceded by initial worsening and reluctance of the patient to continue treatment (see vignettes).[37] Bupropion appears to lack such benefits and may worsen anxiety in some patients.[8,21] The antiobsessional effects of SRIs may be mediated by their central serotonergic actions.[7,36] In the present cases, obsessive ruminations and compulsive behavior were consistently benefited when SRIs were given alone or with bupropion (in 83% of subjects) and unchanged when bupropion was used alone or added to an SRI (Table 2).

It must be acknowledged that a retrospective analysis of a clinical case series such as this is subject to multiple biases. A particular limitation of this study is the lack of independent comparison of a second treatment alone. The findings must be considered cautiously in this context, but they do suggest that combined SRI and bupropion treatment, when dosed cautiously, appears to be safe and may provide special benefits in partial responders to each in monotherapy. This impression encourages methodologically rigorous investigations specifically testing the hypothesis of synergistic action of combined treatment, with separate trials of SRI and bupropion monotherapy prior to or in parallel with their combination.

It is important to be aware that there have been scattered reports of apparent toxic interactions of combined treatment with bupropion and at least one SRI, fluoxetine. Single cases have been reported of delirium and myoclonic jerks,[38] mania,[39] grand mal seizure,[40] and "near catatonia," which did not recur upon rechallenge with bupropion after fluoxetine had been washed out.[41] Whether there was a causal association between these events and concomitant treatment with fluoxetine and bupropion is impossible to determine, and so caution in coadministering these agents is warranted, especially at the relatively high doses described in these reports.

In conclusion, the present open case series summarizes preliminary experiences with combinations of various SRIs with bupropion in 27 affectively ill patients who had had only partial responses to SRI or bupropion monotherapy. The results suggest that, with cautious drug selection and dosing, such combinations can be used safely and may be associated with levels of clinical improvement and beneficial effects on specific target symptoms not obtained with vigorous trials of one of the antidepressants alone. The specific patterns of clinical improvements observed seem to parallel a differential spectrum of clinical activity of these pharmacodynamically dissimilar antidepressants. We encourage further study of the large group of partially responsive depressed patients, including their treatment with systematically investigated combinations of a growing number of dissimilar agents.

*Drug names:* alprazolam (Xanax), bupropion (Wellbutrin), buspirone (BuSpar), carbamazepine (Tegretol and others), clomipramine (Anafranil), clonazepam (Klonopin), divalproex sodium (Depakote), estazolam (ProSom), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), lorazepam (Ativan and others), methylphenidate (Ritalin), nortriptyline (Pamelor and others), paroxetine (Paxil), phenytoin (Dilantin and others), propranolol (Inderal and others), risperidone (Risperdal), sertraline (Zoloft), thioridazine (Mellaril and others), tranylcypromine (Parnate), trazodone (Desyrel and others), venlafaxine (Effexor).

## REFERENCES


1. Baldessarini RJ. Current status of antidepressants: clinical pharmacology and therapy [Festschrift]. J Clin Psychiatry 1989;50:117–126
2. Burke MJ, Preskorn SH. Short-term treatment of mood disorders with standard antidepressants. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995:1053–1065
3. Baldessarini RJ. Drugs and the treatment of psychiatric disorders: antimanic and antidepressant agents. In: Harden W, Rudin W, Molinoff PB, eds. Goodman and Gilman's The Pharmacologic Basis of Therapeutics. New York, NY: McGraw-Hill; 1996:431–459
4. Thase ME, Rush AJ. Treatment resistant depression. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995:1081–1097
5. Ascher JA, Cole JO, Colin J-N, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995;56:395–401
6. Black DW, Wesner R, Bowers W, et al. A comparison of fluvoxamine, cognitive therapy, and placebo in the treatment of panic disorder. Arch Gen Psychiatry 1993;50:44–50
7. Griest JH, Jefferson JW, Koback KA, et al. Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder. Arch Gen Psychiatry 1995;52:53–60
8. Sheehan DV, Davidson J, Manshreck T. Lack of efficacy of a new antidepressant (bupropion) in the treatment of panic disorder with phobia. J Clin Psychopharmacol 1983;3:28–31
9. Wender PH, Reimherr FW. Bupropion treatment of attention-deficit hyperactivity disorder in adults. Am J Psychiatry 1990;147:1018–1020
10. Barrickman L, Perry P, Allen A, et al. Bupropion vs methylphenidate in the treatment of attention deficit disorder. J Am Acad Child Adolesc Psychiatry 1995;34:649–657
11. Spencer T, Biederman J, Wilens T, et al. Pharmacotherapy of attention deficit-hyperactivity disorder across the life-cycle. J Am Acad Child Adolesc Psychiatry 1996;35:409–432
12. Cole JO, Friedman LM, Gold R, et al. Efficacy of bupropion in depressed fluoxetine nonresponders. Presented at the 32nd annual meeting of the New Clinical Drug Evaluation Unit Annual Meeting; May 26–29, 1992; Key Biscayne, Fla
13. Walker PW, Cole JO, Gardner EA, et al. Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. J Clin Psychiatry 1993;54:459–465
14. Labatte LA, Pollack MH. Treatment of fluoxetine-induced sexual dysfunction with bupropion: a case report. Ann Clin Psychiatry 1994;6:13–15
15. Rothschild AJ. SSRI-induced sexual dysfunction: efficacy of a drug holiday. Am J Psychiatry 1995;15:1514–1516
16. Preskorn SH. Comparison of the tolerability of bupropion, fluoxetine,

imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. J Clin Psychiatry 1995;56(suppl 6):12–21
17. Novac A. Fluoxetine and bupropion treatment of bipolar disorder, type II, associated with GAD [letter]. J Clin Psychiatry 1992;53:67
18. Boyer WF, Feighner J. The combined use of fluoxetine and bupropion. In: New Research Program and Abstracts of the 146th Annual Meeting of the American Psychiatric Association; May 27, 1993; San Francisco, Calif. Abstract NR746:247
19. Marshall RD, Johannet CM, Collins PY, et al. Bupropion and sertraline combination treatment in refractory depression. Journal of Psychopharmacology 1995;9:284–286
20. Marshall RD, Liebowitz MR. Paroxetine/bupropion combination treatment for refractory depression. J Clin Psychopharmacol 1996;16:80–81
21. Freemantle N, House A, Song F, et al. Prescribing selective serotonin reuptake inhibitors as strategy for prevention of suicide. BMJ 1994;309: 249–253
22. Davidson J. Seizures and bupropion: a review. J Clin Psychiatry 1989; 50:256–261
23. Popli A, Baldessarini RJ, Cole JO. Interactions of serotonin-reuptake inhibitors with tricyclic antidepressants. Arch Gen Psychiatry 1994;51: 666–667
24. Preskorn SH. Drug-drug interactions [letter with reply]. J Clin Psychiatry 1996;57:223–225
25. Centorrino F, Baldessarini RJ, Frankenburg FR, et al. Serotonin reuptake inhibitors alter metabolism of clozapine. Am J Psychiatry 1996; 153:820–822
26. Feighner JP, Gardner EA, Johnston JA, et al. Double-blind comparison of bupropion and fluoxetine in depressed outpatients. J Clin Psychiatry 1991; 52:329–335
27. Hoehn-Saric R, Lipsey JR, McLeod DR. Apathy and indifference in patients on fluvoxamine and fluoxetine. J Clin Psychopharmacol 1990; 10:343–345
28. Beasley CM, Dornseif BE, Pultz JA, et al. Fluoxetine versus trazodone: efficacy and activating-sedating effects. J Clin Psychiatry 1991; 52:294–299
29. Keck PE Jr, McElroy SL. Ratio of plasma fluoxetine to norfluoxetine concentrations and associated sedation. J Clin Psychiatry 1992;53:127–129
30. Baldessarini RJ, Suppes T, Tondo L. Lithium withdrawal in bipolar disorder: implications for clinical practice and experimental therapeutics research. American Journal of Therapeutics 1996;3:492–496
31. Cohn JB, Wilcox CS. Paroxetine in major depression: a double-blind trial with imipramine and placebo. J Clin Psychiatry 1992;53(2, suppl):52–56
32. Peck AW, Hamilton M. Psychopharmacology of bupropion in normal volunteers. J Clin Psychiatry 1983;44(5, sec 2):202–205
33. Sabalesky DA. Fluoxetine in adults with residual attention deficit disorder and hypersomnolence. J Neuropsychiatry Clin Neurosci 1990;2:463–464
34. Jacobsen JM. Fluoxetine-induced sexual dysfunction and an open trial of yohimbine. J Clin Psychiatry 1992;53:119–122
35. Goddard AW, Woods SW, Sholomskas DE, et al. Effects of fluvoxamine on yohimbine-induced anxiety in panic disorder. Psychiatry Res 1991; 48:119–133
36. Hollander E, DeCaria C, Gully R, et al. Effects of chronic fluoxetine treatment on behavioral and neuroendocrine response to m-chlorophenylpiperazine in obsessive-compulsive disorder. Psychiatry Res 1993; 36:1–18
37. Kahn RS, Kalus O, Wetzler S, et al. The role of serotonin in the regulation of anxiety. In: Brown S, van Praag HM, eds. The Role of Serotonin in Psychiatric Disorders. New York, NY: Brunner/Mazel; 1991:129–160
38. Van Putten T, Shaffer I. Delirium associated with bupropion [letter]. J Clin Psychopharmacol 1990;10:234
39. Zubieta JK, Demitrack MA. Possible bupropion precipitation of mania and a mixed affective state. J Clin Psychopharmacol 1991;11:327–328
40. Ciraulo DA, Shader RJ. Fluoxetine drug-drug interactions, II. J Clin Psychopharmacol 1990;10:213–217
41. Preskorn SH. Should bupropion dosage be adjusted based on therapeutic drug monitoring? Psychopharmacol Bull 1991;27:637–643