Bupropion Sustained Release: A Therapeutic Overview

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Sustained-release bupropion (bupropion SR) represents a new form of an already known effective antidepressant drug. Its pharmacokinetics, mechanism of action, metabolism, and efficacy are reviewed. Benefit relative to placebo has been demonstrated in two large multicenter trials, with low doses (100 or 150 mg) having been shown to have therapeutic efficacy. An overview of all placebo-controlled trials of bupropion SR is given, and the differential properties of bupropion and serotonergic drugs are described. The concept of a catecholamine-indolamine spectrum is presented, along with its implications for possible differential therapeutics of selective antidepressants.

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During the late 1970s and early 1980s, bupropion was one of the few nontricyclic, non-MAO-inhibiting antidepressants under investigational study. With its largely well-tolerated side effect profile, the drug offered promise as a safer, better tolerated, and equally effective alternative to other compounds. It was subsequently marketed in 1989 and has become established as a well-accepted first-line antidepressant. At the time that bupropion was released, a high incidence of seizures was reported in a study of patients suffering from bulimia and added to the already known high rate of seizures at doses above the recommended maximum daily dose of 450 mg (i.e., in the range of 600–900 mg/day). This aspect of bupropion has been previously summarized and reviewed.[1] However, at commonly used therapeutic doses of 450 mg/day and below, the risk of major motor seizure is more acceptable as well as dose related: rates of 0.4% at doses up to 450 mg/day for bupropion immediate release and 0.1% at doses up to 300 mg/day for bupropion sustained release have been observed.

Among the advantages of bupropion relative to serotonergically active drugs are the generally lower incidence of gastrointestinal side effects, the possibly lower incidence of activating effects, and the now established lower incidence of sexual dysfunction.[2,3] Yet another advantage of bupropion over many serotonergic antidepressants is its lack of inhibitory properties on the cytochrome P450 isoenzyme system.[4] Disadvantages of the original, immediate-release form of bupropion (bupropion IR) include the concern about seizure risk at higher doses, the need to give the drug on a t.i.d. basis if used at the 450-mg dose, and a recommended maximum single dose of 150 mg. These restrictions may have served as a constraint to physicians in choosing bupropion IR as a first-line treatment for many depressive patients.

The development of sustained-release bupropion (bupropion SR) provided an opportunity to refine and modify this antidepressant to achieve a better tolerated drug that had fewer side effects, lower risk of seizure, and the potential for a once- or twice-daily administration. The development of bupropion SR also offered the opportunity to safely administer a single dose of greater than 150 mg. The incidence of seizure is believed to be related, in part, to plasma levels of bupropion and its metabolites,[1] so that an SR formulation of the drug resulting in lower plasma levels would be welcome. An additional opportunity afforded by the bupropion SR clinical trials program was the chance to explore the lower end of the therapeutic dose range, given previous evidence which suggested that a daily dose of 150 mg might be therapeutically effective.[5]

PHARMACOKINETICS OF BUPROPION SR

The pharmacokinetics of bupropion IR and bupropion SR have been compared (data on file. Glaxo Wellcome). Following single-dose administration of 150 mg of each drug, the SR formulation is associated with a 50% lower mean peak plasma concentration of bupropion, while maintaining equivalent area-under-the-curve (AUC) values. Following repeated-dose administration (bupropion IR 150 mg t.i.d. or SR 150 mg b.i.d.), the mean peak plasma concentration of bupropion was 15% lower with bupropion SR than with bupropion IR, while the mean bupropion trough level of the SR formulation exceeded

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that of the IR formulation by 7%. Once again, the AUC values were equivalent. Thus, it is to be expected that bupropion SR would be equally effective therapeutically and, at the same time, devoid of some of the more extreme swings between peak and trough levels that characterize bupropion IR. An additional pharmacokinetic study of bupropion SR compared the effects of smoking and not smoking on plasma levels following a single 150-mg SR tablet (data on file. Glaxo Wellcome). No clinically relevant pharmacokinetic differences were noted between smokers and nonsmokers in this study (a smoker was defined as an individual who had smoked an average of at least 16 cigarettes per day for the past year; nonsmokers were those who abstained from smoking or using nicotine-containing products for at least 5 years).

It is important to clarify that use of the term *sustained release* does not in any way imply a slower delivery of effect or a longer half-life. There would be little sense, therefore, in initiating therapy with bupropion IR and then switching to bupropion SR; rather, the presumption is that the clinician will generally want to initiate therapy with bupropion SR. No direct head-to-head comparisons of the two formulations of bupropion have been made, however, with respect to clinical efficacy or side effects.

MECHANISM OF ACTION OF BUPROPION

The postulated mechanism of action of bupropion has been well summarized by Ascher et al.[6] There is no reason to believe that bupropion SR has a different mechanism of action from bupropion IR. On the basis of different models, bupropion was found to produce the following effects:

1. A modest down-regulation of postsynaptic β-receptors and desensitization of norepinephrine-stimulated adenylate cyclase are noted after chronic administration of unusually high doses. These effects are probably not of great clinical relevance.[6]
2. Bupropion does enhance extracellular dopamine levels in the nucleus accumbens after chronic administration.[6]
3. Electrophysiologically, the drug reduces norepinephrine firing from the locus ceruleus and also, at higher doses, reduces dopaminergic firing in the A9 and A10 areas.[6]
4. Immunoreactivity studies have shown that chronic use of bupropion decreases tyrosine hydroxylase reactivity in the locus ceruleus of rats,[7] providing strong evidence to suggest that bupropion can influence the synthesis of norepinephrine and dopamine.
5. Clinically, bupropion has been shown in depressed patients to enhance 6-hydroxy melatonin levels, which have been considered to represent a marker of net functional activity of the norepinephrinergic system. Thus, while whole body norepinephrine turnover was decreased, net functional noradrenergic efficiency was increased.[8]
6. There has been no evidence that either bupropion or its metabolites have any effect upon firing rates of serotonergic neurons in the dorsal raphe, or upon serotonergic turnover in depression. This profile thus means that bupropion is the only antidepressant at the present time that is entirely selective for catecholamine function, having no direct serotonergic effects.
7. Not cited in the review by Ascher et al.[6] is work by Paul et al.,[9] who found that bupropion, in common with all antidepressants tested, reduces the potency of glycine to inhibit 5,7-DCKA binding at strychnine-insensitive glycine receptors. Paul et al. propose that adaptive changes produced by bupropion and other antidepressants in this NMDA receptor/ligand-gated ion channel complex serve as a common pathway of antidepressant action. These findings imply that antidepressants ultimately work by modulating excitotoxic effects of glutamate in the CNS. They propose that glutamatergic changes may be involved in the pathophysiology of depression and that bupropion is active in this manner. NMDA-receptor down-regulating properties of bupropion deserve further study.

The antidepressant effect of bupropion is related to down-regulation of locus ceruleus activity, its effect upon tyrosine hydroxylase synthesis, and the net improvement in functional efficiency of norepinephrine. The above-mentioned effect of bupropion on the NMDA receptor is probably important, but its relationship with other neurochemical effects of the drug needs to be understood. It is unclear what relevance bupropion's dopaminergic properties might have to depression, but in all probability dopamine-enhancing effects in the nucleus accumbens relate to the ability of bupropion to successfully increase rates of abstinence from smoking, possibly by affecting the same neuronal pathways as does nicotine, at least in respect to dopamine. In addition, its noradrenergic down-regulating effects are of potential benefit to patients as they cope with the withdrawal syndrome after quitting.

BUPROPION AND ITS METABOLITES

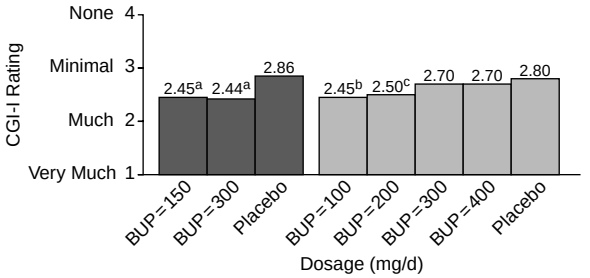
Bupropion is degraded by hydroxylation to hydroxybupropion (#306), threohydrobupropion (#494), and erythrohydrobupropion (#17). Hydroxybupropion is present in CSF at levels six times greater than those of the parent drug, as is also true for erythrohydrobupropion. Threohydrobupropion is present at levels of at least 40 times greater than those of the parent drug. Although hydroxybupropion has weak reuptake blocking properties on norepinephrine, the high levels of this metabolite in brain may

Table 1. Clinical Global Impressions-Severity of Illness (CGI-S) Change Score from Baseline (LOCF) in Study of Two Doses of Bupropion SR*

	Week			
Dosage	2	4	6	8
Bupropion 150 mg/d	0.59	1.13[a]	1.19[b]	1.35[c]
Bupropion 300 mg/d	0.51	0.92	1.21[d]	1.36[c]
Placebo	0.42	0.72	0.90	1.00

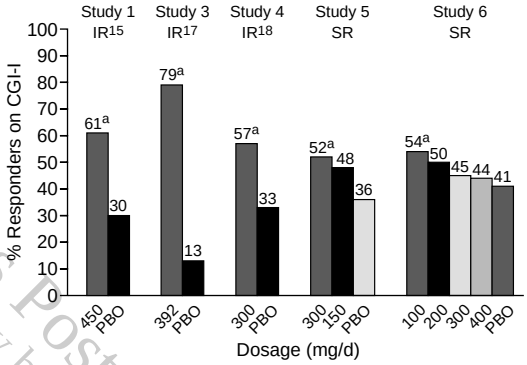
*Data on file, Glaxo Wellcome.
[a]p = .002 vs placebo.
[b]p = .05 vs placebo.
[c]p = .03 vs placebo.
[d]p = .04 vs placebo.

Figure 1. Mean Endpoint Clinical Global Impressions-Improvement (CGI-I) Scores in Two Studies of Bupropion SR Versus Placebo (LOCF) Analysis*



*Data on file, Glaxo Wellcome. Abbreviation: BUP = bupropion.
[a]p = .009 vs placebo.
[b]p = .03 vs placebo.
[c]p = .06 vs placebo.

Figure 2. Rates of Improvement with Bupropion (IR or SR) and Placebo in Major Outcome Studies (Intent-to-Treat Analysis)*



*Data on file, Glaxo Wellcome for Studies 5 and 6. Abbreviation: PBO = placebo. See Table 3 for description of studies.
[a]p < .05 vs placebo.

well be sufficient to produce clinically meaningful blockade of norepinephrine reuptake or the norepinephrine transporter and thereby account for much of the drug's antidepressant effect. Parent bupropion has dopaminergic and noradrenergic effects, metabolite 306 has primarily noradrenergic effects, and metabolite 494 has some dopaminergic and minor noradrenergic effects. Metabolite 17 is devoid of activity.[6]

CLINICAL TRIALS OF BUPROPION SR

Four major clinical trials of bupropion SR have been conducted. These consist of two placebo-controlled trials, one against an active comparator, sertraline, and one large open-label safety surveillance study in which some efficacy measures were also collected.

Two-Dose Study of Bupropion SR Versus Placebo

Two fixed doses of bupropion SR (150 mg/day and 300 mg/day) were compared with placebo in outpatients who had major depressive disorder at six sites (data on file. Glaxo Wellcome). Efficacy was measured using the Hamilton Rating Scale for Depression (HAM-D),[10] the Clinical Global Impressions (CGI) scale,[11] and the Hamilton Rating Scale for Anxiety (HAM-A).[12] Safety of bupropion SR was evaluated by regular assessments of adverse experiences and vital signs.

A total of 362 patients were randomly assigned to three groups, with 121 in the 150 mg/day group, 120 in the 150 mg b.i.d. group, and 121 in the placebo group. Following a 7-day placebo lead-in phase, active treatment or placebo was administered for 8 weeks.

On CGI-Severity of Illness (CGI-S) change score measures, significant effects ($p < .05$) were found for bupropion SR 150 mg/day at Days 21, 28, 35, 49, and 56. For the 300-mg dose, significant differences were found relative to placebo at Days 42 and 56 based on last observation carried forward (LOCF) analyses. In Table 1, comparisons are shown at selected time points.

Mean CGI-Improvement (CGI-I) scores yielded differences in favor of bupropion 150 mg/day and bupropion 300 mg/day at endpoint (Figure 1), based on LOCF analyses. In terms of the number of responders according to the CGI scale, 48% of the bupropion 150 mg/day patients were judged to be responders, as were 52% of the bupropion 300 mg/day patients, compared with 36% of the placebo patients. Comparison of bupropion 150 mg/day versus placebo achieved a chi-square value of 3.1 ($p = .08$), while a comparison of bupropion 300 mg/day versus placebo yielded a chi-square value of 5.3 ($p = .02$) (Figure 2).

On the 28-item HAM-D, there was a significant difference in favor of the bupropion 300 mg/day dose at Day 56 using last-observation-carried-forward (LOCF) analyses. The change in total HAM-D score relative to baseline for the three treatment groups was as follows: bupropion 150 mg/day, 14.1; bupropion 300 mg/day, 14.5; placebo = 11.8. Comparison of bupropion 150 mg/day versus placebo yielded a significant p value of .08. Comparison of bupropion 300 mg/day versus placebo yielded a significant p value of .05.

Table 2. CGI-S Change Score from Baseline (LOCF) in Study of Four Doses of Bupropion SR*

	Week			
Dosage	2	4	6	8
Bupropion 100 mg/d	0.62	1.08	1.39[a]	1.53[b]
Bupropion 200 mg/d	0.49	0.99	1.23	1.34
Bupropion 300 mg/d	0.67	0.98	1.23	1.36
Bupropion 400 mg/d	0.42	0.98	1.11	1.32
Placebo	0.51	0.86	1.03	1.07

*Data on file, Glaxo Wellcome.
[a]p = .03 vs placebo.
[b]p = .04 vs placebo.

Based on the HAM-A, differences were noted at endpoint as follows: change scores relative to baseline for bupropion 150 mg/day, bupropion 300 mg/day, and placebo, respectively, were 6.8, 7.5, and 5.7. Comparison of bupropion 150 mg/day versus placebo yielded no significant difference, whereas comparison of bupropion 300 mg/day versus placebo resulted in a significant difference (p = .03).

The results of this study indicate that bupropion SR is an effective antidepressant at a dose of 150 mg/day on the CGI-S scale and approaches significance on the HAM-D. The same can be said for bupropion SR at a daily dose of 300 mg, with the added benefit that significant changes were found on the HAM-A, suggestive of a dose-response effect to some extent.

Four-Dose Study of Bupropion SR Versus Placebo

The second trial was an 11-center, parallel, randomized, double-blind, placebo-controlled trial, in which outpatients with major depressive disorder first completed a 1-week single-blind placebo lead-in, followed by 8 weeks of randomized treatment with one of four fixed doses of bupropion SR (100, 200, 300 or 400 mg/day) or placebo (data on file. Glaxo Wellcome). Principal efficacy measures were the HAM-D, the HAM-A, and the CGI-S and CGI-I scales.

Six hundred two patients were randomized into the study, as follows: bupropion 100 mg/day (N = 119), bupropion 200 mg/day (N = 120), bupropion 300 mg/day (N = 120), bupropion 400 mg/day (N = 119), placebo (N = 124).

On the CGI-S scale, a significantly greater change was noted in the bupropion 100 mg/day group compared with placebo, although changes were not distinguishable between bupropion 200 mg/day, bupropion 300 mg/day, and bupropion 400 mg/day and placebo (Table 2), using LOCF analyses.

According to the CGI-I scale, a significantly greater degree of improvement was noted at endpoint for bupropion 100 mg/day, and a nearly significant difference was found for bupropion 200 mg/day relative to placebo (Figure 1). In the bupropion 200 mg/day group, a significant difference did emerge at Days 42 and 49. By using the CGI-I measure to dichotomize subjects into responders or nonresponders, it was found that the response rates for the bupropion 100 mg/day, bupropion 200 mg/day, bupropion 300 mg/day, bupropion 400 mg/day, and placebo groups were 54%, 50%, 45%, 44%, and 41%, respectively (Figure 2).

Using the 28-item HAM-D, a statistically significant difference was found in favor of bupropion 100 mg/day at Weeks 5, 6, 7, and 8 according to LOCF analyses. At endpoint, the mean reduction in the HAM-D score for bupropion 100 mg/day was 15.6 as compared with a mean drop of 11.9 for placebo (p = .01). Mean reductions in the HAM-D score for bupropion 200 mg/day, bupropion 300 mg/day, and bupropion 400 mg/day were 14.0, 13.4, and 14.0, respectively, none of which differed statistically from the change observed for placebo.

On the HAM-A, mean scores dropped 7.0 to 8.2 points in each of the bupropion groups, as compared with a mean drop of 7.1 in the placebo group. None of the differences were significant between bupropion and placebo.

In this trial, magnitude of change for bupropion was consistently greater than for placebo, but there were few statistically significant comparisons other than those between bupropion 100 mg/day and placebo and some in favor of bupropion 200 mg/day. A relatively high placebo response rate was noted, which would diminish the likelihood of finding drug versus placebo differences. The study is unusual in finding effectiveness for such a low dose of bupropion, almost certainly below what had previously been thought of as a therapeutic dose. Although this study found no efficacy for 300 mg/day, evidence from other studies indicates that this is generally an effective dose.

Bupropion SR Versus Sertraline

In a clinical trial of bupropion SR versus sertraline, the main focus was to compare each treatment with respect to sexual function during recovery from depression (data on file. Glaxo Wellcome). However, in this 16-week trial each treatment showed equivalent effects on the HAM-D, HAM-A, and CGI scales.

Open-Label Surveillance Study

In a large unpublished multicenter seizure surveillance study, bupropion SR was administered in open-label fashion for 8 weeks, followed by an optional continuation phase (data on file. Glaxo Wellcome). Three thousand one hundred sixty-seven patients were enrolled at 105 different centers, of whom 3094 subjects furnished data available for assessment of antidepressant response. Seventy-two percent of the intent-to-treat analysis cohort were rated as having improved on the CGI-I scale, with 53% showing much or very much improvement, i.e., qualifying as responders. Of the 2057 patients who completed 8 weeks of treatment, 67% were rated as responders. Of the 33% who were judged to have been nonresponders to previous antidepressant treatments, 59% responded to bupropion.

Table 3. Placebo-Controlled Trials of Bupropion (IR and SR)*

Study	Authors	Dosage (mg/day)	Efficacy	Duration (Weeks)	Sample
1	Zung (1983)[15]	450 (IR)	+	4	Inpatients
2	Branconnier et al. (1983)[16]	150 (IR)	+	4	Outpatients
		450 (IR)	+	4	Over 55 y
3	Feighner et al. (1984)[17]	392 (IR)[a]	+	4	Inpatients
4	Lineberry et al. (1990)[18]	300 (IR)	+	6	Outpatients
5	Glaxo Wellcome,	300 (SR)	+	6	Outpatients
	data on file (1995)	150 (SR)	+	6	Outpatients
6	Glaxo Wellcome,	100 (SR)	+	6	Outpatients
	data on file (1995)	200 (SR)	±	6	Outpatients
		300 (SR)	–	6	Outpatients
		400 (SR)	–	6	Outpatients

*Abbreviations: IR = immediate release, SR = sustained release. Symbols: + = positive, ± = equivocal, – = no effect.
[a]In a few instances, subjects received 600 mg/day.

An interesting set of additional analyses has recently been reported from the large cohort obtained in the open-label trial of bupropion SR. Mauskopf et al.[13] looked at ratings of work and social disability on a five-point observer scale, which was included in this trial. The Work and Social Disability Scale[14] (WSDS) rates impairment as being absent (1), mild (2), moderate (3), marked (4), or severe (5). Mauskopf et al. noted that 62% were markedly or severely impaired at entry into the study, whereas at completion of treatment, only 22% remained markedly or severely impaired. When looking at predictors of response, the authors found the following variables to contribute significantly and independently to improvement in score on the WSDS: completion of at least 8 weeks of treatment ($p = .0001$), not having taken previous medication ($p = .0001$), the baseline severity of depression ($p = .0001$), and the mean daily dose of bupropion SR ($p = .003$). With regard to the last mentioned variable, improvement was much more likely to occur (74% improvement rate) in patients who received doses of 300 mg/day, as compared with those who received intermediate doses (150 to 250 mg/day) (49% improved), or doses below 150 mg/day, in whom response rates were only 37%. An equally striking relationship between dose and outcome was noted when marked improvement was used as the outcome variable. This study is therefore interesting for two reasons. First, it is one of the only studies in which work and social disability were assessed in a large number of depressed patients pretreatment and posttreatment, and, second, it did suggest evidence for a dose effect of bupropion SR on this parameter.

OVERVIEW OF EFFICACY STUDIES

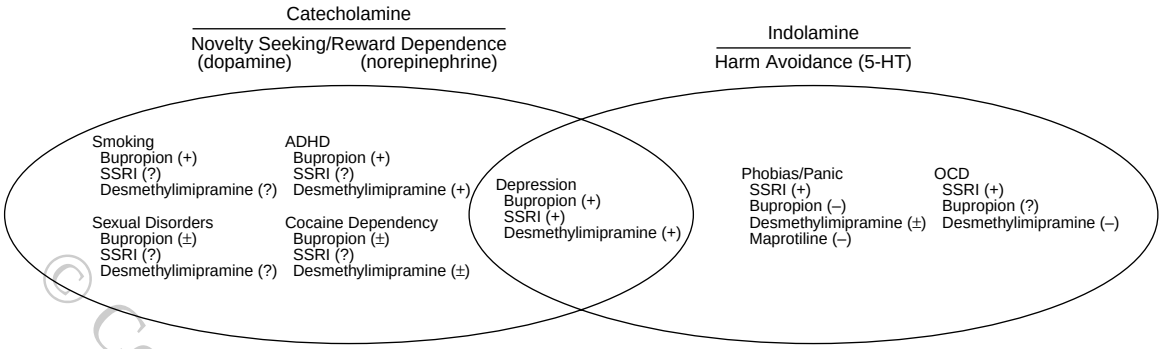
Six studies have assessed either bupropion IR or SR at doses of 450 mg or less relative to placebo for at least 4 weeks (references 15–18 and data on file, Glaxo Wellcome). These are summarized in Figure 2 and Table 3. Figure 2 summarizes these studies wherein response rates are given and shows that response rates are better for bupropion than for placebo in all studies, although in one (unpublished) study, the higher doses were ineffective relative to placebo, which itself carried a high response rate. As shown in Table 3, 300 mg/day was effective in two of three trials, while the lower (100–150 mg/day) doses were effective in three of three studies.

THE CATECHOL-INDOLE SPECTRUM: COMPARISON OF BUPROPION AND SEROTONERGIC DRUGS

Bupropion is the only antidepressant in current use that is entirely devoid of direct serotonergic effects, a distinction that carries a number of theoretical and practical implications, as will be considered. One theoretical point is that as a drug with noradrenergic and dopaminergic effects, bupropion promotes regulation of function in a dysregulated mesolimbic brain system. Thus, disorders wherein there is a deficit of attention/processing as well as disorders of drive related to an inability to execute pleasure-seeking impulses into action[19] may respond well to a dopaminergic drug. Thus, a constellation of states, e.g., attention deficit/hyperactivity disorder (ADHD), bipolar and retarded depressions, disorders of sexual arousal, and addictive (e.g., smoking, cocaine abuse) disorders, may all be responsive to the drug. The evidence for response to bupropion is stronger for some of these states (ADHD, smoking, eating disorder) than others. For some of these conditions, predominantly serotonergic drugs may be less beneficial. Bupropion is an unusual antidepressant due to its activating properties in septal, hippocampal, and other limbic regions,[19] as well as its potential for increasing REM sleep in depressive patients[20] (see Thase in this issue).

On the other hand, serotonergic mechanisms are viewed as integral in the avoidance of harm; thus, excessive harm avoidance disorders (e.g., anxiety disorders) would respond well to serotonergic drugs, but would be

Figure 3. The Catechol-Indole Spectrum and Related Effects of Selective Pharmacotherapy*



*Abbreviation: SSRI = serotonin selective reuptake inhibitors. Symbols: + = effective, ? = unknown, ± = equivocal, – = ineffective. Bupropion, desmethylimipramine, and maprotiline are catecholaminergic drugs.

less responsive to a selective catecholamine drug such as bupropion. In partial support of this hypothesis is one open-label negative trial of bupropion in panic disorder,[21] making it one of the few antidepressants to be ineffective in this disorder.

However, since depression can respond to both catecholaminergic and indolaminergic drugs, both bupropion and serotonin selective reuptake inhibitors (SSRIs) work well in depression. Associated comorbid disorders need to be addressed, since they can help provide further guidance as to the selection of a specific drug. These considerations of bupropion and serotonergic drugs are outlined in Figure 3.

DISCUSSION

Bupropion SR clearly represents an important and significant change in the formulation of an already well-known and effective antidepressant. It has a well-tolerated profile of side effects.[3] Its clinical efficacy is documented in two trials relative to placebo, which both suggest that in many patients a dose in the range of 100 to 150 mg given once a day may well be sufficient.

One measure of acceptability for a drug is the rate of dropout due to adverse events. By comparing dropout rates listed in the package insert for bupropion SR with published rates in the *Physicians' Desk Reference (PDR)*,[22] one can get a sense of the placebo-adjusted dropout rates for some new antidepressants in clinical trials. Furthermore, the *PDR* data allow one to evaluate the impact of dose escalation upon patient dropout rate. It is instructive to look at these data, and in so doing to note that the dropout rates for bupropion SR 300 mg and bupropion SR 400 mg are 5% and 7%, respectively, after subtracting the placebo drop-out rates. By contrast, evidence for paroxetine indicates that at a daily dose of 20 mg, the placebo-adjusted dropout rate is 6%, while at 30 mg it increases substantially to 16%. Similarly, for sertraline, placebo-adjusted dropout rates at 50 and 200 mg/day are 7% and 32%, respectively. For the new antidepressant mirtazapine, the collective dropout rate within the dose range of 15 to 45 mg is 9% after adjusting for placebo. By this yardstick, bupropion SR must be seen as a particularly well-tolerated antidepressant with minimal loss of tolerability as the dose goes up to the high end.

Table 4. Main Contrasts Between Bupropion SR and Serotonin Selective Reuptake Inhibitors (SSRIs)

Characteristic	Bupropion SR	SSRIs
Sexual dysfunction	Rare	Common
Gastrointestinal	Mild to moderate	Moderate to severe
Activation	Sometimes	More often
Cytochrome P450 inhibition	No	Yes
Withdrawal symptoms	None reported	Yes
Can be given effectively in a once-daily dose	At daily doses of ≤ 200 mg	At all doses

On the basis of a review of its clinical profile, the following points can be made in respect of bupropion SR (see Table 4).

1. It can be given once a day at an effective dose of 100–200 mg in many patients.
2. It is therapeutically effective at 300 mg/day, recommended to be given as 150 mg b.i.d.
3. It is associated with a very low dropout rate from side effects, and the rate remains low even at the top dose.
4. It is well tolerated and does not significantly impair sexual function.
5. It does not inhibit any of the cytochrome P450 isoenzymes as far as is known.
6. Bupropion can be contrasted with SSRI drugs by having a clear direct effect on noradrenergic and dopaminergic, reward-dependent and novelty-seeking systems, whereas SSRI drugs have a noticeable effect on the raphe-mediated behavioral inhibition system. Some of their differences in clinical profile could be so accounted.

On the basis of these considerations, bupropion SR can be seen as a viable first-line form of antidepressant therapy in both primary care and specialty settings.

Drug names: bupropion (Wellbutrin), maprotiline (Ludiomil), mirtazapine (Remeron), paroxetine (Paxil), sertraline (Zoloft).

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