

Review of the Pharmacology and Clinical Profile of Bupropion, an Antidepressant and Tobacco Use Cessation Agent

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ABSTRACT

Bupropion hydrochloride ((±)-2-tert-butylamino)-3'-chloropropiophenone · HCl) is a nonselective inhibitor of the dopamine transporter (DAT) and the norepinephrine transporter (NET) and is also an antagonist at neuronal nicotinic acetylcholine receptors (nAChRs). In animal models used commonly to screen for antidepressant activity, bupropion shows a positive response. Also using animal models, bupropion has been shown to attenuate nicotine-induced unconditioned behaviors, to share or enhance discriminative stimulus properties of nicotine and to have a complex effect on nicotine self-administration, i.e., low doses augmenting nicotine self-administration and high doses attenuating self-administration. Current studies show that bupropion facilitates the acquisition of nicotine conditioned place preference in rats, further suggesting that bupropion enhances the rewarding properties of nicotine. Bupropion has been shown to attenuate the expression of nicotine withdrawal symptoms in both animal models and human subjects. With respect to relapse, current studies show that bupropion attenuates nicotine-induced reinstatement in rats, but large individual differences are apparent. Clinically, bupropion is used as a treatment for two indications, as an antidepressant, the indication for which it was developed, and as a tobacco use cessation agent. In clinical trials, bupropion is being tested as a candidate treatment for psychostimulant drug abuse, attention-deficit hyperactivity disorder (ADHD) and obesity. Bupropion is available in three bioequivalent oral formulations, immediate release (IR), sustained release (SR), and extended release (XL). Extensive hepatic

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metabolism of bupropion produces three pharmacologically active metabolites, which may contribute to its clinical profile.

INTRODUCTION

Major depression is characterized by clinically significant depression of mood, feelings of intense sadness and despair, mental slowing, loss of concentration, anhedonia, self-deprecation, and an overall impairment of functioning. Furthermore, major depression is often associated with insomnia or hypersomnia, altered eating patterns, decreased energy, disruption of normal circadian rhythms of activity, body temperature, and endocrine function. Major depression is distinguished from normal grief, sadness, disappointment, and dysphoria often associated with medical illness. Recent clinical studies reveal a strong correlation between the incidence of mood disorders and tobacco smoking. Individuals with clinical depression are more likely to be tobacco smokers, to be dependent on nicotine and to have difficulty quitting, with greater withdrawal symptoms upon cessation. Smokers undergoing cessation experience symptoms of depression, which occur more frequently among those with a history of major depression.

Tricyclic antidepressants have been available since the early 1960s and have been used widely to treat major depression. Compared to tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), bupropion is considered to be an atypical antidepressant with a mixed neuropharmacological profile. Based on preclinical information, bupropion inhibits the reuptake of dopamine (DA) and norepinephrine (NE), as well as acting as an antagonist at nAChRs. Preclinical and clinical evidence also indicates that bupropion has benefit as a tobacco use cessation agent. Bupropion increases tobacco use acutely in non-treatment seeking individuals tested in a laboratory setting. This biphasic response suggests a complex action. The precise mechanism by which bupropion reduces tobacco use remains to be elucidated.

NEUROPHARMACOLOGY

Neurochemical Mechanisms Mediating the Pharmacological Effects of Bupropion

Despite its similarity to classical antidepressants in terms of therapeutic efficacy, the acute presynaptic neurochemical changes produced by bupropion are different from those produced by classical antidepressants. Bupropion neither inhibits the activity of monoamine oxidase inhibitors A or B, nor facilitates the release of monoamines from nerve terminals (2). Instead, bupropion shares some structural, neurochemical and behavioral properties with classical psychostimulants. Similar to amphetamine, bupropion contains a phenylethylamine skeleton. The neurochemical mechanisms mediating the antidepressant effects of bupropion are thought to result from inhibition of DAT and NET; however, its mechanism of action is not understood fully. Bupropion inhibits [³H]DA uptake into rat striatal synaptosomes, [³H]NE uptake into rat hypothalamic synaptosomes, and less potently [³H]serotonin uptake into hypothalamic synaptosomes (2,50,51,113). In a concen-

tration-dependent manner, bupropion also inhibits [^3H]DA uptake into COS-7 cells transfected with human DAT, but lacking vesicular storage mechanisms (45). Furthermore, a competitive interaction with DAT has been demonstrated using [^3H]mazindol binding to rat striatal membranes (38). Thus, bupropion-induced inhibition of both DAT and NET contrasts with classical antidepressants (e.g., imipramine), which selectively inhibit the serotonin transporter and/or NET (197).

In a recent study, bupropion has also been shown to rapidly and reversibly increase vesicular DA uptake via cellular redistribution of the vesicular monoamine transporter-2 (VMAT2) protein (136). The bupropion-induced increase in vesicular DA uptake was prevented by pretreatment with eticlopride, a DA D_2 receptor antagonist, but not by SCH 23390 [R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride], a DA D_1 receptor antagonist. Thus, bupropion may enhance extracellular DA levels by inhibiting the plasmalemma transporter (i.e., DAT) and by increasing VMAT2 function to increase the presynaptic pool of DA available for release into the extracellular space. These combined effects may contribute to its therapeutic efficacy.

While many antidepressants have been suggested to produce their therapeutic effects via downregulation of postsynaptic noradrenergic receptors, bupropion does not appear to have this effect (50). However, bupropion does interact with noradrenergic systems, dose-dependently decreasing the firing rate of noradrenergic neurons located in the locus coeruleus (23,39). The effect on firing rate is inhibited by the α_2 -noradrenergic antagonist, yohimbine, indicating that the bupropion-induced decrease in firing rate is mediated by the noradrenergic system. Bupropion doses required to decrease noradrenergic activity correlate strongly with those that exert an antidepressant effect in animal models of depression (23). Furthermore, mice lacking the gene that encodes dopamine- β -hydroxylase are not responsive to the antidepressant-like effects of bupropion as assessed in the tail-suspension task (29). Collectively, these results suggest that the effects of bupropion on noradrenergic neurons contribute to its antidepressant properties.

Another mechanism potentially contributing to the efficacy of bupropion as an antidepressant as well as a tobacco use cessation agent is its action as a nAChR antagonist. The ability of bupropion to interact with specific nAChR subtypes has been investigated using various cellular expression systems. Bupropion inhibits carbamylcholine-induced $^{86}\text{Rb}^+$ efflux from human neuroblastoma cells expressing the $\alpha 3\beta 4$ ganglionic nAChR subtype and more potently inhibits $^{86}\text{Rb}^+$ efflux from cells expressing the α_1 muscle nAChR subtype (55). In *Xenopus* oocytes expression systems, bupropion also inhibits acetylcholine activation of rat $\alpha 3\beta 2$ and $\alpha 4\beta 2$ nAChR subtypes, as well as the $\alpha 7$ subtype, but with lower affinity (160). Inhibition of these nAChR subtypes by bupropion is not surmounted by increasing agonist concentrations, indicative of a noncompetitive mechanism of action (55,160). Bupropion also does not displace [^3H]nicotine binding to whole rat brain membranes, consistent with a noncompetitive inhibition of $\alpha 4\beta 2^*$ nAChRs (160).

Bupropion alters monoamine function via an action at various nAChRs. For example, bupropion inhibited nicotine-evoked [^3H]DA and [^3H]NE overflow from superfused striatal and hippocampal slices, respectively (112). Interaction with DAT and NET was eliminated in the latter study by inclusion of nomifensine (DAT and NET inhibitor) and desipramine (NET inhibitor), respectively, in the superfusion buffer. The bupropion-induced inhibition of nicotine-evoked [^3H]DA overflow, but not [^3H]NE overflow, was surmounted by increasing concentrations of nicotine (112), suggesting a competitive interaction with nAChR subtypes mediating [^3H]DA, but not [^3H]NE overflow. While the

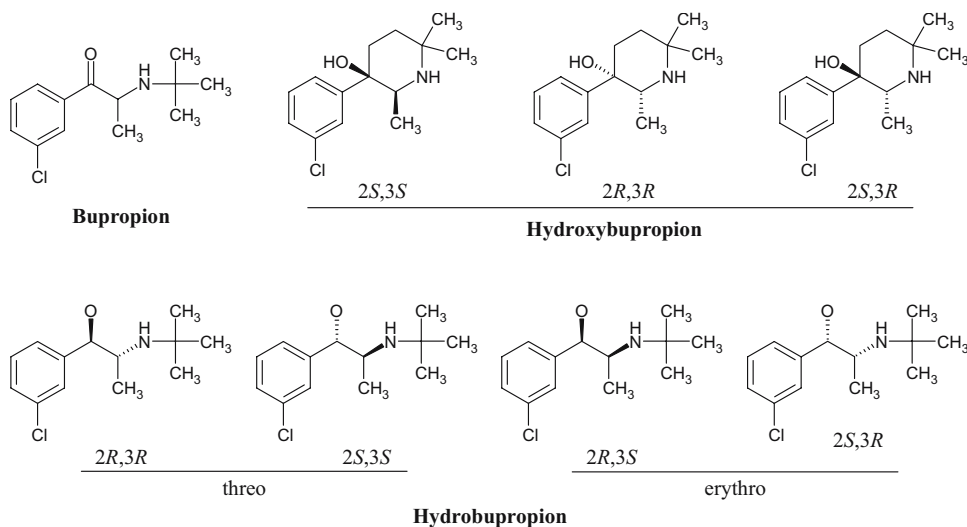


Fig. 1. Structures of bupropion and its metabolites.

exact subunit composition of native nAChRs mediating nicotine-evoked DA release have not been elucidated conclusively, six different nAChR subtypes ($\alpha 6\beta 2\beta 3^*$, $\alpha 4\alpha 6\beta 2\beta 3^*$, $\alpha 6\beta 2^*$, $\alpha 4\alpha 6\beta 2^*$, $\alpha 4\beta 2^*$, and $\alpha 4\alpha 5\beta 2^*$) have been implicated (147). Furthermore, evidence has accumulated that different nAChR subtypes are responsible for agonist stimulation of DA and NE release, and that $\alpha 3\beta 4^*$ nAChRs play a major role in nicotine-evoked NE release from hippocampus (101,142), although other subtypes are likely also involved (56,154). Thus, bupropion inhibits nAChR function across a similar concentration range as that inhibiting DAT and NET function; the combined inhibition of neurotransmitter transporters and nAChRs may provide a beneficial pharmacological profile affording clinical efficacy as an antidepressant and tobacco cessation agent.

Role of Bupropion Metabolites in Mediation of Its Pharmacological Effects

Metabolites of bupropion (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion; Fig. 1) have been suggested to contribute to and/or be responsible for the antidepressant effects of bupropion and may also contribute to its efficacy as a tobacco use cessation agent. While bupropion is a chiral compound, the racemic mixture is used clinically. Hydroxybupropion and threohydrobupropion are major metabolites in humans, and erythrohydrobupropion is formed in lesser amounts. The 2S,3S-hydroxybupropion metabolite is equipotent with bupropion in inhibiting [^3H]DA uptake and [^3H]NE uptake into synaptosomes of rat cerebral cortex (32). Furthermore, 2S,3S-hydroxybupropion is 4-fold more potent as an antagonist at $\alpha 4\beta 2$ nAChRs heterologously expressed in SH-EP1 cells than either the 2S,3R-isomer or the parent compound, as demonstrated by inhibition of carbamylcholine-evoked $^{86}\text{Rb}^+$ efflux (32). Hydroxybupropion has also been shown to decrease the firing rate of locus coeruleus noradrenergic neurons, an effect that is reversed

by yohimbine (23). Thus, the metabolites appear to contribute to the pharmacology of bupropion.

BEHAVIORAL PHARMACOLOGY

Anxiolytic/Anxiogenic Effects

Preclinical research has examined whether bupropion has either anxiolytic or anxiogenic effects. Bupropion prevents triazolam withdrawal-induced anxiety in mice assessed in the mirrored chamber test (88) and ameliorates the anxiogenic effects of high doses of nicotine in the elevated plus maze test in mice (18). However, Redolat et al. (140) found that the effects of bupropion on anxiety and/or aggression in male OF1 mice are complex and depend on a variety of factors. That is, bupropion failed to alter performance in the elevated plus-maze and social-interaction tests, and ethological indexes of anxiety (e.g., head dipping and stretched attend posture) were not altered by bupropion, suggesting that bupropion is not an anxiolytic. These latter results are consistent with those from previous studies (17,22). However, Redolat et al. (140) also found that bupropion decreased the number of head-dips in the hole-board task and decreased digging in the isolation-induced aggression task, suggesting that bupropion has anxiogenic effects. When mice were divided into "short attack latency" or "long attack latency" subgroups, bupropion did not alter performance in the short attack latency mice relative to control mice; however, bupropion dose-dependently decreased time spent digging and increased attack duration in these mice. These results suggest that bupropion specifically facilitates aggression in mice with such tendencies. Bupropion-induced aggression also has been observed in rats in the muricide paradigm (165). Biochemical mechanisms mediating anxiogenic or pro-aggressive effects of bupropion have not been elucidated.

Antidepressant Effects

Animal models of depression

In animal models of depression, bupropion has been shown to be as efficacious as the classical tricyclic antidepressants (e.g., imipramine) and monoamine oxidase inhibitors (e.g., phenelzine). For example, similar to tricyclics and monoamine oxidase inhibitors, bupropion reverses sedation and ptosis induced by tetrabenazine (2,118) and hypothermia induced by reserpine (106). Furthermore, bupropion has been shown to reduce immobility in the behavioral despair (16,106) and tail-suspension (144) tests, and to attenuate behavioral deficits in a chronic-stress paradigm (89).

Genetic factors also influence the effects of bupropion assessed using animal models. Ripoll et al. (144) determined the effects of bupropion in the tail-suspension test using C57BL/6J and DBA/2 inbred mouse strains. C57BL/6J mice showed greater baseline immobility scores compared to DBA/2, and more importantly showed an antidepressant effect of bupropion. In contrast, bupropion was not effective in producing an antidepressant effect in DBA/2 mice, indicative of a genetic influence on the response. Strain differences in mice also were observed with respect to bupropion effects in the forced swimming test (33). Furthermore, rats bred for low or high activity in the forced swim test were differentially sensitive to the antidepressant effects of bupropion (191). That is, rats

bred for low swim activity were responsive to the antidepressant effects of chronic, but not acute, bupropion administration. Conversely, bupropion was ineffective in producing an antidepressant effect in rats bred for high swim activity, regardless of whether it was administered acutely or chronically. These studies highlight the importance of genetics when assessing antidepressant effects of bupropion in animal models of depression.

Role of bupropion metabolites in mediating its antidepressant effects

The role of bupropion metabolites in mediating the antidepressant effects of bupropion observed in animal models cannot be discounted. Hydroxybupropion, the major metabolite of bupropion, is behaviorally active in mice, reducing immobility in the behavioral despair forced swimming test in rats and antagonizing reserpine-induced hypothermia in mice (2,32,106). This latter effect is reversed by prazosin and propranolol, results similar to those with bupropion. Furthermore, hydroxybupropion accumulates in significant quantities in plasma from mice (106), consistent with pharmacokinetic studies in humans (62). Collectively, these results suggest that hydroxybupropion may contribute to the antidepressant effects of bupropion.

Psychoactive Effects

Unconditioned behaviors associated with the psychoactive effects of bupropion

Bupropion, like amphetamine, increases locomotor activity (106,121,123), sniffing (202), as well as decreases core body temperature and food consumption (201,203) in rodents. Bupropion produces dose-related increases in locomotor activity in mice; however, both hydroxybupropion and threohydrobupropion produce biphasic effects on locomotor activity, with low doses increasing activity and high doses decreasing activity (106). Thus, the metabolites of bupropion may also contribute to the unconditioned stimulant effects of bupropion.

In another study, when bupropion was administered following methamphetamine, it augmented methamphetamine stereotypy. However, when bupropion was administered prior to methamphetamine, it antagonized methamphetamine-induced stereotypy (116). The time-dependent effects of bupropion may be explained in part by the appearance of its active metabolites. Thus, temporal factors of administration also appear to influence the effect of bupropion on unconditioned behaviors.

Psychoactive effects of bupropion are most likely related to its effects on DA systems. For example, doses of bupropion required to inhibit DAT are correlated strongly with those required to increase locomotor activity (51). Moreover, pretreatment with the DA D₂ receptor antagonist, pimozone, or the DA-depleting agent, reserpine attenuates bupropion-induced increases in locomotor activity (203). Pretreatment with DA D₁ or DA D₂-receptor antagonists (SCH 23390 or sulpiride, respectively) or reserpine decreases bupropion-induced sniffing, whereas pretreatment with noradrenergic receptor antagonists (e.g., phenoxybenzamine or propranolol) do not (202). Pretreatment with sulpiride, but not SCH 23390, also attenuates bupropion-induced decreases in core body temperature (201). Antagonists at other receptor systems (e.g., muscarinic, noradrenergic, or serotonergic) do not alter bupropion-induced decreases in core body temperature. Pretreatment with pimozone attenuates bupropion-induced decreases in food consumption, whereas pretreatment with other non-DA antagonists has no effect (203). Collectively, these results suggest that

activation of DA D_2 receptors mediates many of the unconditioned behaviors associated with the psychoactive effects of bupropion.

*Conditioned behaviors associated
with the psychoactive effects of bupropion*

In studies examining conditioned behaviors, bupropion produces conditioned place preference (127), is self-administered in both rats and nonhuman primates (8,94,172), and substitutes for other classical psychostimulants such as cocaine, amphetamine and methamphetamine as well as for the combination of cocaine and heroin (speedball) in operant drug discrimination studies (72,83,90,94,117,119,149). In drug discrimination studies in humans, bupropion produces some d-amphetamine-like participant-rated drug effects. It did not, however, produce significant levels of d-amphetamine appropriate responding (146), suggesting dissociation between its subjective and behavioral effects.

In other studies examining schedule-controlled behavior, bupropion increased the response rate and decreased the reinforcement rate on a differential-reinforcement-of-low-rate 72-sec schedule (152), a pattern similar to that for amphetamine (130). However, the pattern with bupropion was different from that of other antidepressants classes, which decrease response rate and increase reinforcement rate on this operant schedule (152). Furthermore, using a stimulus-shock termination schedule, in which responding to a cue light omits several programmed shocks, bupropion increases responding on a fixed-interval schedule of stimulus-shock termination comparable to other psychostimulants; whereas other classes of antidepressants decrease responding on such schedules (110,161). Thus, bupropion appears to have a profile similar to that of psychostimulant drugs, and dissimilar to other antidepressants.

Considerable evidence provides strong support for the role of DA systems in mediating some of the conditioned behaviors associated with psychostimulant effects of bupropion. Operant drug discrimination studies show that bupropion substitutes fully for agents with selective effects on DA systems (e.g., GBR 12909 [1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine]; 111) and fails to substitute for drugs not affecting DA levels or effects, such as selective NET inhibitors (e.g., reboxetine; 37) or β_2 -noradrenergic agonists (e.g., clenbuterol; 102). Moreover, discriminative stimulus effects of bupropion are bidirectional; selective DA agents (e.g., nomifensine; 87,173) substitute for bupropion, whereas non-DA agents do not (e.g., nortriptyline; 11,87,173). Moreover, pretreatment with either DA D_1 or DA D_2 receptor antagonists block the discriminative stimulus effects of bupropion (173), whereas pretreatment with serotonergic or α_1 -noradrenergic receptor antagonists do not (11,174).

Despite the findings discussed above, the role of DA systems in mediating the rewarding and/or reinforcing properties of bupropion is controversial. On one hand, acute bupropion pretreatment decreases intracranial self-stimulation reinforcement thresholds (28), suggesting that bupropion enhances the reinforcing effect of intracranial self-stimulation. Self-administration of bupropion has also been shown to upregulate DAT (172). On the other hand, chronic bupropion pretreatment fails to alter intracranial self-stimulation reinforcement thresholds (108). Moreover, bupropion-induced conditioned place preference is not blocked by pretreatment with DA D_2 -receptor antagonists (127). The reason for the discrepancies between studies is unclear and further research is needed to determine more conclusively the biochemical mechanisms mediating the rewarding effects of bupropion.

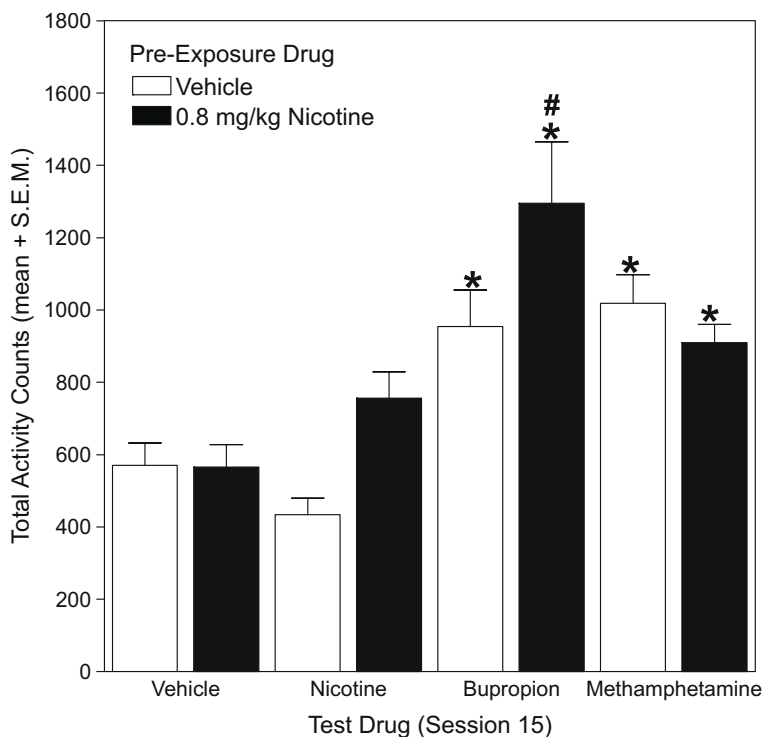


Fig. 2. Pre-exposure to nicotine enhances the locomotor stimulant effect of bupropion, but not methamphetamine. Male Sprague–Dawley rats were pre-exposed to injections of nicotine (0.8 mg/kg s.c.) or vehicle (physiological saline) for 14 consecutive sessions (i.e., nicotine sensitization training). On Sessions 1 and 14, the rats received nicotine or vehicle immediately before placement in the locomotor chambers. On the intervening sessions, the rats received nicotine or vehicle in their home cages. Session 15 (test) occurred 24 h after the last nicotine sensitization session. On this session (results shown above), previously nicotine-exposed or vehicle-exposed rats received a s.c. injection of vehicle, nicotine (0.2 mg/kg), bupropion (10 mg/kg), or methamphetamine (0.5 mg/kg). Asterisks (*) and pound (#) symbols denote a significant difference from Vehicle and Vehicle plus Bupropion groups, respectively. $p < 0.05$. $N = 6$ rats/group.

Effects on Nicotine-induced Behaviors

Effects on unconditioned nicotine-controlled behaviors

Using various behavioral tests, Slemmer et al., (160) determined the ability of bupropion to attenuate various nicotine-controlled behaviors. Bupropion dose-dependently attenuated nicotine-induced antinociception, assessed using tail-flick and hot plate assays. Bupropion also attenuated nicotine-induced hypoactivity, hypothermia and convulsions. Bupropion ameliorated anxiogenic effects of high nicotine doses in the elevated plus maze test in mice (18). Despite the ability of bupropion to antagonize various nicotine-controlled behaviors when these drugs are given in combination, other work shows that repeated prior administration of nicotine potentiates the locomotor stimulant effect of subsequently administered bupropion (Fig. 2; 195), but not methamphetamine (Fig. 2). These results suggest that a critical variable determining the effect of bupropion is whether it is given in combination with nicotine or following repeated nicotine exposure.

Effects on the discriminative stimulus properties of nicotine

Drug discrimination studies, utilizing operant conditioning paradigms, show that bupropion substitutes fully for nicotine in rats (193,200), suggesting that bupropion and nicotine share discriminative stimulus properties. However, other studies failed to show that bupropion substitutes for nicotine (158). A low bupropion dose (3 mg/kg, s.c.) when administered alone fails to substitute for nicotine, but shifts the nicotine dose-response curve to the left when co-administered with nicotine (200). This latter result suggests that low doses of bupropion enhance the discriminative stimulus properties of nicotine. Drug discrimination studies, utilizing classical conditioning paradigms, show that bupropion substitutes completely for nicotine when nicotine serves as a feature-negative stimulus (10), while only substituting partially for nicotine when nicotine serves as an excitatory conditioned stimulus (9).

Effects on nicotine reward

Acute bupropion pretreatment has been reported to produce a biphasic dose-response curve, with low doses of bupropion increasing i.v. nicotine self-administration, and high doses decreasing the number of nicotine infusions self-administered in rats (139,158; however, see 15,61). Shoaib et al. (158) have reported that chronic pretreatment with low doses of bupropion increase nicotine self-administration in rats. While increases in nicotine self-administration may represent either an increase or a decrease in reinforcing efficacy (see 199), these preclinical results parallel the finding that bupropion and amphetamine pretreatment increases smoking behavior in humans not attempting to quit (25, 204). In another study, pretreatment with a high dose of bupropion decreased nicotine self-administration in rats, and this effect was enhanced with repeated bupropion pretreatment (138). In another line of work, Epping-Jordan et al. (44) found that bupropion reverses the nicotine-induced decrease in brain stimulation reward threshold, suggesting that bupropion may attenuate the reinforcing effect of nicotine.

Research has examined the ability of bupropion to alter nicotine conditioned place preference. The conditioned place preference model is thought to measure conditioned drug reward, which contrasts with the primary reinforcing effect measured by the drug self-administration model (5). In one recent study from our laboratory, sub-threshold doses of nicotine (0.2 mg/kg, s.c.) and bupropion (5 mg/kg, s.c.), neither of which produced conditioned place preference alone, produced conditioned place preference when co-administered (Fig. 3). The observation that bupropion facilitates acquisition of nicotine conditioned place preference suggests that in contrast to the primary reinforcing effect measured by brain stimulation thresholds, bupropion may enhance nicotine conditioned reward. Conversely, nicotine may be enhancing bupropion conditioned reward.

Effects on nicotine withdrawal

Human and non-human animal studies have shown that acute or chronic bupropion pretreatment attenuates the expression of somatic (28,103) and affective (28,77,85,103, 157) symptoms associated with nicotine withdrawal in nicotine-dependent subjects. For example, bupropion attenuates the increase in brain stimulation reward threshold occurring during nicotine withdrawal in nicotine-dependent rats (28). Furthermore, chronic bupropion pretreatment attenuates the acquisition of mecamylamine-precipitated conditioned place aversion in nicotine-dependent rats (103). The effects of bupropion on

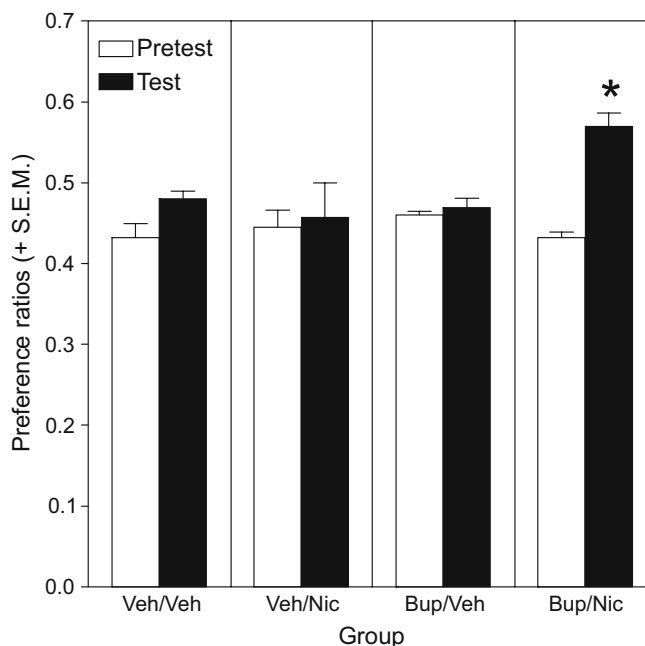


Fig. 3. Bupropion potentiates the ability of nicotine to produce conditioned place preference. Rats received a s.c. injection of vehicle (physiological saline) and their initial compartment preference (pretest) was determined using a three-compartment conditioned place preference apparatus. 24 h later, the conditioning phase began. Rats received an injection of either bupropion (Bup, 5 mg/kg) or vehicle (Veh, physiological saline) 15 min prior to a second s.c. injection either of nicotine (Nic, 0.2 mg/kg) or vehicle (physiological saline) and were placed in the non-preferred compartment for a 10-min period during 4 alternating sessions (drug sessions). During the intervening sessions, rats received a s.c. injection of vehicle followed 15 min later by a second s.c. injection of vehicle and were placed in the preferred compartment for a 10-min period (non-drug sessions). 24 h after the last conditioning session, rats received an injection of vehicle and were placed in the middle compartment and permitted to explore all compartments for a 10-min period (test). Evidence for conditioned place preference was demonstrated by significantly more positive preference ratios on the test session relative to the pretest session. The asterisk (*) denotes a significant within-group pretest-test difference, $p < 0.05$. $N = 7-8$ rats/group.

craving following a period of withdrawal is unclear presently, as bupropion has been reported to either reduce craving (13,77,85) or to have no effect on craving (25,157) in human smokers. On balance, these studies suggest that bupropion attenuates some of the aversive effects of nicotine withdrawal.

Effects on nicotine avoidance

Using a two-bottle choice task, the ability of bupropion to attenuate nicotine-conditioned taste avoidance has been investigated (158). Rats were injected with either bupropion or saline and 15 min later were presented either one of two solutions of saccharin or saline to drink for a 15-min period. Immediately following the second 15-min drinking period, rats received an injection of either nicotine or saline and then were returned to their home cages. Bupropion did not attenuate the acquisition of nicotine-conditioned taste avoidance, suggesting that bupropion does not antagonize the avoidance properties of nicotine. However, one caveat of the latter study by Shoaib et al. (158) is that bupropion was

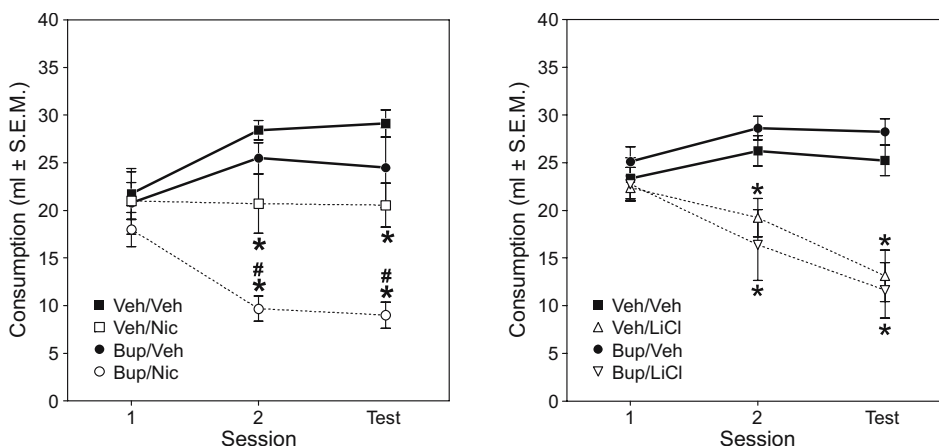


Fig. 4. Bupropion potentiates conditioned taste avoidance produced by nicotine, but not by lithium chloride. Following 15 min consumption of a 0.6% sodium chloride solution, rats received a s.c. injection of either bupropion (Bup, 5 mg/kg) or vehicle (Veh, physiological saline) followed immediately by a second s.c. injection of either nicotine (Nic, 0.4 mg/kg; Fig. 3, left panel), lithium chloride (LiCl, 0.19 M; Fig. 3, right panel) or vehicle (Veh, physiological saline) during conditioned taste avoidance training (Sessions 1 and 2 of the conditioning phase) and were tested 120 h later. Asterisks (*) and pound (#) symbols denote significant differences from Veh/Veh and Veh/Nic Groups, respectively, during the indicated sessions. $p < 0.05$. $N = 6-8$ rats/group.

administered 30 min prior to nicotine during the conditioning sessions. In an earlier study (159), these investigators showed that administration of a nAChR antagonist, dihydro- β -erythroidine, 30 min prior to nicotine, also failed to attenuate the acquisition of nicotine-conditioned taste avoidance. In contrast, co-administration of dihydro- β -erythroidine with nicotine effectively attenuated the acquisition of nicotine-conditioned taste avoidance. These results suggest that the temporal arrangement between antagonist and agonist is an important variable in evaluating the ability of bupropion to attenuate nicotine-conditioned taste avoidance.

To evaluate this issue further, we co-administered bupropion and nicotine, following a 15-min drinking session of a sodium chloride solution, and found that bupropion facilitates the acquisition of nicotine-conditioned taste avoidance (Fig. 4). Moreover, the bupropion-induced facilitation of the acquisition of conditioned taste avoidance was specific to nicotine, as bupropion failed to alter lithium chloride-conditioned taste avoidance (Fig. 4). The nature of the bupropion-induced facilitation of the acquisition of nicotine-conditioned taste avoidance observed when the drugs were co-administered is unclear. On one hand, avoidance of gustatory cues associated with nicotine has been suggested to stem from aversive properties of nicotine (93). However, more recent evidence indicates that avoidance of gustatory cues associated with drugs of abuse such as nicotine does not elicit aversive reactions like those obtained following lithium chloride (129), but instead may reflect an anticipatory contrast effect related to the rewarding effect of the drug (67). If this latter interpretation is correct, then bupropion may enhance the rewarding properties of nicotine, consistent with the conclusions drawn from the study showing that bupropion facilitates the acquisition of nicotine conditioned place preference.

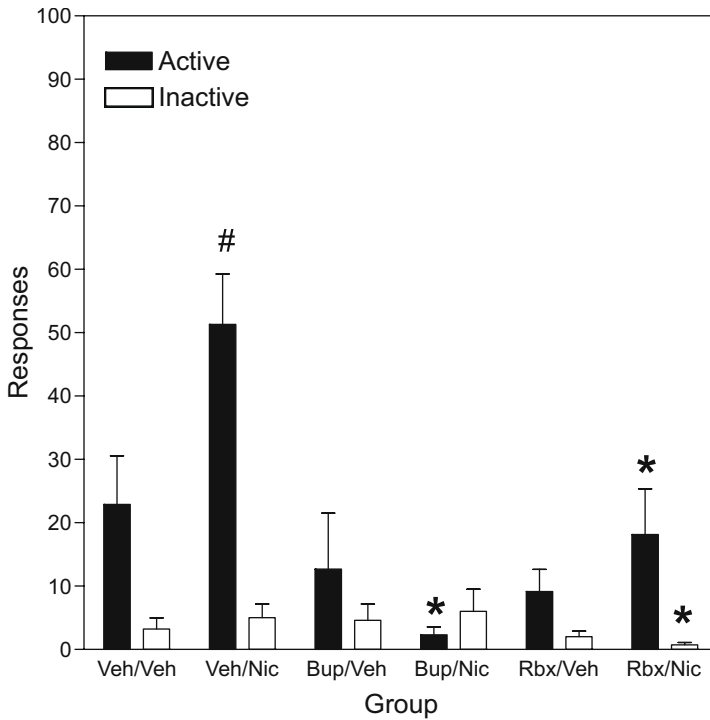


Fig. 5. Bupropion and reboxetine attenuate nicotine-induced reinstatement following extinction. Rats self-administered nicotine (0.02 mg/kg/infusion, i.v.) on a two lever (active vs. inactive), fixed-ratio 5 schedule of reinforcement (acquisition). Following the acquisition phase, rats self-administered saline on a fixed-ratio 5 schedule of reinforcement (extinction). On the reinstatement test session following extinction, rats received an injection (s.c.) of either vehicle (Veh; phosphate buffered saline), bupropion (Bup; 70 mg/kg) or reboxetine (Rbx; 5.6 mg/kg) followed 15 min later by a second s.c. injection of either vehicle (Veh; a physiological saline solution) or nicotine (Nic; 0.15 mg/kg) prior to a 60-min session in which rats self-administered physiological saline. Pound symbol (#) denotes a significant difference in responding compared to Veh/Veh group. Asterisks (*) denote a significant difference in responding from Veh/Nic group. $p < 0.05$. **Note:** Dramatic individual differences were observed in rats in the Bup/Veh and Bup/Nic groups, with some rats showing an increase in responding and other rats showing no change (results not shown). Due to this variability, only rats that did not show a bupropion-induced increase in responding on the reinstatement test are represented in this analysis.

Effects on nicotine reinstatement

In the reinstatement model, various stimuli (drug and non-drug) are assessed for their ability to reactivate behavior following a period of extinction, which may be relevant to drug relapse (155). A preliminary study in our laboratory found that a high dose of bupropion (70 mg/kg, s.c.) attenuates nicotine-induced reinstatement; a similar finding was obtained using the selective NET inhibitor, reboxetine (Fig. 5). This preclinical finding is consistent with studies reporting that bupropion promotes smoking abstinence in humans (13,71,77,85) and attenuates the smoking-elicited “buzz” once smoking is reinitiated (25). Furthermore, Brody et al. (13) found that chronic bupropion treatment reduces overall levels of craving and smoking-related cue-induced craving, suggesting that bupropion attenuates the conditioned reinforcing properties of nicotine during periods of diminished

tobacco use. Collectively, these results suggest that bupropion attenuates the pharmacological and conditioned reinforcing properties of nicotine during relapse to smoking.

Effects of bupropion metabolites on nicotine controlled behaviors

The role of bupropion metabolites in mediating the effects of bupropion on nicotine-controlled behaviors also cannot be discounted. Discriminative stimulus effects of bupropion metabolites were examined using a drug discrimination procedure in which rats were trained to discriminate either nicotine or amphetamine from vehicle (14). Both isomers of threohydrobupropion partially substituted for both nicotine and amphetamine, suggesting that threohydrobupropion may contribute to the nicotine-like actions of bupropion. *R,R*-Hydroxybupropion, the major bupropion metabolite in humans (167), produced vehicle appropriate responding in nicotine-trained animals; however, when administered in combination with nicotine, *R,R*-hydroxybupropion dose-dependently attenuated the effect of nicotine by as much as 50% (14). Although the major metabolite in humans, only low levels of *R,R*-hydroxybupropion are found in rat plasma following bupropion administration (189). These results suggest that *R,R*-hydroxybupropion does not contribute to the nicotine-like effect of bupropion, but may contribute to the attenuation of the discriminative stimulus properties of nicotine in rats. In contrast, *S,S*-hydroxybupropion, the minor hydroxybupropion metabolite, partially substitutes for nicotine (14), suggesting that this metabolite may contribute to the nicotine-like actions of bupropion. Although a minor metabolite, *S,S*-hydroxybupropion generalizes completely to amphetamine, and with a similar potency as bupropion ($ED_{50} = 4.4$ and 5.4 mg/kg, *s.c.*, respectively). As such, *S,S*-hydroxybupropion may in part be responsible for the stimulant properties of bupropion, particularly if this metabolite accumulates with chronic bupropion dosing.

Neurochemical mechanisms mediating effects of bupropion on nicotine-controlled behaviors

The neurochemical mechanisms mediating the effects of bupropion on nicotine-controlled behaviors have not been elucidated completely. Slemmer et al. (160) suggested that the ability of bupropion to antagonize the unconditioned behavioral effects of nicotine (antinociception, hypoactivity, hypothermia and convulsions) are mediated by nAChRs (e.g., the $\alpha 4\beta 2^*$ nAChR subtype). However, the ability of bupropion to alter other behavioral effects of nicotine, most likely involves other neurochemical mechanisms. Mecamylamine, the noncompetitive and nonselective nAChR antagonist, fails to block the ability of bupropion to substitute for nicotine in drug discrimination studies (193,200), indicating that the discriminative stimulus properties of bupropion are not nAChR mediated. Indeed, the strongest evidence suggests that the discriminative stimulus properties of bupropion are mediated by DA systems (87,173).

The ability of bupropion to facilitate nicotine self-administration (139,158), conditioned place preference (Fig. 3), and conditioned taste avoidance (Fig. 4) appear not to be mediated solely by nAChRs, as classic nAChR antagonists only attenuate these effects of nicotine (57,93,137,187). Rauhut et al. (139) suggested that facilitation of both DA and NE system function may underlie the bupropion-induced increase in nicotine self-administration, based on results that methamphetamine, but not apomorphine or reboxetine, increase nicotine self-administration. Malin et al. (103) also suggested that catecholaminergic mechanisms might account for the ability of acute bupropion pretreatment to antagonize the somatic signs of nicotine withdrawal in rats. Thus, the ability of bupropion

to alter the behavioral effects of nicotine involves both nicotinic and catecholaminergic mechanisms.

CLINICAL STUDIES

Bupropion was introduced clinically in 1985 as an antidepressant medication. Dr. Linda Ferry, an astute clinician, noted that depressed patients treated with bupropion spontaneously reduced or quit using tobacco. An initial controlled clinical trial in non-depressed individuals supported the efficacy of bupropion over placebo for smoking cessation (52). This initial research was pivotal with respect to the introduction of bupropion as the first non-nicotine tobacco use cessation product in 1997. Although first introduced as an immediate release (IR) formulation, the incidence of seizures prompted the switch to slow release formulations (SR or XR). Also, clinical trials have been performed to test bupropion as a candidate treatment for psychostimulant drug abuse, ADHD and obesity.

Effects of Bupropion as an Antidepressant

Early reports demonstrated that bupropion administered orally has antidepressant efficacy without reported abuse liability, and its efficacy is comparable to that of classical tricyclic antidepressants, such as imipramine or amitriptyline (66,126,197). In these studies, comparison with the tricyclic antidepressants revealed that bupropion was better tolerated, and, unlike the tricyclic antidepressants, bupropion did not increase uric acid or cholesterol levels and was not associated with weight gain. Furthermore, in contrast with amitriptyline, bupropion did not increase heart rate, alter blood pressure or produce orthostatic hypotension, in depressed adult outpatients, elderly patients or patients with cardiovascular disease (190). Subsequently, a large number of controlled and large-scale studies confirmed that bupropion has antidepressant efficacy. In a multi-center study involving random assignment of 362 depressed patients, Reimherr et al. (141) assessed the effect of bupropion (150 mg, once or twice daily, orally) compared to placebo for its ability to alter scores on the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions (CGI) scales. Bupropion was shown to be effective in reducing depressive symptoms within 8 weeks after initiation of treatment. Bupropion was well tolerated, with no serious side effects or clinically meaningful changes in vital signs, although a dose-dependent reduction in body weight was noted. The efficacy of bupropion does not appear to be specific to “typical” unipolar depression, as evidence suggests that patients with atypical and bipolar depression also benefited (65).

A number of studies compared directly the effects of bupropion to those of SSRIs, such as fluoxetine. In contrast to SSRIs, bupropion has greater affinity for inhibiting catecholamine transporters than serotonin transporters, although the exact mechanism of action is not known (see above). A recent review of studies published from 1980–2005 revealed no reliable difference in efficacy among the various second-generation antidepressants, including SSRIs and bupropion (69). In a double-blind direct comparison between bupropion and fluoxetine, Feighner et al. (48) found no reliable differences between efficacy of bupropion and fluoxetine based on scores from either the HAM-D or CGI scales. Drop out rates and safety profiles also did not differ between bupropion and fluoxetine. A recent report suggests that bupropion, while sharing many side effects with SSRIs, has relatively

lower incidence of several side effects, including nausea, diarrhea, somnolence and sexual dysfunction (122). In addition, in contrast to many SSRIs, bupropion does not suppress rapid eye movement sleep (128). Despite these potential advantages, a survey of office-based physicians in the United States indicated that bupropion prescriptions accounted for only 9% of all medications used to treat depression (163), which was well below that for SSRIs, perhaps suggesting a general belief that bupropion has limited benefits in major depression. A recent review of the literature on combining bupropion with SSRIs or NE reuptake inhibitors suggests that, although not an approved indication, the drug combination can augment antidepressant response and is generally well tolerated (205).

In terms of the side effect profile compared to SSRIs, recent evidence suggests that bupropion may produce greater changes in cardiovascular and autonomic function following application of mental and physical stressors (164), which may limit its use among patients with coronary heart disease. Additionally, there may be limitations to the clinical use of bupropion during some portions of the life span. Pregnancy and postpartum periods are generally considered to be high risk times for depressive episodes in women. Since information about the teratogenic risks for bupropion are incomplete (58), use during this period may be problematic, although there is also risk associated with untreated depression. In one recent report, women with postpartum depression showed a significant bupropion-induced reduction in depressive symptoms on the HAM-D (124), and the drug was well tolerated in these patients. However, a clinical issue related to the treatment of postpartum depression is the excretion of bupropion in breast milk. Both bupropion and at least two of its metabolites can be measured in breast milk following low dose oral administration, and the accumulation of bupropion in breast milk with repeated dosing can exceed the concentration observed in maternal plasma (12). Pharmacokinetic issues also require consideration when bupropion is administered to elderly patients. In this population, the apparent half-life of bupropion and its metabolites can be prolonged (169). Nonetheless, widespread incidence of geriatric depression along with evidence for antidepressant efficacy with bupropion in this population (171) makes it a useful alternative to SSRIs.

Effects of Bupropion in Tobacco Use Cessation

Clinical studies reveal a correlation between the incidence of tobacco use and mood disorders (60,135). Individuals with major depression are more likely to be tobacco smokers, to become more dependent on nicotine and to experience difficulty quitting due to greater withdrawal symptoms upon cessation (26,27). Furthermore, smokers undergoing cessation experience symptoms of depression, and these symptoms occur more frequently among smokers with a history of major depression (27).

Two reviews on bupropion as a treatment for smoking cessation have appeared recently in the literature (115,186). A number of double-blind placebo-controlled studies show that chronic bupropion is an effective, non-nicotine, tobacco smoking cessation and relapse prevention agent (31,63,71,77,85,175). Bupropion-induced amelioration of withdrawal symptoms associated with smoking cessation may be responsible, at least in part, for the decrease in smoking behavior (85,97,157). The ability of bupropion to reduce craving also contributes to its efficacy in relapse prevention (31,43,175). An advantage of bupropion treatment for smoking cessation is that the typical weight gain associated with smoking cessation is attenuated, and attenuation of weight gain can persist with long-term treat-

ment (71,74,77,131,175). Compared to placebo control, bupropion doubles cessation rates (53), and similar efficacy has been reported among depressed and non-depressed smokers (148), as well as among men and women (150). Smokers are often provided with a combination of smoking cessation treatments, such as bupropion and nicotine together with behavioral treatment. Recently, recurrent-event models have determined the effect of bupropion on occurrence of lapses and recoveries from lapse in 1070 subjects across two similar double-blind randomized clinical trials of bupropion versus placebo (194). Analyses used discrete time-varying covariates between treatment and follow-up phases of the studies. Bupropion was associated with slower lapse during treatment for both sexes, and was associated with faster recovery following a lapse in females, but not in males.

Recently, the efficacy of bupropion has been compared to a new non-nicotine smoking cessation agent, varenicline (64,86). In a randomized double-blind parallel-group, placebo-controlled phase 3 clinical trial conducted at 19 US Centers from 2003–2005, bupropion SR was shown to be less efficacious than varenicline (29.5 vs. 44.0% abstinence rates at weeks 9–12; and 16.1 vs. 21.9% at weeks 9–52). Varenicline is an analog of cytisine and is suggested to be a partial agonist at $\alpha 4\beta 2$ nAChRs. Since varenicline and bupropion appear to have somewhat different mechanisms of action, further improvements in abstinence rates may be realized by employing these drugs in combination.

Recent evidence supports a role for genetic factors contributing to individual differences observed in responsiveness to bupropion with respect to abstinence and time to relapse (96,98). Specifically, a higher quit rate was observed in response to bupropion in smokers homozygous for the Ins C allele of the DRD2 gene compared to those carrying the Del C allele in an open label, 6 month randomized trial. In contrast, individuals carrying the Del C allele were more responsive to nicotine replacement. These results suggest that efficacy for bupropion in smoking cessation may be increased if pharmacogenetic variables are taken into account.

The issue of abuse liability for bupropion as a smoking cessation agent is important, because tobacco dependence is associated with increased risk for dependence on other drugs of abuse, suggesting that tobacco users are more likely to be addiction prone. Importantly, a recent review of bupropion as a tobacco smoking cessation agent revealed no evidence for abuse liability (143). Nonetheless, there have been case reports of bupropion insufflation in adolescents (91,109), indicating that some caution may be needed among adolescents diagnosed with substance use disorders.

Paradoxically, while bupropion is efficacious as a smoking cessation pharmacotherapy, acute exposure to bupropion in a controlled laboratory setting has been reported to increase smoking behavior (25). In this study, smokers who were not attempting to quit were administered bupropion (150 or 300 mg, orally) following overnight abstinence from smoking. When bupropion was administered on the next day and subjects were allowed to smoke, bupropion increased the number of cigarettes smoked under ad libitum conditions. Although the reason for this increase in smoking behavior remains to be elucidated, these results are consistent with the finding that stimulants such as amphetamine also increase smoking behavior under similar experimental conditions (25), suggesting that bupropion may produce stimulant-like increases in the rate of ongoing behavior. Regardless of the mechanism, these results are consistent with preclinical evidence discussed earlier showing that bupropion increases nicotine self-administration in rats (139).

Effect of Bupropion in Substance Abuse

Recent results suggest that bupropion may have potential as a treatment for psychostimulant abuse. Several reviews discussing the use of antidepressants for the treatment of substance abuse have recently appeared in the literature (125,176,182). Results from a multi-site, placebo-controlled randomized double-blind clinical trial comparing bupropion (300 mg/day, orally) to placebo for the treatment of cocaine abuse in 149 methadone-maintained subjects did not reveal robust effects of bupropion as a treatment for cocaine abuse, although exploratory analyses suggested that patients with greater levels of depression may have obtained benefit from bupropion (105). A more recent study (133) determined the efficacy of bupropion plus contingency management for reducing cocaine in 106 methadone-maintained individuals comorbid for opioid and cocaine dependence in a 25-week, placebo-controlled, randomized, double-blind trial. Results showed that cocaine-positive urines decreased in the group receiving bupropion plus contingency management relative to baseline (week 3 results, within-subject comparison). Contingency management is based on the idea that reinforcement of preferred behaviors increases the likelihood of their repetition, i.e., participants receive increasing amounts of money or purchase vouchers for providing successively greater numbers of negative urine samples. There was no significant improvement in cessation of cocaine use in either the voucher control plus bupropion group or the voucher control plus placebo group; the voucher control condition provided money irrespective of positive or negative urine samples. The results suggest that pairing contingency management with bupropion for the treatment of cocaine abuse may significantly improve treatment outcome relative to either bupropion or behavioral intervention alone (133). Thus, bupropion was efficacious only within the context of the behavioral intervention.

In another line of work, bupropion has been shown to reduce methamphetamine-induced neurotoxicity in DA systems (104,107,153,183,196) and to decrease amphetamine self-administration in rats (139). In an FDA-approved human laboratory study, the ability of bupropion to reduce methamphetamine abuse was determined in 26 non-treatment seeking subjects who used methamphetamine twice-weekly in the 4–6 weeks prior to screening (120). Low doses of both bupropion XL (75 mg, orally) and methamphetamine (0, 15, and 30 mg, i.v.) were administered in this study to avoid the onset of seizures. Subjects received a baseline series of methamphetamine doses, and a second identical series of methamphetamine doses, were administered 6 days later after initiation of twice-daily bupropion or placebo (assigned randomly). Bupropion was found to reduce acute methamphetamine-induced subjective effects and cue-induced cravings, thus providing rationale for the evaluation of bupropion in the treatment of methamphetamine dependence.

Effects of Bupropion in ADHD

Some patients with ADHD do not experience symptom relief from currently available first-line treatments (i.e., amphetamine and methylphenidate) or cannot tolerate effective stimulant doses. Bupropion XL (up to 450 mg/day, orally once daily for 8 weeks) has been evaluated for efficacy in treating ADHD in a multi-site, randomized, placebo-controlled trial employing 162 adults with ADHD (192). Bupropion was effective, with bupropion responders (53%) significantly exceeding placebo responders (31%).

Effects of Bupropion in Eating Disorders

Not long after the introduction of bupropion, it was used as a treatment for individuals with bulimia, but was voluntarily withdrawn due to an increased risk of seizures (75). A subsequent study demonstrated no clinical correlation between bulimia and seizure risk (84). Nevertheless, bupropion is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa due to the higher incidence of seizures in patients treated for bulimia with bupropion and due to the ability of bupropion to decrease food consumption in animal studies (203) and to decrease appetite in humans (20,30,188). As far as the potential for use of bupropion as an appetite suppressant, treatment with bupropion SR (300 mg/day, orally for 26 weeks) was reported to produce weight loss (5% of body weight) compared to placebo (2% of body weight) in a randomized, double-blind, controlled clinical study employing 193 obese adults not meeting criteria for major depression (80).

Side Effects, Clinical Safety, and Overdose

During the nearly 30 years since the introduction of bupropion, side effects associated with bupropion use have been well characterized. Common adverse effects include dry mouth, nausea, constipation, headache, agitation, insomnia, tremor and skin rash. Evidence from two large clinical trials showed relatively low rates (2–11%) of adverse effects including restlessness, agitation, anxiety and insomnia leading to discontinuation of drug use (77,85). Incidence of insomnia was greater (~30%) in smoking-cessation trials, although symptoms were sufficiently severe to discontinue use in less than 1% of patients. Weight loss of more than 5 pounds occurred in 28% of patients. Other reported side effects include vivid dreams and changes in attention, memory and perception (6). Neuropsychiatric side effects including visual hallucinations and delusions (1), vertigo (170), and catatonia (79) have been reported; however, the latter effects are not common. There have been few reported cases of drug dependence and withdrawal associated with bupropion.

Adults and children with major depression may experience exacerbation of depression and the emergence of suicidal ideation and behavior in the absence or presence of treatment with antidepressant medications. However, concern has been expressed that antidepressants may worsen depression and the emergence of suicidal thinking and behavior in certain patients, specifically in pediatric patients and adolescents with major depression and adults with co-morbid psychiatric disorders (40). In mid-2005, the FDA issued a warning regarding the ability of bupropion to increase the incidence of suicidal thoughts and actions in 1 out of 50 people 18 years of age or younger (47). Thus, all children treated with antidepressants and adults with co-morbid psychiatric disorders should be closely observed for clinical worsening, unusual changes in behavior (anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania), and suicidality, especially during initial months of treatment or upon adjustment in dose. Medications should be changed or discontinued in patients with worsening depression, suicidal thoughts or unusual severe behaviors that were not a component of presenting symptoms. In general, suicide rates for individuals taking SSRIs and other newer generation antidepressants such as bupropion are lower than those in the general population (59).

Bupropion lowers seizure threshold and increases the likelihood of seizures. The underlying mechanism responsible for this untoward effect is, however, not known. Thus, bupropion is contraindicated in individuals with a history of seizures or epilepsy or in patients taking other medications (e.g., sedatives, antipsychotics, theophylline, systemic steroids) or drugs of abuse (e.g., addictions to alcohol, opiates, cocaine or stimulants) which lower seizure threshold (145). Other predisposing factors increasing the risk of seizures include head trauma, CNS tumor and severe hepatic cirrhosis. Bupropion is also contraindicated in patients treated with any other form of bupropion or any medication containing bupropion because the incidence of seizures is dose-dependent. The risk of seizure is reported to be less than 1% in clinical trials with bupropion (34,42,181) vs. 0.07–0.09% in the general population (114). However, recent retrospective studies indicate that nearly 1% of patients experience seizures with commonly prescribed doses of bupropion (132, 156). Studies using animal models suggest that clonazepam, but not phenytoin, carbamazepine, lamotrigine or tiagabine, may be useful to prevent seizures resulting from bupropion overdose; however, clinical testing is needed to verify the utility of clonazepam in this regard (179).

As noted earlier, bupropion is contraindicated in patients with current or prior diagnosis of bulimia or anorexia nervosa (20,30,188,203). Bupropion is also contraindicated in patients currently treated with monoamine oxidase inhibitors due to concerns of precipitating a hypertensive crisis. Recommendations are that at least 14 days intervene between discontinuation of monoamine oxidase inhibitors and initiation of bupropion treatment. However, this drug combination has been used cautiously in psychiatry after weighing the danger of hypertensive crisis vs. the risk of inadequate treatment, notably without documented reports of hypertensive crisis or fatalities (49). There are also contraindications for patients showing anaphylactic reactions or allergic response to bupropion, including dyspnea, angioedema, urticaria and pruritus, which have been reported to occur in 1 to 3 cases per 1000 patients. Delayed hypersensitivity to bupropion is indicated by symptoms of arthralgia, myalgia, and fever with rash, resembling serum sickness.

In preclinical studies, the toxicological profile of bupropion was determined using exaggerated doses (overdose conditions) in rats, mice, rabbits and dogs (178). In these studies, mild reversible hepatotoxicity and anemia occurred in dogs with chronic dosing. Lifetime administration in rats resulted in hepatocellular hypertrophy and focal hepatic hyperplasia, and an increase in liver weight related to hepatic enzyme induction in rats and dogs (178). In retrospective overdose studies and case reports ranging from accidental ingestion by children and adolescents to intentional overdose in adults, the most common symptom was single or recurrent clonic-tonic seizures. Seizure incidence was dose-dependent and occurred most commonly once or twice at 24 to 72 h following overdose and lasted ~30 sec (3,4,7,162). Time to seizure presentation following overdose was correlated to the bupropion formulation. Generally, individuals who overdosed on the SR formulation continued to have seizures for a longer time, while those on IR formulation had seizures ending ~5 h after drug ingestion. One report described a 27 year-old woman who ingested 8.9 g of bupropion SR alone and developed seizures after 4 h, with the last seizure occurring 10 h after overdose (82). In another case, an individual co-ingested 4.2 g of bupropion SR and 105 mg of midazolam; although seizures were not experienced, paranoid delusions developed (185). Due to the co-administration of bupropion and midazolam, the contribution of bupropion to this effect is not clear. Seizures following overdose of bupropion IR most commonly occurred between 2 and 5 h, and occurred in 37% of cases (4).

Additional reported effects included agitation in 32% as well as tremors and hallucination in 21% of cases. Seizure incidence was increased to 42% in individuals co-ingesting ethanol with bupropion.

The cardiotoxicity of bupropion was prospectively investigated in 59 cases of deliberate self-poisoning (78). Tachycardia and QTc prolongation occurred in 76% of these patients and 47% experienced hypertension. These investigators indicated that QTc prolongation may not be the result of intrinsic cardiotoxicity, but an overcorrection due to tachycardia. Reported bupropion overdoses have been rarely fatal, even when the quantity consumed reached 13.5 g in an adult (177). However, one death due to cardiac arrest was reported in a 26 year-old man who ingested 23 g of bupropion, and seizures were recurrent and persisted until his death 4 days after seeking medical treatment (70). There are no reported deaths by bupropion overdose in children or infants.

In summary, bupropion appears to have a low risk of side effects associated with its prescribed dose and very few reports of fatal overdoses involving bupropion-alone exposure exist in the literature. Work remains to be done on the toxicology associated with bupropion metabolites and their potential roles in both observed benefits and adverse effects of the drug.

PHARMACOKINETICS

Absorption, Distribution, Protein Binding, Metabolism, and Excretion

The pharmacokinetics of bupropion has been reviewed recently (81). Bupropion pharmacokinetics was evaluated in early studies using nonhuman animals and healthy male and female human subjects following administration of single oral doses of 50, 100, and 200 mg (54,151). Generally, bupropion appears rapidly in plasma, is completely absorbed and widely distributed in tissues. Bupropion is metabolized extensively prior to excretion, such that less than 10% of the dose is found as the parent drug in urine or feces. Also, no differences in pharmacokinetic parameters were found between men and women. The pharmacokinetics of bupropion was reported to be linear across the 50–200 mg dose range. Drug plasma concentration-time data from the human subjects were fitted to a two-compartment open model of drug disposition. Following oral bupropion administration, peak plasma concentrations appeared at ~2 h, and mean distribution $t_{1/2}$ was 1.2 to 1.4 h. The elimination $t_{1/2}$ was between 10–20 h. Furthermore, bupropion is extensively bound (84%) to human plasma protein over a wide concentration range.

Although 2- to 5-fold less potent than bupropion, three metabolites of bupropion have been reported to be pharmacologically active, including hydroxybupropion [3,5,5-trimethyl-2-hydroxy-2-(3-chlorophenyl)morpholine] formed from hydroxylation of the tert-butyl group of bupropion, and two amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion [(*R*,R**)-2-(tert-butylamino)-1-(3-chlorophenyl)propranol and (+)-(*R*,S**)-2-(tert-butylamino)-1-(3-chlorophenyl)propranol, respectively] formed from carbonyl reductase, a non-microsomal enzyme (151). Additional metabolites of bupropion, m-chlorobenzoic acid and m-chlorohippuric acid and their conjugates, formed from the side chain oxidation are pharmacologically inactive and rapidly excreted. Bupropion is a substrate for and extensively metabolized by cytochrome (CYP) 4502B6 to form the hydroxybupropion metabolite (46,73). Conversion of bupropion to hydroxybupropion is

being used currently as a highly specific probe to assess CYP 4502B6 activity (99,100, 180). These bupropion metabolites were reported to have $t_{1/2}$ values either similar to the parent drug or 2- to 3-fold longer than the parent drug depending on the bupropion formulation. They accumulate in adult human plasma at concentrations at least 20-times higher than that of bupropion following steady state dosing (21,24,76,95).

While there have been some contradictory findings regarding the association between antidepressant response and plasma levels of bupropion metabolites, Golden et al. (62) reported that hydroxybupropion levels were higher in non-responders relative to responders. Another study reported recently that children (11–17 years of age) metabolize bupropion faster to the active metabolites such that 20–80% higher plasma concentrations were observed relative to adults (35,36). These higher metabolite levels were associated with antidepressant responsiveness in these young patients. Another study showed that active metabolites of bupropion accumulate in plasma from patients with renal failure (198). Together, these studies provide further impetus for the comprehensive investigation of the clinical pharmacology of the active metabolites.

The influence of pharmacogenomics on drug metabolism has also been demonstrated. CYP 2D6 is a highly polymorphic enzyme regulating the metabolism of a wide variety of drugs and endogenous substrates (168). In a study by Pollock et al. (134), individuals having the poor CYP 2D6 metabolizer phenotype accumulated hydroxybupropion in plasma; and the accumulated hydroxybupropion was hypothesized to contribute to bupropion toxicity. However, studies to test this hypothesis were not conducted. Bupropion has also been shown to inhibit CYP 2D6, converting extensive CYP 2D6 metabolizers to the poor metabolizer phenotype (68,73,92), although the mechanism mediating this effect is unclear. Inhibition of CYP 2D6 may be of clinical significance, as also indicated by studies using animal models (184). Clinically relevant drug interactions may occur in individuals co-administered pharmaceuticals which are metabolized by CYP 2B6 or CYP 2D6, as bupropion administration results in reduced metabolism, an increased $t_{1/2}$, and potentially altered distribution to brain.

Bupropion and its metabolites are distributed via breast milk and have been linked to seizures in infants in two cases (19). However, one study examining metabolites present in breast milk of a woman taking bupropion (300 mg/d, orally) revealed that the metabolites were transmitted in the breast milk, but were undetectable in her 14-month-old child's plasma (12), suggesting that the metabolites do not accumulate, and may pose little risk to the infant. The use of bupropion during pregnancy and breast feeding was recently reviewed with respect to safety (58); the potential teratogenic risks of bupropion are unknown. The physician must weigh the potential risks of continued depression vs. possible teratogenic risks to the fetus until further research is conducted (58).

Distinct differences exist in the metabolism of bupropion in various species of animals (166,189). In mice and guinea pigs, rapid formation and accumulation of basic metabolites was observed. However, rat forms little of the basic, active metabolites of bupropion, but extensively metabolizes bupropion to the acidic metabolites. Guinea pigs, when compared to rats or mice, constitute an animal model that most closely resembles that of bupropion metabolism in humans (166). Moreover, species differences in bupropion metabolism may explain species differences in pharmacological response, considering the pharmacological activity of the metabolites of bupropion.

Dosing and Administration

Dosage and administration of bupropion are summarized herein based on information provided in Drug Facts and Comparisons (41). Each of the three bioequivalent bupropion formulations (bupropion IR, wellbutrin SR, and bupropion XL) are administered in a gradual manner to minimize risk of seizure, agitation, motor restlessness and insomnia. Insomnia also may be minimized by avoiding bedtime administration. Full antidepressant efficacy may not be evident until at least 4 weeks, and acute episodes of depression typically require treatment for at least several months. Oral doses of bupropion IR are recommended to begin at 200 mg/day, given as 100 mg twice daily, and not to exceed 150 mg in a single dose. Doses may be increased to 300 mg/day, but are not to be increased by 100 mg/day within a 3-day period. An increase up to 450 mg/day (divided doses of 150 mg each) may be administered to nonresponsive patients after several weeks at 300 mg/day, but should be discontinued in nonresponsive patients after an appropriate treatment period. Initial adult dose of Wellbutrin SR is recommended as 150 mg/day, increasing after 4 days to 300 mg/day (150 mg twice daily). An increase to 400 mg/day, may be considered for nonresponsive patients after several weeks of treatment at 300 mg/day. Initial adult dose of bupropion XL is 150 mg/day, but may be increased after 4 days to 300 mg/day (once daily in the morning). An increase to 450 mg/day (single dose) may be given to nonresponsive patients after several weeks of 300 mg/day.

As a tobacco smoking cessation therapy, the maximum oral dose is 300 mg/day (150 mg twice daily). Dosing is initiated while the patient is using tobacco and beginning at 150 mg/day for the first 3 days, after which the dose is increased to 300 mg/day (150 mg twice daily) across the first week of treatment, which is required to reach steady-state levels. A target quit date is chosen during the second week of bupropion treatment, and treatment is recommended for 7 to 12 weeks. Patients who are successful quitting smoking are recommended to consider bupropion treatment for 6 months. Tapering of the dose is not required when discontinuing bupropion treatment.

CONCLUSIONS AND FUTURE DIRECTIONS

The preclinical and clinical literature cited in the current review demonstrates that bupropion nonselectively inhibits DAT and NET, as well as having nAChR antagonist activity, and each of these effects may contribute to its efficacy as an antidepressant and tobacco use cessation agent. Elucidation of which specific mechanism, or combination of mechanisms, is responsible for the clinical efficacy of bupropion will be an important avenue of investigation for future preclinical research. Given the reported individual differences between responders and nonresponders to bupropion, it will also be important to take advantage of the advancements in pharmacogenomic approaches to identify a priori who will benefit from treatment with bupropion. Further challenges in terms of clinical trials will be to determine if bupropion has use in indications beyond depression and tobacco dependence, and if the metabolites of bupropion have a role in clinical efficacy. Finally, novel structural modifications of the bupropion and its metabolites may provide leads for more efficacious medications for depression and tobacco dependence.

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