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Pharmacokinetic Optimisation of Sustained-Release Bupropion for Smoking Cessation

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Abstract

Sustained-release bupropion (bupropion SR) is a unique, non-nicotine smoking cessation aid that is hypothesised to act upon neurological pathways involved in nicotine dependence. Pharmacokinetic and metabolism studies reveal that bupropion SR is metabolised by multiple pathways with no single pathway predominating. When one pathway is inhibited, others are available to compensate. Therefore, only a few clinically relevant drug-drug interactions involving bupropion SR have been observed, although the potential for interactions exists, as with any extensively metabolised drug. Population pharmacokinetic/pharmacodynamic analyses of data from patients receiving daily oral doses of 100mg, 150mg, or 300mg reveal that the anti-smoking efficacy of bupropion SR is directly related to dose. The incidences of dry mouth and insomnia were directly related to bupropion plasma concentrations while the incidence of anxiety was inversely proportional to bupropion plasma concentrations. To maximise efficacy (with an acceptable safety profile), the optimal daily dose for the majority of patients is 300mg.

1. Introduction

Approximately one in four North American adults and one in three European adults are daily cigarette smokers.[1-4] The prevalence of cigarette smoking has not appreciably declined during the past decade in most developed countries, despite the well established health risks of tobacco use and increased efforts to educate the public about the dangers of smoking and the benefits of smoking cessation.[3-5] Evidence-based guidelines characterise nicotine addiction as a major public health problem and recommend pharmacological therapy – i.e. nicotine replacement therapy or the recently introduced sustained-release bupropion (bupropion SR; Zyban®)[1] – in conjunction with behavioural intervention for the management of smoking cessation.[6] This review examines the pharmacokinetics of bupropion SR and considers the implications of the pharmacokinetic data for optimising smoking cessation therapy. Section 1 provides background on the hypothesised mechanism of action of bupropion SR and its clinical efficacy and tolerability. Section 2 reviews single- and multiple-dose pharmacokinetic data, including findings

1 Tradenames are used for identification purposes only and do not imply endorsement.

regarding drug interactions and special patient populations. Section 3 considers new data establishing the relationship between bupropion exposure and the therapeutic effects of the drug. Section 4 considers practical strategies for pharmacokinetic optimisation of smoking cessation therapy with bupropion SR.

2. Background

2.1 Mechanism of Action

Bupropion SR is a unique, non-nicotine treatment hypothesised to act upon neurological pathways involved in nicotine dependence.[7] Chemically unrelated to other interventions for nicotine addiction, bupropion SR is a norepinephrine and dopamine reuptake inhibitor.[8] Its precise mechanism of action in smoking cessation is not definitively known, although its effects on dopaminergic and noradrenergic neurotransmission are putatively involved.

- Dopaminergic pathways are hypothesised to mediate the rewarding properties of nicotine.[9,10] Nicotine and other drugs of abuse increase the activity of a 'reward circuit' of dopamine-releasing neurons projecting from the brain stem to the forebrain nucleus accumbens. Bupropion has been shown to reduce the activity of these dopamine-releasing neurons and thereby may deactivate the reward circuit and reduce craving.[7,8] Furthermore, bupropion has recently been shown to bind to the dopamine transporter in a positron emission tomography study conducted in healthy volunteers. Chronic twice-daily administration of bupropion SR 150mg resulted in an average receptor occupancy of 26%, as measured by the displacement of C-βCIT,[11] over a 24-hour period at steady-state.[11]
- Noradrenergic pathways are hypothesised to mediate some aspects of the aversive state of drug withdrawal.[12-14] Abstinence from nicotine and other drugs of abuse in drug-dependent subjects increases the activity of norepinephrine-releasing neurons projecting from the brain stem locus coeruleus to the forebrain. Bupropion has been shown to reduce the activity of norepinephrine-releasing neurons in animals.[8] Moreover, at clinically relevant doses in man, bupropion reduced whole-body turnover of norepinephrine without altering plasma norepinephrine levels.[15] These noradrenergic effects may contribute to the ability of bupropion to mitigate symptoms of withdrawal.
- Besides inhibiting norepinephrine and dopamine reuptake, recent *in vitro* data indicate that bupropion SR may be a noncompetitive, functional inhibitor of nicotinic acetylcholine receptors.[16,17] This anti-nicotinic activity of bupropion SR may also contribute to its efficacy in the treatment of nicotine dependence.

The postulated mechanism of action of bupropion SR thus differs from that of nicotine replacement therapy, which replaces the nicotine in cigarette smoke with nicotine delivered by an alternative route. Nicotine replacement therapy suppresses nicotine cravings and other withdrawal symptoms associated with smoking cessation: the dependence on nicotine is overcome by successive reductions in nicotine intake.

Clinical data support the possibility that the anti-craving and withdrawal-mitigating effects of bupropion SR contribute to its therapeutic efficacy in smoking cessation. In clinical trials, enhancement of smoking cessation rates by bupropion SR was accompanied by reductions in measures of craving and withdrawal.[18-20] Although these data suggest that the effects of bupropion SR on craving and withdrawal are important determinants of its efficacy in smoking cessation, other data suggest that additional, as yet undelineated, effects may also be important. First, robust anti-craving effects are not uniformly observed with bupropion SR, although the drug is consistently effective in improving smoking cessation rates.[21,22] Second, the abstinence-promoting effect of bupropion SR tends to be more pronounced than its anti-craving or anti-withdrawal effects.[22]

2.2 Efficacy

The clinical efficacy of bupropion SR has been established in several well controlled trials.[18,20,21,23] The 300mg daily dose was significantly more effective than a 100mg daily dose at promoting short- and long-term abstinence.[21] Bupropion SR has also been shown to be effective in patients with chronic obstructive pulmonary disease or cardiovascular disease.[20,24] Furthermore, the efficacy of bupropion SR does not significantly vary with patients' age, sex, history of depression or alcoholism, or degree of dependence on smoking.[25,26]

Besides being effective at improving smoking cessation rates when administered for short (7- to 12-week) treatment periods, bupropion SR administered for 12 months was effective in delaying relapse in patients who stopped smoking within 7 weeks of bupropion SR initiation.[27] In another study, bupropion SR enhanced long-term smoking cessation rates in patients who initially failed attempts to quit.[23]

2.3 Tolerability

Bupropion SR is generally well tolerated.[28,29] The most common adverse events associated with bupropion SR treatment for smoking cessation are dry mouth and insomnia, which were reported approximately 2-times more frequently with bupropion SR than with placebo in controlled clinical trials.[18,21,28] The most medically important serious adverse event reported with bupropion is seizure, which occurs infrequently and is associated with risk factors such as the presence of a seizure disorder (e.g. epilepsy) or an eating disorder (e.g. bulimia or anorexia nervosa).[28] When bupropion is administered as outlined in the product information, the rate of seizure is approximately 0.1%. Animal studies suggest that seizures are probably related to the bupropion maximum plasma concentration (C_{max}) although a role of the metabolites cannot be ruled out (GlaxoSmithKline, unpublished data). A pharmacokinetic/pharmacodynamic (PK/PD) model is not available for seizures because they are so rare. However, seizures may be related to the absolute C_{max}, the rate of rise in the C_{max}, or the number of times an individual is exposed to the C_{max} of bupropion (and, theoretically, and less likely, its metabolites).

3. Pharmacokinetics

First introduced for the treatment of major depression, the bupropion SR formulation was developed with the following aims: (i) enhancing convenience of administration relative to that with the immediate-release (IR) formulation of bupropion; and (ii) reducing the C_{max} of bupropion and the number of times an individual is exposed to the C_{max} and, thereby, the incidence of peak-related adverse events relative to those observed with bupropion IR. Peak plasma bupropion levels are in fact lower after administration of bupropion SR (150mg twice daily) compared with bupropion IR (100mg three times daily), but the formulations are bioequivalent at steady-state.

3.1 Absorption and Distribution

Bupropion C_{max} is achieved within 3 hours of administration of bupropion SR to healthy volunteers. The mean steady-state C_{max} after a 150mg dose every 12 hours is approximately 136 μg/L.[28]

Food does not appreciably alter the absorption of bupropion. In a randomised, crossover study of 24 healthy volunteers, the values for C_{max} and area under the plasma concentration-time curve (AUC) for bupropion increased 11% and 17%, respectively, when the drug was administered with food compared with administration without food (GlaxoSmithKline, unpublished data).

Protein binding of bupropion is approximately 84%.[28,30] Protein binding of hydroxybupropion (77%), the major active metabolite of bupropion, is similar to that of the parent drug. Protein binding of threohydrobupropion (42%), another bupropion metabolite, is approximately half that observed with bupropion.

The volume of distribution estimated from a single 150mg dose is approximately 2000L.[28]

3.2 Metabolism and Elimination

Bupropion is extensively metabolised by multiple pathways with no single pathway predominating.[31] Bupropion is metabolised to three active metabolites: hydroxybupropion (formed via hydroxylation of the tert-butyl group and the amino-alcohol isomers), threohydrobupropion, and erythrohydrobupropion (formed by reduction of the carbonyl group) [figure 1].[32]

A study of [^{14}C]bupropion IR in healthy volunteers showed that bupropion is extensively metabolised.[31] Approximately 87% and 10% of the radiolabelled dose was recovered – primarily as metabolites – in the urine and faeces, respectively. The fraction of the radioactivity excreted in the urine as unchanged bupropion was only 0.5%, while <10% of the dose was accounted for in the urine as active metabolites. The remaining radioactivity in the urine was associated with at least nine other metabolites (free acids, bases, and conjugated metabolites), some of which have not been fully characterised. Overall, this study shows that essentially all of the dose could be accounted for in the urine or faeces; that bupropion is extensively metabolised; and that renal elimination is not an important pathway for the elimination of bupropion or its active metabolites, but is important for the elimination of the inactive metabolites of bupropion.

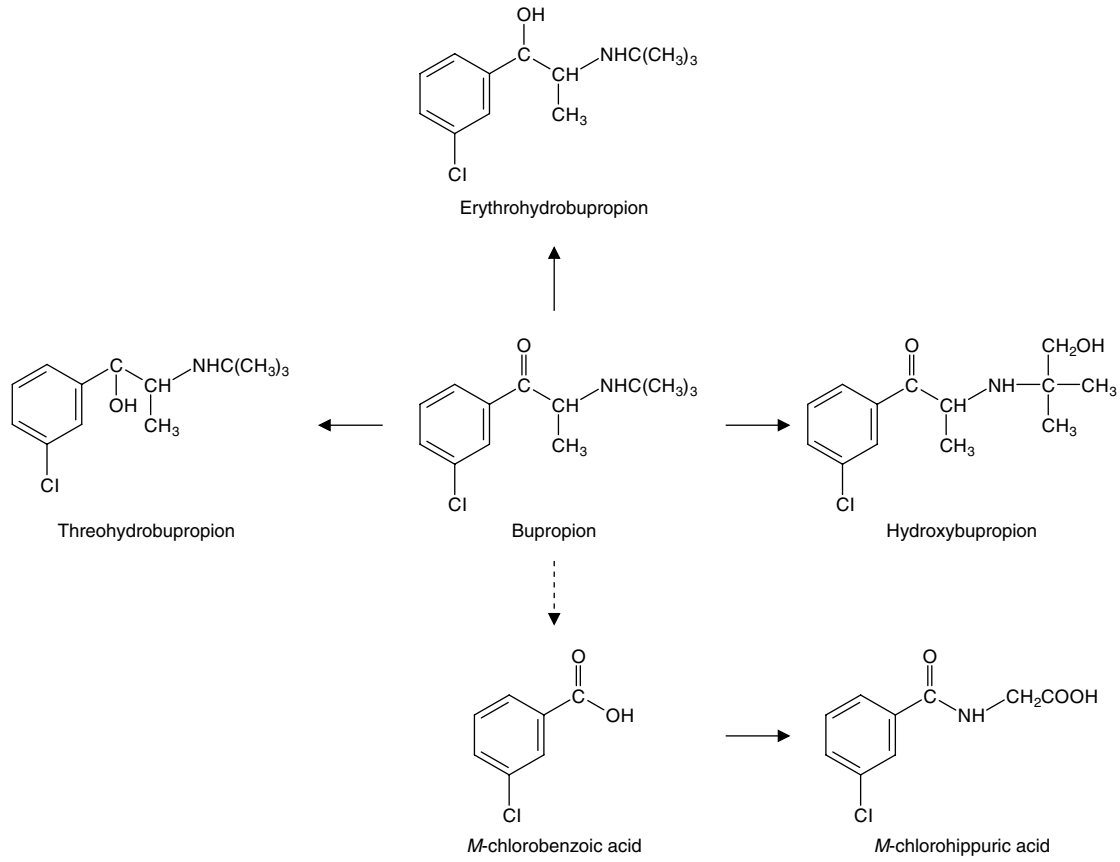

Fig. 1. Metabolic pathway of bupropion in humans. (Reproduced from Hsyu PH, Singh A, Giargiari TD, et al. J Clin Pharmacol 1997; 37: 737-43.[32] Copyright© 1997 by Sage Publications, Inc. Reprinted by permission of Sage Publications, Inc.)

Table I. Summary of pharmacokinetic parameters [mean (standard deviation)] in nonsmokers and smokers given a single oral dose of sustained-release bupropion 150mg (Reproduced from Hsyu PH, Singh A, Giargiari TD, et al. J Clin Pharmacol 1997; 37: 737-43.[32] Copyright© 1997 by Sage Publications, Inc. Reprinted by permission of Sage Publications, Inc.)

	Nonsmokers (n = 15)		Smokers (n = 15)	
	male	female	male	female
Bupropion				
AUC_∞(h•μg/L)	1.168 (227)	1160 (227)	1073 (287)	1260 (281)
C_{max} (μg/L)	142 (28)	146 (31)	139 (43)	147 (36)
t_{max} (h)	3.11 (0.33)	2.89 (0.64)	2.89 (0.60)	2.88 (0.35)
$t_{½}$ (h)	17 (3)	22 (6)	17 (4)	19 (3)
Cl (L/h)	133 (28)	134 (39)	150 (44)	125 (32)
Hydroxybupropion				
AUC_∞(h•μg/L)	15 799 (6208)	14 609 (6848)	18 081 (6731)	15 043 (4500)
C_{max} (μg/L)	431 (134)	429 (215)	493 (192)	365 (89)
t_{max} (h)	6.68 (1.72)	9.00 (6.61)	6.56 (1.88)	5.63 (1.51)
$t_{½}$ (h)	21 (5)	23 (7)	22 (7)	23 (7)
Threohydrobupropion + erythrohydrobupropion				
AUC_∞ (h•μg/L)	5873 (1546)	5501 (1924)	6571 (2402)	6814 (2583)
C_{max} (μg/L)	139 (41)	131 (25)	151 (41)	148 (45)
t_{max} (h)	6.00 (0.99)	4.88 (1.13)	5.44 (1.24)	4.25 (0.71)
$t_{½}$ (h)	45 (12)	52 (17)	49 (20)	45 (14)

AUC∞ = area under the plasma concentration-time curve from zero to infinity; **Cl** = clearance; $\mathbf{C}_{max}$ = maximum plasma concentration; $\mathbf{t}_{max}$ = time to C_{max}; $\mathbf{t}_{½}$ = elimination half-life.

Results of *in vitro* studies show that bupropion is metabolised to hydroxybupropion, primarily by the human cytochrome P450 (CYP) 2B6 and to a much lesser extent by CYP1A2, 2A6, 2C9, 2E1, and 3A4 isoenzymes.[31,33] CYP isoenzymes are not involved in the formation of threohydrobupropion or erythrohydrobupropion.

In *in vitro* studies, the potency of hydroxybupropion is comparable to that of bupropion, while the active metabolites threohydrobupropion and erythrohydrobupropion are one-fifth as potent as bupropion (GlaxoSmithKline, unpublished data). The AUC for the bupropion metabolites was greater than that for bupropion in both smokers and nonsmokers after a single oral 150mg dose of bupropion SR in one study (table I).[32] After chronic administration, the C_{max} and AUC values of the metabolites exceed those of bupropion.[28]

The mean elimination half-life ($t_{½}$) of bupropion is approximately 21 hours.[28] Half-lives of the metabolites estimated from a multiple-dose study were 20 hours for hydroxybupropion, 37 hours for threohydrobupropion, and 33 hours for erythrohydrobupropion. Steady-state plasma concentrations of bupropion and its active metabolites are reached within 5 and 8 days, respectively.

3.3 Effect of Patient Characteristics on Bupropion Pharmacokinetics

Patient characteristics that can alter drug metabolism and/or elimination could theoretically alter bupropion accumulation or other pharmacokinetic parameters. The results of several studies conducted to explore this possibility show that bupropion pharmacokinetics are not clinically significantly altered by many patient characteristics.

3.3.1 Effect of Gender

No clinically significant gender-related differences in pharmacokinetics of bupropion have been observed. In one study, $t_{½}$ was the only pharmacokinetic parameter that statistically significantly differed between men (17 hours) and women (20 hours) given a single oral dose of bupropion SR 150mg.[32] The authors did not consider this difference to be clinically relevant. Similarly, adoles-

cent females (13 to 18 years of age) compared with males had slightly higher AUC and C_{max} values for bupropion and its metabolites after administration of a single 75mg oral dose of bupropion SR, but the differences are unlikely to be clinically significant.[33]

3.3.2 Effect of Age

A pharmacokinetic study conducted in healthy elderly (aged 66 to 76 years) and young (aged 20 to 37 years) volunteers demonstrates no age-related differences in bupropion AUC from zero to infinity (AUC_∞; 3.18 ± 0.75 *vs* 3.28 ± 0.86 μmol•h/L, respectively) or time to maximum plasma concentration (t_{max}; 1.67 ± 0.84 *vs* 1.65 ± 0.79h, respectively) of bupropion after a single dose of bupropion IR 150mg tablets (GlaxoSmithKline, unpublished data). The C_{max} of bupropion was higher (by ~28 to 40%) in elderly volunteers than in young volunteers ($p < 0.05$). The C_{max} of hydroxybupropion and threohydrobupropion as well as the AUC_∞ of hydroxybupropion also tended to be higher (~24 to 28%), although not statistically significantly so, in elderly volunteers than in young volunteers.

A separate study of the pharmacokinetics of single and multiple doses of bupropion in six elderly patients (aged 63 to 76 years) with depression shows that bupropion and its metabolites may accumulate in elderly patients after multiple administration of one to three 100 mg/day bupropion IR tablets for approximately 10 days.[34] Age-related differences in the extent of accumulation cannot be quantified because the study did not include a young comparator group, and relevant pharmacokinetic information [e.g. AUC from 0 to 24 hours (AUC_{24h})] was not reported.

On the basis of these studies, exposure to bupropion appears to be similar in elderly and in adult patients. However, peak concentrations of bupropion were higher and peak concentrations of the metabolites tended to be higher in elderly patients receiving single doses of bupropion. In addition, after chronic administration of bupropion, bupropion or metabolite concentrations may accumulate excessively in elderly patients. Clinical experience has not identified any differences in tolerability between elderly and other adult patients, although the greater sensitivity of some elderly individuals to the effects of bupropion cannot be ruled out.

3.3.3 Smoking Status

The polycyclic aromatic hydrocarbons in cigarette smoke can robustly induce hepatic enzymes to cause pharmacokinetic interactions with medications such as theophylline, tacrine, propranolol, and tricyclic antidepressants.[35] A study in which healthy smokers and nonsmokers matched for race, sex, body frame, age, and weight were given a single oral 150mg dose of bupropion SR revealed no significant pharmacokinetic interaction between cigarette smoking and bupropion SR (table I).[32] Moreover, cigarette smoking did not alter the single-dose pharmacokinetics of bupropion SR 75mg in adolescent smokers (aged 13 to 18 years) compared with nonsmokers.[33]

3.3.4 Effect of Hepatic Impairment and Renal Impairment

The effect of hepatic impairment on the pharmacokinetics of bupropion has been evaluated in two studies. In the first study, there were no statistically significant differences in the pharmacokinetics of bupropion between patients with alcoholic liver disease and healthy volunteers given a single oral 200mg dose of bupropion IR.[36] The $t_{½}$ of hydroxybupropion was longer in patients with alcoholic liver disease than in healthy volunteers (32 hours *vs* 21 hours; table II). The authors note that the pharmacokinetic profile of bupropion is largely variable in alcoholic patients. This finding is not surprising given its extensive metabolism.

In the second study assessing the effects of hepatic impairment on bupropion pharmacokinetics, no statistically significant differences in pharmacokinetic parameters of bupropion or its metabolites were observed in patients with mild-to-moderate hepatic cirrhosis ($n = 9$) compared with healthy volunteers ($n = 8$).[28] However, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC values were greater and the $t_{½}$ was

Table II. Summary of pharmacokinetic parameters [mean (standard deviation)] in alcoholic males and healthy volunteers given a single oral dose of sustained-release bupropion 200mg (Reproduced from DeVane et al.,[36] with permission.)

	Alcoholic patients (n = 8)	Healthy volunteers (n = 8)
Bupropion		
AUC_∞(h•μg/L)	1664 (1150)	1058 (354)
$t_{1/2}$ (h)	16.5 (10.4)	17.3 (8.6)
Cl (L/h)	145 (81)	187 (85)
Hydroxybupropion		
AUC_∞(h•μg/L)	15 659 (8184)	10 209 (4482)
$t_{1/2}$ (h)	32.2[a] (13.5)	21.1 (4.9)
Threohydrobupropion		
AUC_∞ (h•μg/L)	3055 (1094)	3260 (1644)
$t_{1/2}$ (h)	23.4 (10.7)	25.5 (8.6)
Erythrohydrobupropion		
AUC_∞ (h•μg/L)	946 (539)	956 (554)
$t_{1/2}$ (h)	29.8 (6.9)	26.1 (13.3)

a $p < 0.05$ versus healthy volunteers.

AUC_∞ = area under the plasma concentration-time curve from zero to infinity; **Cl** = clearance; **$t_{1/2}$** = elimination half-life.

longer. Furthermore, for bupropion metabolites, the C_{max} was lower and the AUC was higher in patients with severe hepatic cirrhosis compared with healthy volunteers. As in the study of patients with alcoholic liver disease, the pharmacokinetics were more variable in hepatically impaired patients than in healthy volunteers.

No clinical studies have been conducted with bupropion in patients with renal impairment. Both bupropion and its active metabolites are eliminated by metabolism to inactive metabolites. Since elimination of bupropion or its active metabolites accounts for <10% of the dose, excessive accumulation of bupropion or its active metabolites in patients with renal impairment is not expected. However, the administration of any drug to patients with renal impairment should be undertaken cautiously.

3.4 Pharmacokinetic Interactions

Bupropion is metabolised by multiple pathways, with no single pathway predominating. Therefore, when one metabolic pathway is inhibited, other pathways are likely to compensate. However, there are three categories of medications that, used concomitantly with bupropion, potentially result in clinically significant interactions: drugs affecting the CYP2B6 isoenzyme, drugs extensively metabolised by CYP2D6, and general enzyme inducers/inhibitors.

3.4.1 Bupropion and Drugs Affecting CYP2B6 Metabolism

In vitro studies indicate that bupropion is metabolised to hydroxybupropion primarily by the CYP2B6 isoenzyme and to a much lesser extent by the CYP1A2, 2A6, 2C9, 2E1, and 3A4 isoenzymes. Potential interactions between bupropion and drugs (such as orphenadrine or cyclophosphamide) that affect CYP2B6 metabolism might be expected, although no clinical studies have been conducted to assess this possibility.[37] In evaluating the extent of any interaction with concomitant bupropion administration, the fact that hydroxybupropion accounts for a small portion of the metabolism of bupropion and that other CYP isoenzymes are also capable of producing hydroxybupropion (albeit at a rate much lower than that of CYP2B6) should be considered.

3.4.2 Bupropion and Drugs Metabolised by CYP2D6

Bupropion is not metabolised by CYP2D6. However, bupropion and hydroxybupropion inhibit CYP2D6 *in vitro*. A clinical study in 15 volunteers genotyped as extensive metabolisers of the CYP2D6 pathway evaluated the effect of chronic treatment with bupropion on the *in vivo* disposition of desipramine, which is metabolised by the CYP2D6 isoenzyme (GlaxoSmithKline, unpublished data). Twice-daily administration of bupropion SR 150mg for 10 days increased the C_{max}, AUC and $t_{1/2}$ values of desipramine (50mg single dose) by averages of approximately 2-, 5- and 2-fold, respectively. These effects persisted for at least 7 days after the last dose of bupropion.

In humans, CYP2D6 is expressed polymorphically, and there is high between-subject variability in plasma levels of drugs principally metabolised

by this enzyme. Most individuals are extensive metabolisers of CYP2D6 and have normal levels of enzymes. Fewer than 10% of individuals are ultrarapid extensive metabolisers of CYP2D6. A third group of individuals (approximately 8%) are poor metabolisers of CYP2D6 and have extremely low or undetectable levels of the enzyme. Poor metabolisers of CYP2D6 would be expected to have the highest concentrations of a CYP2D6 substrate upon commencing treatment. Poor metabolisers are generally unaffected by the presence of a CYP2D6 inhibitor because little or no enzyme is present to inhibit. However, the addition of a CYP2D6 inhibitor such as bupropion can convert an extensive metaboliser to a poor metaboliser, although the extent of this effect may vary between individuals.

Typically, physicians prescribe drugs metabolised by CYP2D6 without knowing the patient's CYP2D6 genotype status (i.e. whether they are poor or extensive metabolisers) and start with low doses before titrating the dose to reach optimal effect. If the same starting dose of drug is administered to a patient receiving bupropion, the resulting plasma level may be higher but should not be outside the normal range for the CYP2D6-metabolised drug administered alone. The upper limit of this normal range is defined by the poor-metabolising population, which has no CYP2D6 and is therefore unaffected by the presence of a CYP2D6 inhibitor.

3.4.3 Bupropion and Enzyme Inducers

General enzyme inducers coadministered with bupropion SR could theoretically induce the metabolism of bupropion. In one study of patients with mood disorders, chronic administration (for a minimum of 3 weeks) of the enzyme inducer carbamazepine compared with placebo decreased the bupropion C_{max} by 87% and AUC_{24h} by 90% after a single oral 150mg dose.[38] C_{max} and AUC_{24h} were increased for hydroxybupropion and decreased for threohydrobupropion and erythrohydrobupropion.

3.4.4 Bupropion and Enzyme Inhibitors

General enzyme inhibitors coadministered with bupropion SR could theoretically inhibit the metabolism of bupropion. However, results of clinical studies have been inconsistent regarding this possibility. One randomised, crossover study of the P450 inhibitor cimetidine (800mg) coadministered with two 150mg tablets of bupropion SR was conducted in 24 healthy subjects. The results show that cimetidine did not significantly affect the pharmacokinetics of bupropion or hydroxybupropion.[39] Small, statistically significant increases in combined threohydrobupropion and erythrohydrobupropion AUC and C_{max} values were observed. These changes were deemed not to be clinically significant. Another study shows that chronic administration of valproate (a weak inhibitor of hepatic metabolism) had no effect on bupropion plasma concentrations but resulted in a higher C_{max} of hydroxybupropion.[38]

3.4.5 Bupropion and Other Medications

It was shown that steady-state bupropion SR (150mg twice daily) did not cause clinically relevant changes in the pharmacokinetics of a single 100mg dose of lamotrigine (which undergoes extensive N-glucuronidation in humans) in a randomised, open-label, two-way crossover study conducted in 12 healthy subjects.[40] Likewise, in a study in eight healthy volunteers, bupropion administered as a single 100mg dose did not exhibit clinically significant pharmacokinetic interaction with alcohol.[41]

3.5 Pharmacodynamic Interactions

The product labelling for bupropion SR describes potential pharmacodynamic interactions involving bupropion. In many cases, the potential interactions are based on theoretical considerations; limited clinical data demonstrating drug-drug interactions are available.

3.5.1 Bupropion and Levodopa

Limited clinical data suggest that addition of bupropion to a levodopa regimen increases the incidence of adverse experiences (e.g. gastrointesti-

nal effects, excitement, restlessness) compared with use of levodopa alone.[42] In a study of 20 patients with Parkinson's disease receiving levodopa to which bupropion (at a mean daily maintenance dose of 400mg) had been added, 8 experienced nausea/vomiting and 9 experienced excitement or restlessness. Adverse effects were dose limiting in five patients.

3.5.2 Bupropion and the Nicotine Patch

It has been observed that the incidence of treatment-emergent hypertension is elevated among patients treated concurrently with bupropion SR and the nicotine patch compared with patients treated with bupropion SR alone. In a randomised, double-blind clinical trial, the incidence of hypertension or worsening hypertension during the treatment period were higher among those receiving the combination of bupropion SR 300 mg/day and the nicotine patch (6.1%) than among those receiving bupropion SR alone (2.5%), the nicotine patch alone (1.6%), or placebo (3.1%).[18] These differences between groups were not statistically significant. Most of the patients with treatment-emergent hypertension in this study had evidence of pre-existing hypertension.[28]

3.5.3 Medications that Lower Seizure Threshold

The product labelling for bupropion SR recommends that it be administered cautiously to patients taking medications or undergoing treatment regimens that may lower the seizure threshold.[28] Medications such as antipsychotics, antidepressants, theophylline, and systemic corticosteroids may lower the seizure threshold. Moreover, abrupt discontinuation of alcohol and some medications (e.g. benzodiazepines) may also the lower seizure threshold.

3.5.4 Monoamine Oxidase Inhibitors

The concurrent administration of bupropion SR and a monoamine oxidase inhibitor is contraindicated because studies in animals show that the acute toxicity of bupropion was enhanced by concomitant administration of the monoamine oxidase inhibitor phenelzine.[28] The product labelling recommends that at least 14 days elapse between discontinuation of a monoamine oxidase inhibitor and initiation of treatment with bupropion SR.

4. Relationship Between Drug Exposure and Clinical Effect: Population Pharmacokinetic/ Pharmacodynamic Data

To explore means of optimising smoking cessation therapy with bupropion SR, population pharmacokinetic analyses that evaluated the relationships between dose, plasma concentrations of bupropion SR and its metabolites, and the efficacy and tolerability of bupropion SR were recently conducted.[26] These analyses drew upon data from a randomised, double-blind, multicenter trial in which 519 chronic cigarette smokers were randomised to receive 7 weeks of bupropion SR (100 mg/day, 150 mg/day, 300 mg/day) or placebo.[21]

The results demonstrate that the efficacy of bupropion SR in facilitating smoking cessation is directly related to dose (figure 2). Compared with placebo, patients receiving bupropion SR 100 mg/day, 150 mg/day, or 300 mg/day were 1.42-, 1.69-, and 2.84-times more likely to quit smoking. Besides dose of bupropion, the only other variable to predict efficacy of bupropion SR was the number of cigarettes smoked per day, which was inversely related to the likelihood of quitting. The efficacy of bupropion SR was not predicted by age, race, gender, history of depression, presence of depressive symptoms, or severity of addiction.

Similarly to total daily bupropion dose, plasma concentrations of bupropion and each of its metabolites were directly related to therapeutic response (figure 2). Furthermore, bupropion SR total daily dose was strongly and positively correlated with plasma concentrations of bupropion ($r = 0.87$) and each of its metabolites (hydroxybupropion $r = 0.56$; threohydrobupropion $r = 0.57$; erythrohydrobupropion $r = 0.58$).

As with the therapeutic response, the incidences of insomnia and dry mouth – the only two adverse events reported significantly more often in bupropion SR-treated patients than in placebo-treated pa-

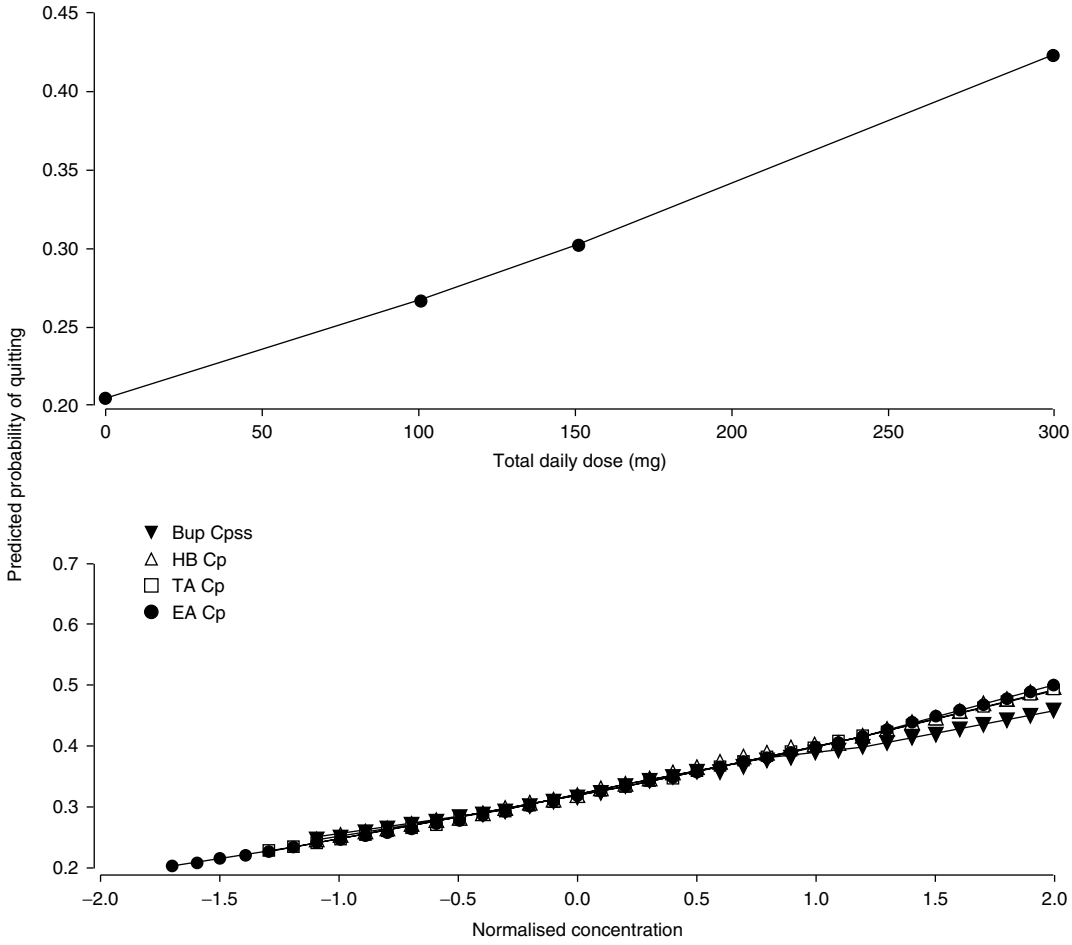

Fig. 2. Model-based predicted probability of quitting based on total daily dose (top panel, p = 0.0001) and normalised concentration (bottom panel, p = 0.0002 for bupropion and p < 0.0001 for each metabolite) from univariate analyses. Bupropion and metabolite concentrations were normalised for presentation on the same scale. The X-axis represents the number of standard deviations above or below the mean (0 = mean). **Bup Cpss** = predicted steady-state average bupropion concentration (ng/ml); **HB Cp** = mean hydroxybupropion concentration (ng/ml); **TA Cp** = mean threohydrobupropion concentration (ng/ml); **EA Cp** = mean erythrohydrobupropion concentration (ng/ml) . (Reproduced with permission from Johnston JA, Fiedler-Kelly J, Glover ED, et al. Relationship between drug exposure and the efficacy and safety of bupropion sustained-release for smoking cessation. Nicotine Tob Res 2001; 3: 131-40.[26] Available from URL: http://www.tandf.co.uk/journals. Copyright© Taylor & Francis Ltd.)

tients in the study – were directly related to bupropion exposure. Whereas insomnia was most strongly correlated with erythrohydrobupropion plasma levels, dry mouth was most strongly correlated with threohydrobupropion plasma levels.

The incidence of anxiety, which was reported less frequently by bupropion SR-treated patients than placebo-treated patients, was inversely related to mean concentrations of bupropion SR metabolites. This finding is consistent with the observation that anxiety is a symptom of nicotine withdrawal and with previous research showing that bupropion SR ameliorates this withdrawal symptom.[22] There was no relationship between

dose, plasma concentration and the following adverse events: constipation, depression, concentration disturbance, dizziness, dream abnormality, headache, irritability, or nausea.

5. Pharmacokinetic Optimisation

The data reviewed in sections 1 through 3 have practical implications for patient care and can be applied in clinical practice to optimise bupropion SR therapy and tailor it to the needs of the individual.

5.1 Administration of Bupropion SR

- Population pharmacokinetic data show that the anti-smoking efficacy of bupropion SR is directly related to dose and that the optimum dose of bupropion SR for smoking cessation is 300 mg/day.[26] Patients receiving the 300mg daily dose are substantially more likely to quit smoking than those receiving lower daily doses (i.e. 150mg). Unless special circumstances dictate otherwise (see section 5.2), patients should be started on a dose of 150mg per day, which should then be increased to a maximum daily dose of 300mg (administered as 150mg twice daily).
- Steady-state plasma concentrations of bupropion and its active metabolites are achieved at approximately 8 days after initiation of therapy.[28] To maximise the chances of therapeutic success, bupropion SR therapy should be initiated 1 to 2 weeks before the target quit date to allow steady-state drug and metabolite levels to be attained.

5.2 Special Patient Populations

- The pharmacokinetics of bupropion SR do not clinically significantly vary as a function of age or gender among adolescents or adults.[32,33] Dose requirements do not differ as a function of gender.
- The overall exposure to bupropion is similar in elderly and young patients receiving a single dose; however, in elderly patients, the C_{max} of bupropion was higher, the C_{max} of the active metabolites tended to be higher, and there was a tendency for a greater extent of accumulation of the active metabolites after multiple administration with bupropion. Clinical experience has not identified any differences in tolerability of bupropion between elderly and adult patients. However, there is a possibility that some elderly patients may be more sensitive to the effects of bupropion and may therefore require lower doses (150 mg/day) or a reduced frequency of administration (150mg every other day).
- Mild-to-moderate hepatic impairment does not significantly affect the pharmacokinetics of bupropion.[28,36] Because severe hepatic impairment affects the pharmacokinetics of bupropion SR,[28] the drug should be administered at a reduced dose frequency (150mg every other day) in patients with severe hepatic cirrhosis. A reduced frequency of administration should be considered for patients with mild-to-moderate hepatic cirrhosis. Patients with hepatic impairment should be monitored while on bupropion SR therapy for adverse effects that might reflect high levels of bupropion or its metabolites.

5.3 Drug Interactions

As with any drug that is extensively metabolised, there is a theoretical possibility of drug-drug interactions involving bupropion SR.

- Bupropion SR does not interact with cigarette smoke and therefore can be administered without dose adjustment to patients who may relapse to smoking while on therapy.[32,36]
- Animal data show increased toxicity of bupropion SR in animals given concurrent bupropion and a nonspecific monoamine oxidase inhibitor (GlaxoSmithKline, unpublished data). The concurrent administration of bupropion SR and a monoamine oxidase inhibitor is contraindicated. The prescribing information for bupropion SR recommends a 2-week washout period between discontinuation of monoamine oxidase

inhibitor therapy and initiation of bupropion SR therapy.[28]

- Although the risk of seizures with bupropion SR administered at therapeutic doses in appropriate patients appears to be very low, bupropion SR should be used cautiously with medications that lower the seizure threshold (e.g. neuroleptics, antidepressants, theophylline, systemic corticosteroids).
- Some data suggest that the risk of treatment-emergent hypertension is slightly elevated in patients receiving concomitant bupropion SR and the nicotine patch relative to those receiving placebo, bupropion SR alone, or the nicotine patch alone.[18] Thus, monitoring for treatment-emergent hypertension is recommended in patients receiving the combination of bupropion and the nicotine patch.
- Because bupropion and hydroxybupropion inhibit the activity of CYP2D6 *in vitro*, coadministration of drugs metabolised by CYP2D6 that have a narrow therapeutic index (e.g. certain tricyclic antidepressants; selective serotonin reuptake inhibitors; antipsychotics including haloperidol, risperidone, and thioridazine; β-blockers; and type 1C antiarrhythmics such as propafenone or flecainide) should be initiated at the lower end of the dose range in patients treated with bupropion. Conversely, existing medication may need to be reduced if initiating bupropion treatment.
- In vitro data suggest that if medications that are mainly metabolised by or that inhibit CYP2B6 are administered concomitantly with bupropion, plasma concentrations of bupropion or the concomitant medication may be increased.
- Bupropion is extensively metabolised. Thus, the coadministration of other drugs known to induce metabolism (e.g. carbamazepine, phenobarbital, phenytoin) or inhibit metabolism (e.g. valproate) may affect its clinical activity.

5.4 Managing Adverse Events

Bupropion SR is a well tolerated aid to smoking cessation. Population pharmacokinetic data show that the incidences of insomnia and dry mouth – the most common adverse events associated with bupropion SR treatment – are directly related to bupropion exposure.[26] With regard to insomnia, the second dose should not be administered too close to bedtime, while maintaining a minimum of 8 hours between the first and second dose. When necessary, bupropion SR dose can be reduced to minimise the incidence of insomnia or dry mouth. While dose reduction may reduce the incidence of these adverse events, it may also cause a corresponding reduction in efficacy.

6. Conclusions

Bupropion SR is a unique, non-nicotine smoking cessation aid hypothesised to act upon neurological pathways involved in nicotine dependence. Pharmacokinetic studies reveal that bupropion SR is metabolised by multiple pathways, with no single pathway predominating. When one pathway is inhibited, others are available to compensate. Therefore, only a few clinically relevant drug-drug interactions involving bupropion SR have been observed, although the potential for interactions exists as with any extensively metabolised drug. Population PK/PD analyses of data from patients given daily doses of 150mg, or 300mg reveal that anti-smoking efficacy of bupropion SR is directly related to dose. The incidences of dry mouth and insomnia were directly related to plasma concentrations, while the incidence of anxiety was inversely proportional to plasma concentrations. To maximise efficacy (with an acceptable safety profile), the optimal daily dose for the majority of patients is 300mg.

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