A Review of the Neuropharmacology of Bupropion, a Dual Norepinephrine and Dopamine Reuptake Inhibitor

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Background: The neurochemical and biological effects of antidepressant medications have become better defined over the last decade. When the antidepressant bupropion was introduced in the United States in 1989, the specific pharmacologic basis of its clinical effects was uncertain. Research conducted over the past decade has significantly advanced the understanding of the neuropharmacology of bupropion and has demonstrated a novel mechanism of antidepressant activity. This article discusses the mechanism of action of bupropion and relates the drug's neuropharmacologic effects to its clinical efficacy and tolerability profiles.

Data Sources: Data were obtained via the MEDLINE database in an English-language search spanning the period 1965 to May 2002 and using the search terms *bupropion*, *bupropion SR*, and *antidepressants*, as well as from the manufacturer's bupropion databases.

Conclusions: The preclinical and clinical data show that bupropion acts via dual inhibition of norepinephrine and dopamine reuptake and is devoid of clinically significant serotonergic effects or direct effects on postsynaptic receptors. Dual norepinephrine and dopamine reuptake inhibition is associated with a unique clinical profile. Bupropion has demonstrated efficacy comparable to that of other antidepressants. However, because bupropion is a selective norepinephrine and dopamine reuptake inhibitor with no serotonergic activity, common antidepressant-associated side effects, such as sexual dysfunction, weight gain, and sedation, are not associated with bupropion therapy.

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When introduced in the United States in 1989, bupropion was categorized as an "atypical" antidepressant because its neurotransmitter effects were undefined but known to differ from those of classical antidepressants (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) and selective serotonin reuptake inhibitors (SSRIs). Though the efficacy of bupropion is comparable to that of other antidepressants, including the SSRIs and TCAs,[1–6] bupropion does not affect serotonin or postsynaptic receptors and therefore is an antidepressant with unique pharmacologic properties.[7] This article discusses the pharmacology of bupropion, a compound currently available in 3 distinct but bioequivalent formulations[8] (Wellbutrin, Wellbutrin SR [sustained-release], and Wellbutrin XL [extended release]) (Table 1), and relates the drug's neurotransmitter effects to clinical efficacy and tolerability. By understanding the neuropharmacologic basis of the clinical effects of antidepressants, health care providers can select among pharmacotherapies to better tailor treatments to the needs of their individual patients.

NEUROBIOLOGY OF DEPRESSION

For nearly 4 decades, the monoamine hypothesis of depression has predominated.[9] According to the monoamine hypothesis, depression is a neurochemical disorder arising from hypofunctioning of brain monoamine systems including the serotonergic, noradrenergic, and/or dopaminergic pathways. This hypothesis arose from observations that the administration of classical antidepressants increased monoaminergic function, whereas monoamine depleters such as reserpine precipitated depressive symptoms in susceptible individuals.[10,11] A large body of evidence from animal models and clinical studies in depressed patients also supported the monoamine hypothesis. For example, depressed patients were found to have subnormal cerebrospinal fluid levels of serotonin and norepinephrine metabolites as well as blunted neuroendocrine responses to monoamine agonists[12–14]; moreover, all currently available antidepressants acutely enhance some aspect of monoaminergic function (Table 2).[11,15–18]

Table 1. Pharmacokinetic Parameters of Bupropion Formulations at Steady State From Bupropion Bioequivalence Analyses[a]

Pharmacokinetic Parameter	Geometric Least Squares Mean Ratio	90% CI
Wellbutrin (100 mg tid) vs Wellbutrin XL (300 mg qam)		
AUC_{24}	0.89	0.86 to 0.93
C_{max}	0.97	0.91 to 1.03
C_{min}	0.80	0.76 to 0.85
Degree of fluctuation	1.13	1.05 to 1.21
Wellbutrin SR (150 mg bid) vs Wellbutrin XL (300 mg qam)		
AUC_{24}	0.90	0.87 to 0.94
C_{max}	1.06	0.99 to 1.13
C_{min}	0.91	0.86 to 0.97
Degree of fluctuation	1.21	1.13 to 1.29

[a]Data on file, GlaxoSmithKline, Research Triangle Park, NC.[8]
Abbreviations: AUC_{24} = area under the plasma concentration-time curve at 24 hours, C_{max} = maximum plasma concentration of bupropion produced by a given dose during the dosing interval, C_{min} = minimum plasma concentration of bupropion produced by a given dose during the dosing interval, SR = sustained release, XL = extended release.

In current conceptualizations of the neurobiology of depression, monoaminergic dysregulation is viewed more as an associated factor than as a primary cause. Depression and responses to antidepressants are thought to be mediated by yet to be fully defined final common physiologic pathway(s), the functions of which are modulated by the monoamines. Activity of specific monoaminergic pathways in this context are viewed as "upstream" events that influence "downstream" events, such as changes in gene expression and protein synthesis, which ultimately cause depression and modulate responses to antidepressants.[14,16,19] Several observations support an "upstream" rather than primary role of monoamines in depression. First, whereas monoamine-enhancing effects of antidepressants are observed at the synaptic level within hours of the initial dose, the onset of clinical efficacy does not occur until days or weeks after initiation of antidepressant therapy,[20] an observation consistent with the possibility that events downstream of and dependent upon monoamine activation are involved in the etiology of depression. Second, though all antidepressants marketed to date enhance monoaminergic neurotransmission, they have widely varying potencies for monoaminergic effects. For example, antidepressants differ by more than 1000-fold in potency at inhibiting monoamine reuptake, yet their efficacies are comparable and seemingly unrelated to potency.[21] Third, although all antidepressants enhance monoaminergic neurotransmission, they do so via disparate mechanisms, consistent with the possibility that multiple monoamines influence final common pathways relevant to depression. Finally, more recent evidence suggests that antidepressants increase levels of brain-derived neurotrophic factor, a protein that has been found to promote cellular health.[22] Antidepressants may thus play a neuroprotective role, a possibility supported by observations that hippocampal neurogenesis may be required for the behavior effects of antidepressants in mice[23] and that progressive loss of hippocampal volume occurs during chronically untreated depression in humans.[24,25]

NEUROPHARMACOLOGY AND MECHANISM OF ACTION OF BUPROPION

Animal research has demonstrated that bupropion enhances monoaminergic neurotransmission differently from other antidepressants.[7] In rat and mouse studies, bupropion and its metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion) did not alter serotonergic neurotransmission either presynaptically (by affecting serotonin release or reuptake) or postsynaptically (by binding to serotonin receptors).[7,26] Rather, bupropion and its primary metabolite, hydroxybupropion, decreased the reuptake of dopamine and norepinephrine into rat and mouse synaptosomes (sacs formed by presynaptic neuronal membranes that mimic presynaptic neuronal terminal activity). In addition, the acute administration of bupropion reduced firing of dopamine and norepinephrine neurons in the brain stems of rats in a dose-dependent manner,[7,26] an effect consistent with an increase in synaptic levels of dopamine and norepinephrine that in turn inhibits neuronal firing via an autoreceptor-mediated negative feedback mechanism. Furthermore, microdialysis studies that measured neurotransmitter levels in the nucleus accumbens of freely moving mice found extracellular dopamine and norepinephrine concentrations increased in response to bupropion administration in the Porsolt animal model of depression,[27,28] and another microdialysis study[29] has shown increased dopamine and norepinephrine concentrations in the rat prefrontal cortex in response to bupropion administration. Lastly, administration of dopamine- or norepinephrine-blocking drugs reduced the antidepressant effects of bupropion and its metabolite hydroxybupropion in animal models of depression.[30] These preclinical data indicate that the mechanism of action of bupropion most likely involves its dual-reuptake inhibition of dopamine and norepinephrine (Figure 1).

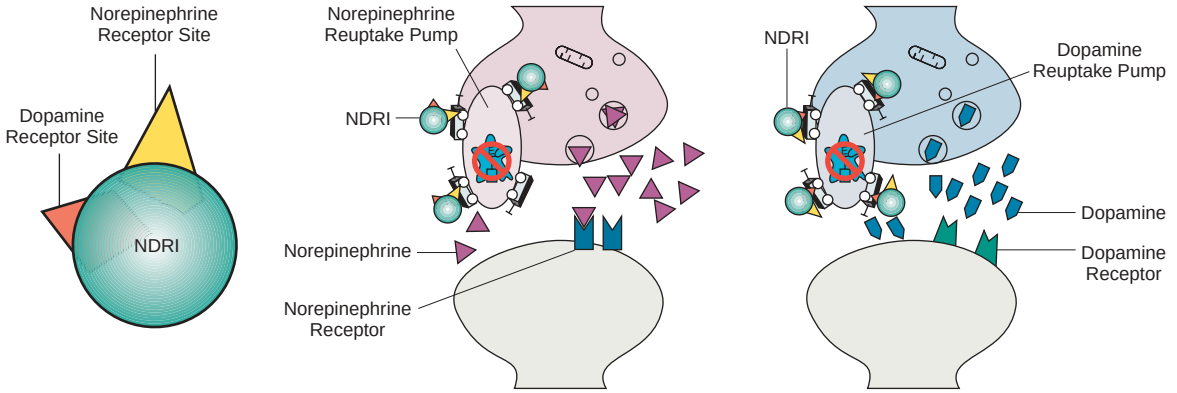
Clinical research and studies of human dopamine, norepinephrine, and serotonin transporters extend the preclinical findings. Therapeutic doses of bupropion given to depressed patients (N = 11) showed reduced whole-body turnover of norepinephrine without altering plasma norepinephrine levels, a finding that indicates significant central noradrenergic activity.[31] In addition, 3 studies[32–34] have investigated human dopamine transporter occupancy by bupropion and its metabolites. In a study[32] conducted in healthy volunteers (N = 6) using positron emission tomography (PET), bupropion and its metabolites effectively bound to striatal dopamine transporters under steady-state conditions with therapeutic oral dosing of bupropion SR

Table 2. Monoaminergic Effects of Common Antidepressants[a]

Class of Antidepressant	Monoaminergic Effect
Monoamine oxidase inhibitor (eg, phenelzine)	Enhances monoaminergic function by inhibiting the enzyme responsible for the breakdown of monoamines (norepinephrine, serotonin, and dopamine)
Tricyclic antidepressant (eg, amitriptyline)	Enhances monoaminergic function by inhibiting neuronal reuptake of serotonin and/or norepinephrine to prolong their concentration and time in the synaptic cleft
Selective serotonin reuptake inhibitor (eg, sertraline, fluoxetine, paroxetine, citalopram, escitalopram)	Enhances monoaminergic function by inhibiting neuronal reuptake of serotonin to prolong their concentration and time in the synaptic cleft
Serotonin-norepinephrine reuptake inhibitor (eg, venlafaxine)	Enhances monoaminergic function by inhibiting neuronal reuptake of serotonin and norepinephrine to prolong its concentration and time in the synaptic cleft
Norepinephrine-dopamine reuptake inhibitor (eg, bupropion)	Enhances monoaminergic function by inhibiting neuronal reuptake of norepinephrine and dopamine to prolong their concentration and time in the synaptic cleft
α_2 antagonist (eg, mirtazapine)	Enhances monoaminergic function by presynaptic α_2 receptor blockade, which disinhibits norepinephrine and serotonin release
Serotonin antagonist/reuptake inhibitor (eg, nefazodone)	Blocks serotonin-2 receptors. Enhances monoaminergic function by inhibiting neuronal reuptake of serotonin and norepinephrine to prolong their concentration and time in the synaptic cleft

[a]Based on references 11, 15–18.

Figure 1. Norepinephrine-Dopamine Reuptake Inhibitor (NDRI) Molecule Blocking Both Norepinephrine and Dopamine Reuptake Pumps[a]

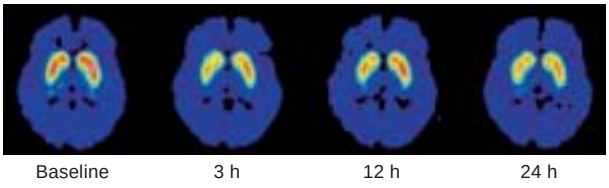


[a]Adapted with permission from Stahl.[16] In this diagram, the norepinephrine reuptake inhibitor and the dopamine reuptake inhibitor portions of the NDRI molecule are shown inserted in the norepinephrine and the dopamine reuptake pumps, respectively, blocking them and causing an antidepressant effect.

(150 mg b.i.d.). The mean dopamine transporter occupancy was 26.0% (SD = 8.3) at 3 hours after the last dose of bupropion SR, and this level was maintained through the last PET assessment at 24 hours after dosing (25.2% occupancy, SD = 9.7) (Figures 2 and 3). This degree of dopamine transporter occupancy was corroborated in a study of depressed patients[33] (N = 7) using single photon emission computed tomography (SPECT), which found a mean bupropion dopamine transporter occupancy of 25.4% (SD = 20.9) at steady state following therapeutic dosing of bupropion SR (150 mg b.i.d.). In contrast, Meyer and colleagues[34] reported dopamine transporter occupancy in depressed patients (N = 8) of only 14% following treatment with bupropion. However, interpretation of these data is difficult given that the report lacks an index of the variability in the data, the time course of dopamine effects, and evidence that patients were at steady state.

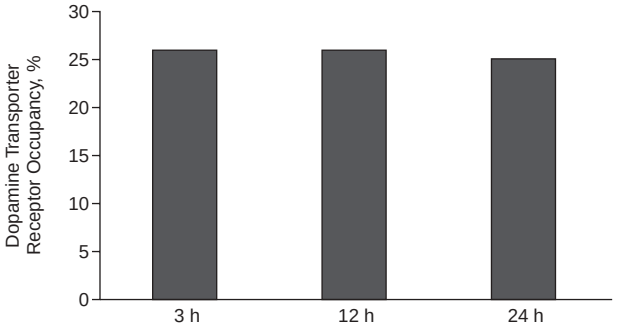
The effects of bupropion and its metabolites on monoamine reuptake have been further characterized in vitro using cells expressing human transporters for dopamine, norepinephrine, and serotonin.[8] Bupropion with its metabolites inhibited reuptake at human transporters for both dopamine and norepinephrine, with slightly greater functional potency at the dopamine transporter than at the norepinephrine transporter. Inhibition of serotonin reuptake via the serotonin transporter was negligible even at the highest concentration tested. Combined relative potencies for bupropion and its metabolites at human dopamine and norepinephrine transporters are presented in Figure 4. When interpreting these data, it is important to note both the relatively high (~10:1) brain-to-plasma ratio for bupropion and its metabolites as well as the plasma pharmacokinetic profile of parent drug and metabolites. Brain concentrations of bupropion and its major metabolites

Figure 2. In Vivo Binding of ^{11}C-βCIT-FE, a Selective Dopamine Transporter-Binding Radioligand, at Baseline and 3, 12, and 24 Hours After Cessation of Steady-State Dosing With Bupropion SR[a]



[a]Adapted with permission from Learned-Coughlin et al.[32]
Abbreviations: ^{11}C-βCIT-FE = ^{11}C-labeled N-ω-fluoroalkyl-2β-carboxy-3-β-(4-iodophenyl) nortropane ester, SR = sustained release.

Figure 3. Mean Dopamine Transporter Receptor Occupancy of Bupropion 3, 12, and 24 Hours After Cessation of Steady-State Dosing With Bupropion SR[a]



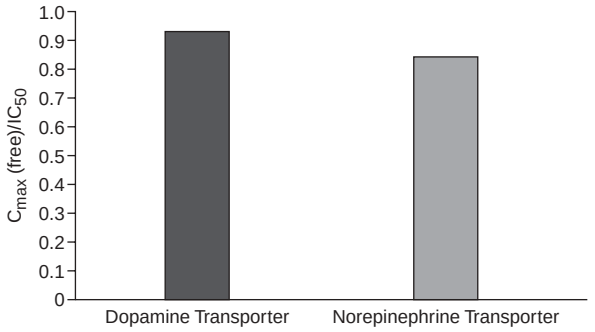
[a]Adapted with permission from Learned-Coughlin et al.[32]
Abbreviation: SR = sustained release.

remain above the 50% inhibitory concentrations (IC_{50}) for brain dopamine and norepinephrine transporters throughout the typical 12-hour dosing interval of bupropion SR. These data confirm that bupropion is a dual norepinephrine and dopamine reuptake inhibitor (NDRI) in humans at clinically relevant doses.[31]

Results of other studies[15,26] have shown that bupropion and its metabolites do not have appreciable affinity for postsynaptic receptors including histamine, α- or β-adrenergic, serotonin, dopamine, or acetylcholine receptors. The lack of affinity for these postsynaptic receptors differentiates bupropion from the TCAs and some of the other new-generation antidepressants that have relatively high affinities for histamine, acetylcholine, and/or α-adrenergic receptors.[20]

Considered in aggregate, these data demonstrate that bupropion inhibits the reuptake of norepinephrine and dopamine in humans without affecting release or transport of other neurotransmitters and without binding to other neurotransmitter receptors. This pharmacologic profile is unique to bupropion, which is currently the only available

Figure 4. Combined Relative In Vitro Potency (C_{max}/IC_{50}) for Bupropion and Metabolites at Human Dopamine and Norepinephrine Transporters[a]



[a]Data on file, GlaxoSmithKline, Research Triangle Park, NC.[8] Data were calculated using maximum human plasma concentrations of bupropion and its metabolites at steady state following dosing with bupropion SR 150 mg twice daily.
Abbreviations: C_{max} = maximum plasma concentration of bupropion produced by a given dose during the dosing interval, IC_{50} = 50% inhibitory concentrations.

NDRI shown to increase dopamine neurotransmission in both the nucleus accumbens and the prefrontal cortex.

NEUROPHARMACOLOGY OF BUPROPION

Clinical Efficacy

The specific neurotransmitter(s) affected by antidepressants and the potency of these neurotransmitter effects do not necessarily predict antidepressant efficacy. Regardless of pharmacologic profiles, the effectiveness of antidepressant medications is generally comparable among and within classes, as was found in the evidence report of the Agency for Healthcare Policy and Research[35] and is reflected in the positions of the American Psychiatric Association,[36,37] reviewers for the Cochrane Library,[38] and clinical experts publishing independently of these organizations.[39,40] Though bupropion is distinguished from other antidepressants by its pharmacology, multiple head-to-head trials[1–6] comparing bupropion with SSRIs and TCAs have demonstrated comparable antidepressant efficacy, and a pooled analysis[41] of all bupropion comparative trials with SSRIs demonstrated identical remission rates (47%). Moreover, bupropion has demonstrated comparable efficacy when administered in conjunction with the SSRI sertraline in treating depression (and anxious symptoms of depression) even among patients with high levels of anxiety at baseline.[42,43]

The distinctive neuropharmacologic properties of bupropion do, however, have clinical implications with regard to clinical application and therapeutic spectrum in individual patients. For example, in addition to its use as a first-line antidepressant, bupropion is frequently used

to augment the efficacy[44–49] and mitigate side effects[50–59] of serotonergic antidepressants. Bupropion is also effective for other disorders characterized by dysfunctional noradrenergic and/or dopaminergic neurotransmission. By inhibiting dopamine reuptake, bupropion confers anticraving and antiwithdrawal effects that make it an effective smoking-cessation aid.[60] Smoking-cessation clinical trial results with bupropion show that short- and long-term abstinence rates approximately double when compared with placebo or the nicotine patch.[60] Bupropion has also demonstrated efficacy in the treatment of attention-deficit/hyperactivity disorder (ADHD),[61–63] which is thought to involve both noradrenergic and dopaminergic dysregulation, and it is the only antidepressant to have demonstrated efficacy in reducing the risk of seasonal depressive relapse when taken prophylactically for seasonal affective disorder (SAD)[64]; noradrenergic and dopaminergic abnormalities have been implicated in the pathogenesis of both ADHD[61–63] and SAD.[65–67] Further data suggesting that bupropion is less likely than TCAs to cause a switch into mania in bipolar depression have made bupropion a preferred treatment option for bipolar depression.[36,68–70] It has been hypothesized that bupropion's relatively low risk of inducing mania may be related to its absence of serotonergic properties or effects on postsynaptic β-receptors.[71,72] In contrast, although other antidepressants such as the SSRIs, dual serotonin and norepinephrine reuptake inhibitors (SNRIs), TCAs, and MAOIs are frequently used to treat a wide variety of anxiety disorders, bupropion has not been well studied for the treatment of anxiety disorders.

Table 3. Biochemical Pharmacologic Mechanisms and Their Possible Side Effect[a]

Mechanism	Possible Side Effect
Enhancement of serotonin function (by stimulating specific receptors or blocking reuptake)	Agitation Apathy Decreased libido Diarrhea Erectile dysfunction Increased awakenings Insomnia Nausea Orgasm dysfunction Weight gain (with long-term treatment)
Enhancement of noradrenergic function	Agitation Dry mouth Hypertension (peripheral effect)
Enhancement of dopaminergic function	Agitation Constipation Insomnia
Blockade of H_1 histamine receptors	Drowsiness Sedation Weight gain
Blockade of muscarinic cholinergic receptors	Blurred vision Cognitive impairment Constipation Decreased sweating Dry mouth Memory impairment Urinary retention
Blockade of noradrenergic receptors	Hypotension
Blockade of dopamine receptors	Decreased attention Sedation

[a]Based on references 17, 18, 20, 74, 75.

Clinical Tolerability

Unlike therapeutic effects, which may not be observed for several weeks, most side effects occur within hours to days of initiation of an antidepressant.[73] This observation suggests that acute tolerability of antidepressants, unlike antidepressant efficacy, is directly related to acute synaptic effects on monoaminergic and other systems.

Clinical data demonstrate that specific neurotransmitter effects are associated with distinct side effect profiles (Table 3).[17,18,20,74,75] Antidepressant-induced side effects are attributed to drug activity at central or peripheral synapses where agents either bind to neurotransmitter receptors and influence cellular function or alter concentrations of endogenous neurotransmitters that then bind to neurotransmitter receptors. Because the acute pharmacologic effects of bupropion are unique among currently marketed antidepressants, bupropion also demonstrates a distinct tolerability profile. Across 3 randomized, placebo-controlled studies (987 patients treated with bupropion SR [100–400 mg/day] and 385 placebo-treated patients), adverse events occurring significantly more frequently with bupropion than placebo were dry mouth (16% vs. 7%), nausea (12.5% vs. 7.5%), and insomnia (10.5% vs. 6.5%), respectively.[76] These side effects have also been reported with other antidepressants. However, bupropion's tolerability profile differs from those of other antidepressants in that some adverse events do not occur significantly more frequently with bupropion than placebo, including sexual dysfunction, weight gain, and sedation—side effects that occur often with other antidepressants.

The association of SSRIs, TCAs, MAOIs, and SNRIs with sexual dysfunction is well established.[77,78] In a study reported in 2002,[79] 37% of 6297 patients consulting 1101 U.S. primary care clinics reported sexual problems associated with antidepressant use. Sexual dysfunction as measured by the Changes in Sexual Functioning Questionnaire was 4 to 6 times more likely to occur with antidepressants affecting serotonergic function compared with bupropion, which was associated with the lowest risk of sexual dysfunction. Comparator studies of bupropion and SSRIs corroborate these findings.[2,3,80–82] In addition, bupropion has been successfully substituted for other antidepressants that cause sexual dysfunction[83,84] and has been effective as an antidote for sexual dysfunction caused by other antidepressants in numerous uncontrolled studies[50,54–56,59] and in 2 of 3 placebo-controlled clinical trials.[51,52,57] Adjunctive bupropion treatment to reverse a variety of antidepressant-induced sexual side effects was more successful when administered as regular daily

doses rather than occasional as-needed use.[50] In the trial in which bupropion was not effective as an antidote,[57] it is possible that an inadequate dose of bupropion was used and/or that the sexual functioning rating scale used (the Arizona Sexual Experience Scale) lacked adequate sensitivity to detect antidepressant-associated sexual dysfunction.

In addition to sexual dysfunction, weight gain may occur frequently with some classes of antidepressants.[85–89] With respect to SSRIs, evidence suggests weight gain may occur during long-term treatment (possibly via a serotonergic mechanism such as down-regulation of 5-HT_{2C} receptors, although antihistaminergic effects may also contribute).[90,91] In contrast, bupropion has not been associated with weight gain. Depression trials suggest that bupropion is weight-neutral in patients at or below ideal body weight at baseline but is associated with modest weight loss, proportional to initial body mass index.[76,92–94] In addition, bupropion has demonstrated efficacy as an adjunct for weight loss in nondepressed, obese individuals.[95,96] The mechanism of the weight-reducing effect of bupropion has not been determined, although it is noteworthy that both dopaminergic and noradrenergic brain pathways have critical roles in the regulation of appetite, satiety, and feeding behavior.[97,98]

Bupropion, unlike many other antidepressants, is not associated with sedation. The incidence of sedation in controlled clinical trials of bupropion did not differ between bupropion SR and placebo.[76] In addition, in a pooled analysis[41] of all studies comparing bupropion with SSRIs, bupropion was associated with significantly lower rates of sedation than were the SSRIs.

An often-debated issue is the incidence of seizure associated with antidepressant therapy. Most antidepressant clinical trials report that the seizure incidence ranges from 0.1% to 0.3% for the newer-generation antidepressants [99–103] and up to 1.1% for the TCAs.[104–106] The spontaneous seizure rate reported in the general population is approximately 0.1%.[107,108] For bupropion, the incidence of seizure reported in the product information for the older, immediate-release formulation (Wellbutrin) is 0.4% at doses up to 450 mg/day,[109] and for Wellbutrin SR and Zyban (also a sustained-release formulation), 0.1% for doses up to 300 mg/day.[109] In addition, a recently conducted review[8] by the manufacturer of its clinical trials database for the sustained-release formulation of bupropion (N = 15,213) showed an overall seizure incidence of 0.07% at doses up to 400 mg/day. The mechanisms by which antidepressants may lower the seizure threshold are largely unknown.

Considered together, these data show that dual inhibition of norepinephrine and dopamine reuptake with bupropion results in a side effect profile distinct from that of antidepressants with other mechanisms of action. Although many antidepressants are associated with side effects such as sexual dysfunction, weight gain, and sedation, bupropion's side effect profile differs and consists primarily of dry mouth, nausea, and insomnia.

CONCLUSIONS

Preclinical and clinical data demonstrate that bupropion acts via dual inhibition of norepinephrine and dopamine reuptake, which constitutes a novel mechanism of antidepressant action. As such, bupropion is associated with a unique clinical profile with efficacy comparable to that of other antidepressants. Devoid of clinically significant serotonergic effects or direct effects on postsynaptic receptors, bupropion—the only currently available NDRI—is as effective as other antidepressants but does not cause common antidepressant-associated side effects such as sexual dysfunction, weight gain, and sedation. These data support the use of bupropion as a first-line antidepressant as well as its possible utility as augmentation therapy.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin, Zyban, and others), citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac and others), mirtazapine (Remeron), paroxetine (Paxil and others), phenelzine (Nardil), reserpine (Serpalan and others), sertraline (Zoloft), venlafaxine (Effexor).

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