Bupropion Sustained Release: Side Effect Profile

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Bupropion IR (immediate release) has been on the market since 1988 and is an effective and usually well-tolerated antidepressant. In late 1996, a new sustained-release formulation, bupropion SR, was approved and is now available. Compared with the IR formulation, the SR formulation demonstrates similar efficacy and has been found to have similar, but to some degree fewer, side effects. Its efficacy is similar to that of other newer antidepressants. Side effects of bupropion SR are limited and are not dissimilar to those of the serotonergic antidepressants; however, bupropion SR produces neither substantial sexual side effects nor drug interactions. Study data demonstrate that seizure incidence, which is a concern with high-dose IR, is substantially lower with the new SR formulation.

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"Use it quickly, while it's still safe."
—Anonymous clinician.

Eight years and millions of prescriptions later, bupropion is still safe, and its use is increasing. The Food and Drug Administration (FDA) in late 1996 approved the new sustained-release formulation of bupropion (bupropion SR), which I would characterize as much the same, but even safer.

We were fortunate enough to serve as an investigative site for bupropion SR protocols during its development. Our experience with this drug and its sustained-release form is therefore extensive, giving us considerable clinical experience as well as familiarity with investigative findings in regard to side effects.

Even though several newer antidepressants have been marketed, bupropion remains unique in its pharmacology. It is one of the very few antidepressant drugs that does not directly affect serotonin, but rather acts through the norepinephrine and dopamine systems. These effects will be reviewed in more detail elsewhere in this supplement, but they quite likely play a part in the distinct side effect profile of this compound.

Bupropion has side effects that differ notably from those of the older tricyclic compounds and also differ in some consequential ways from the side effects associated with the other newer antidepressants.

COMPARISON WITH TRICYCLICS

The side effects of antidepressants are rarely life-threatening or disabling, but they wreak havoc with compliance. This is especially true with tricyclics, whose side effects may become unbearable during long-term or maintenance use. The best way to view antidepressant side effects is through the underlying mechanisms of action that produce them. Tricyclic antidepressant medications all block muscarinic, histaminic, and α-adrenergic receptors. Blockade of these receptors is not required for antidepressant activity and is a "dirty" effect of these medications.

The side effects produced by these unwanted blockade actions are numerous: dry mouth, blurred vision, urinary retention, constipation, and memory dysfunction are caused by muscarinic blockade; sedation or drowsiness, weight gain, hypotension, and potentiation of CNS depressants are caused by histaminic blockade. These side effects are standard and frequent with the tricyclic antidepressants. Muscarinic, or anticholinergic, problems are the most common and most discussed side effects of tricyclic antidepressants. During short-term treatment, anticholinergic side effects are the most frequent cause for noncompliance or cessation of treatment. Bupropion SR, along with several of the other newer antidepressants, has essentially no effects on muscarinic, histaminic, or α-adrenergic receptors and therefore is relatively free of these problems. The newer agents, in spite of their lack of anticholinergic properties, do on occasion produce mild dry mouth and constipation. Bupropion is highly concen-

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Table 1. Unwanted Antidepressant Effects

Side Effect	Bupropion SR	SSRIs	Tricyclics
Anticholinergic	0	0	yes
Antihistaminic	0	0	yes
Sedation	0	rare	yes
Cardiac	0	0	yes
Weight gain	0	rare	yes

Table 2. Antidepressant Side Effects: Bupropion Versus SSRIs

Side Effect	Bupropion SR	SSRIs
Insomnia	yes	yes
Headache	yes	yes
Nausea	yes	yes
Stimulation	yes	yes
Sexual function	0	yes

trated in saliva and does occasionally produce dry mouth, quite likely due to some localized numbing effect.[1]

Table 1 notes, in more detail, the differences between bupropion SR and the older tricyclic agents. Certainly this drug is far better tolerated than tricyclics. In clinical practice, increased tolerability leads to better patient compliance and acceptance.

Sedation

Sedation is often listed near the top of the list of antidepressant side effects, but in clinical practice is less of a problem than this would indicate. Sedation is related to the degree of histaminic blockade. Consequently, all of the tricyclic antidepressants, and some of the newer antidepressants, produce some degree of sedation. Bupropion, with no histaminic effect, is nonsedating. It is extremely unusual in clinical practice to find sedation to be a problem in bupropion treatment.

Weight Gain

Weight gain is second only to anticholinergic problems as the major cause of noncompliance with tricyclic antidepressant treatment. In the maintenance phase of treatment, it is likely the chief cause of noncompliance. This is often an insidious side effect that becomes manifest only after several months of treatment when concern about side effects may be diminishing. There are few specific controlled data on this topic, and a review by Garland et al. found only five studies that addressed weight gain systematically.[2] Studies of longer duration typically find weight gain in one third to one half of patients treated with tricyclics for more than 6 months.[3,4]

The precise cause of weight gain is uncertain but is generally thought to be somewhat related to histaminic blockade. The tricyclic antidepressants have substantial histaminic blockade, and patients often complain bitterly of inexorable weight gain. The somewhat less histaminic compounds desipramine and nortriptyline may produce somewhat less weight gain but can still be a problem. Interestingly, pure antihistamines themselves do not invariably cause weight gain, whereas both lithium and valproate, with minimal direct antihistaminic activity, frequently will cause increased weight. It would seem then that weight gain is a complex problem, albeit associated with substantial histaminic blockade input.

Because of the mounting concern of weight gain with antidepressants, bupropion has been closely studied in this regard. In contrast to the tricyclic compounds, it rarely causes weight gain or carbohydrate craving. In fact, bupropion therapy typically has been associated with a slight weight loss.[5,6]

The bupropion SR formulation was closely evaluated for effects on weight during the investigative protocols. As with the IR form, weight gain was extremely unusual, and indeed weight gain of 10 pounds (≥ 4.5 kg) or more occurred no more than with placebo (data on file. Glaxo Wellcome). Conversely, weight loss of greater than 5 pounds (> 2.25 kg) was found in roughly 15% of patients, and loss of 10 pounds or more was found in 2% of patients taking 300 mg/day and 6% of patients taking 400 mg/day. It would appear that weight gain is not a problem with bupropion SR, which is a major advantage for maintenance treatment.

COMPARISON WITH SSRIs

Although bupropion SR is chemically and pharmacologically distinct from the SSRI compounds, there are some clinical similarities. As Table 1 indicates, they share a lack of problematic effects and side effects seen with older antidepressant agents. As a result, both the SSRIs and bupropion SR are far safer and far better tolerated than tricyclic agents.

It is interesting to note that although the putative mechanisms of action of SSRIs and bupropion are quite dissimilar, their side effect profiles, while different, are not totally distinct. Both can cause stimulation, both can cause some degree of nausea, and both can occasionally cause agitation. A direct comparison of bupropion IR versus fluoxetine found that "the incidence of treatment-emergent adverse events was low with no statistically significant difference between treatments."[7(p329)]

Table 2 notes the basic side effect properties of these newer agents. It is clear that both the SSRIs and bupropion SR offer real advantages to many patients. Clinically, some patients will do better, or have fewer side effects while taking one versus the other. It is usually difficult to predict in advance which drug will be the winner in any individual patient.

As is discussed elsewhere in this supplement,[8,9] sexual side effects and the drug interaction difficulties with the SSRIs are quite real and, in some patients, treatment limiting. In these two areas, bupropion SR has clear advantages over SSRIs for some patients.

Table 3. Percentage of Patients Taking Bupropion SR Who Experienced Dose-Related Adverse Effects Versus Daily Dose*

Adverse Event	Daily Dose 150 mg (N = 120)	300 mg (N = 229)	400 mg (N = 114)	Placebo (N = 235)
Stimulation				
Agitation	1.7	3.1	8.8	1.7
Dizziness	5.8	6.1	8.8	3.0
Insomnia	6.7	12.7	14.0	6.4
Tremor	3.3	7.4	1.8	0.4
Gastrointestinal				
Dry mouth	13.3	16.6	23.7	5.5
Nausea	8.3	10.0	12.3	5.1
Abdominal pain	2.6	2.9	8.8	1.6

*Data on file, Glaxo Wellcome.

TYPICAL SIDE EFFECT PROFILE

As previously noted, side effects with bupropion SR are virtually identical to those with bupropion IR, but "less so." In general, side effects are infrequent and benign, and the medication is well tolerated.[10] The more common side effects that occur with bupropion SR are dry mouth, overstimulation, headache, dizziness, and nausea.

The investigational protocols of bupropion SR monitored side effects very closely, and results from the two most relevant protocols are summarized in Table 3 (data on file. Glaxo Wellcome). This table lists side effects occurring in more than 5% of patients, and differing from placebo. Side effects with bupropion SR are generally mild and transient and many are dose related.

As Table 3 notes, many of the side effects of SR can be divided into a stimulation component and a gastrointestinal component. Gastrointestinal side effects with bupropion SR are certainly less frequent than with SSRIs and I find less likely to limit treatment. Nevertheless, nausea and infrequent abdominal pain and cramping are noted. Although these data indicate the gastrointestinal effects to be somewhat dose related, many clinicians feel dose is of less importance than individual patient sensitivity.

The most common side effect cluster encompasses effects referable to the energizing properties of bupropion. In cases where adverse effects limit or prevent treatment with bupropion SR, stimulation will be the most likely culprit. These activating effects are usually dose related and clinically are clearly related to the size of the starting dose and the rapidity of dosage increase.

Activating effects seen with bupropion SR include agitation, tremor, and, most commonly, insomnia. Insomnia is a somewhat dose-related effect and during investigational studies occurred in 7%, 13%, and 14% of patients at 150 mg/day, 300 mg/day, and 400 mg/day, respectively (data on file. Glaxo Wellcome). Clinically, these incidences are not dissimilar to what is seen with SSRIs. Many clinicians find most newer antidepressants to be poor sleep agents, especially during the early phases of treatment before they have a chance to "bite." It is my standard practice to use a brief initial course of a hypnotic in patients taking new antidepressant agents if insomnia is a significant problem. Insomnia can also be greatly limited by not giving doses close to bedtime. Many patients on long-term bupropion use, however, tolerate h.s. doses without difficulty.

Table 4. Discontinuation Due to Side Effects*

Bupropion SR 300 mg/d	9%
Bupropion SR 400 mg/d	11%
Placebo	4%

*Data on file, Glaxo Wellcome.

As noted, the side effect profile of bupropion SR is generally benign. Discontinuation due to adverse events is uncommon. Table 4 notes rates of discontinuation due to side effects with bupropion SR (data on file. Glaxo Wellcome). The discontinuation rates are comparable to or lower than discontinuation rates found with all other new antidepressants to date in clinical trials, as noted in their package inserts.

CARDIOVASCULAR AND LABORATORY SAFETY

Cardiovascular effects of bupropion SR were monitored in the investigational protocols. As with the IR formulation, no significant cardiovascular difficulties were found, and this compound seems very safe in regard to cardiac effects. We have limited data on using bupropion IR in depressed patients with already impaired ejection fractions, arrhythmias, or other cardiac disturbances.[11] In this report, Roose and colleagues concluded that bupropion seemed relatively safe even in patients with preexisting cardiovascular disease.

Standard laboratory parameters were closely monitored during the bupropion SR protocols and documented no abnormal effects on standard laboratory values, much as with the IR formulation.

BUPROPION SR AND SEIZURES

Virtually all antidepressants increase seizure risk in a dose-related, but usually not clinically relevant fashion.[12] The most important concern is not so much the specific antidepressant used as dosage and predisposing factors. Initial bupropion IR trials found seizure incidence roughly compatible to that of other antidepressants unless dosage exceeded 450 mg/day, at which point seizure risk did increase significantly. However, just before bupropion IR was marketed, seizures were reported in 4 of 55 nondepressed, bulimic patients receiving the agent.[13] A prospective surveillance study was then undertaken that studied seizures with bupropion IR in over 3000 patients. Dosage was increased to the full dose of 450 mg/day whenever possible, and an overall seizure incidence of 0.4% (4 per

1000) was found.[14] This 0.4% incidence associated with the maximum recommended dosage of bupropion IR would probably best be compared with a 0.1% to 0.2% (1–2 per 1000) incidence associated with SSRI medications. Direct comparison is difficult since no similar comprehensive study has been done for any other antidepressant.

It has been clear that the seizure risk is strongly correlated with dosage and peak plasma level. Therefore, it has been expected that the bupropion SR formulation would have a lower risk of seizure. To investigate this further, a second surveillance survey was undertaken, again with over 3000 patients involved. In the seizure safety surveillance study, bupropion SR dosage of 300 mg/day or less was associated with a seizure rate of 0.06% (less than 1 per 1000), and the combination of treatment and continuation phases with this dosage (≤ 300 mg/day) was associated with a seizure rate of 0.10% (1 per 1000) (data on file. Glaxo Wellcome). These rates are comparable to rates with other non-tricyclic antidepressant agents.

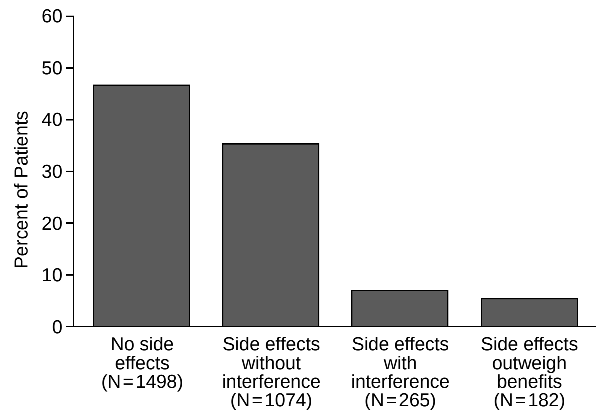
Based on this surveillance study data, the package insert of the SR formulation notes a seizure risk of 0.1% ("1 per 1000") at doses up to 300 mg/day. At this point, however, the package insert becomes rather confusing, as it goes on to state that there may be a 0.4% (4 per 1000) incidence of seizures at doses up to 400 mg/day. In fact, there has not yet been a seizure with bupropion SR at a dosage of 400 mg/day. Only three seizures have been seen in total with bupropion SR in study protocols, and each of these three patients had predisposing factors. All three seizures seen thus far with bupropion SR have occurred at doses of 300 mg/day or less (data on file. Glaxo Wellcome). In investigational studies to date, there were no seizures with doses greater than 300 mg/day. The FDA's position seems to be that we simply have inadequate data at higher doses, and they have chosen to take the most conservative position by noting that seizure incidence at 400 mg/day with bupropion SR may be the same as at 450 mg with bupropion IR. The data thus far do not support that position, but admittedly we need more data on higher doses of bupropion SR to reach informed conclusions.

Clinically, it would appear that the incidence of seizures with bupropion SR is not a significant clinical issue in doses up to 400 mg/day. This does not necessarily imply, however, that the SR formulation is safe at any dose, and restricting dosage to a maximum of 400–450 mg/day would be prudent until more information is gathered.

IDIOSYNCRATIC SIDE EFFECTS

Antidepressants in general are well known for their almost endless lists of rare, idiosyncratic, or even bizarre side effects. Like virtually all other antidepressants, bupropion does uncommonly produce alopecia and sweating.[10] These are rarely serious and essentially are ubiquitous with all antidepressants.

Figure 1. Tolerance of Bupropion SR (Data From Safety Surveillance Study)*



*N = 3094 for entire study. Effects unknown for 75 patients. Data on file, Glaxo Wellcome.

TOLERABILITY

In spite of the above mentioned occasional side effects, bupropion SR is generally quite well tolerated. Even patients poorly tolerant to previous antidepressants often tolerate bupropion well. The recent safety surveillance study of the SR formulation found excellent tolerability, as is noted in Figure 1. As this chart indicates, roughly 85% of patients treated with bupropion SR had either no side effects or side effects that were felt to be negligible (data on file. Glaxo Wellcome).

CONCLUSION

Bupropion, both IR and SR, is a highly effective antidepressant compound that has some unique characteristics. Its side effect profile is generally benign with the exception of some increased seizure risk with higher-than-recommended doses of the IR formulation. The new SR formulation has significantly ameliorated this seizure concern and at doses up to 400 mg/day is a very safe and highly effective compound.

Drug names: bupropion (Wellbutrin), desipramine (Norpramin and others), fluoxetine (Prozac), nortriptyline (Pamelor and others), trazodone (Desyrel and others).

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