WHAT IS KNOWN AND OBJECTIVE

Cigarette smoking harms nearly every organ system in the body and places a huge economic burden on our society nationally and worldwide (US Department of Health and Human Services 2004). Between 2006 and 2010, $170 billion per year of annual health care spending was attributed to cigarette smoking in the United States, whereas the cost is over $500 billion each year globally. A number of studies reported that chronic conditions associated with cigarette smoking include cancer, respiratory and vascular diseases. In 2000, 4.83 million premature deaths around the world were attributed to smoking, with the leading causes of death being...
cardiovascular disease, chronic obstructive pulmonary disease and lung cancer.\textsuperscript{5} Many of these diseases linked to cigarette smoking can be prevented and disease progression can be reduced with smoking cessation. The Centers for Disease Control and Prevention (CDC) have reported that in 2010, 68.8% of adult smokers had a desire for quitting with overall rate of cessation at 6.2% in the United States. The report also noted that since 1965, the prevalence of cigarette smoking has decreased with the help of smoking cessation medications. Current treatments for smoking cessation include nicotine replacement therapies, bupropion and varenicline.\textsuperscript{6-8}

Given the staggering success of smoking cessation rates, this article reviews the potential impact of pharmacogenomics on differences in response to nicotine replacement therapies, varenicline and bupropion—with bupropion pharmacogenetics being the main focus. Understanding the genetic variations in the pharmacokinetic and pharmacodynamic properties of these agents may enable clinicians to develop personalized treatment approaches to optimize a patient's success with smoking cessation.

2 | METHODS

Literature search was conducted for the period 1960-2018 using PubMed, EMBASE and SCOPUS databases with keywords like bupropion, CYP2B6 polymorphism and smoking cessation. The search for bupropion AND CYP2B6 gave approximately 600 hits, whereas the search for bupropion AND CYP2B6 AND smoking cessation yielded 95 hits. Duplicate hits were eliminated in the final compilation of the search results. Additional general information on CYP2B6 polymorphism, bupropion metabolism and smoking cessation therapy guidelines was sought through literature search using the above-mentioned databases and the keywords pertinent for the search. The search results included articles belonging to the categories of basic research, preclinical in vitro and in vivo screenings, clinical trials and case reports. Cited articles within the identified articles also provided more information and additional resources for the topic discussed in this manuscript. Approximately 50 articles were assessed for their relevance to the topic; the relevant articles are included in the bibliographical section.

3 | RESULTS

3.1 | Treatments for smoking cessation

3.1.1 | Nicotine replacement therapy

This method of treatment replaces nicotine that is normally obtained from cigarette smoking. Replacement therapies aim to reduce withdrawal symptoms that occur while attempting to quit smoking. A variety of nicotine replacement therapies exist, including nicotine chewing gum, intranasal sprays, inhalers, tablets and transdermal patches. There is little evidence that suggests one treatment options are more effective than another.\textsuperscript{6,9} However, it should be noted that each treatment option present with different side effects such as skin irritation from using transdermal patches and mouth and gum irritation from tablets.\textsuperscript{6}

Although nicotine replacement therapy increases the rates for smoking cessation, a significant percentage of smokers on these therapies will relapse.\textsuperscript{50} A combination treatment approach using several nicotine replacement therapies may provide a solution, as this method is more effective compared to a single nicotine replacement therapy approach.\textsuperscript{6,11} However, additional research is needed to further assess the efficacy of these combination treatments and to determine which combinations and dosages are most effective for smoking cessation. Nicotine is metabolized by CYP2A6 to cotinine and subsequently 3′-hydroxycotinine.\textsuperscript{12} There is a potential role for genetic variations in CYP2A6 to influence the effects of nicotine replacement therapy.\textsuperscript{13,14}

3.1.2 | Varenicline

The α4β2 nicotinic acetylcholine receptor subtype has been suggested to have a role in mediating the effects of nicotine in the nucleus accumbens.\textsuperscript{8,15,16} Agonists for this receptor, like varenicline, have been developed as a smoking cessation aid. Varenicline is postulated to exert its effects by stimulating the release of dopamine in the nucleus accumbens and reduce withdrawal and craving symptoms.\textsuperscript{17} This medication is also thought to exhibit partial antagonistic behaviour as a competitive inhibitor of nicotine and diminishing nicotine's effect.\textsuperscript{17} Varenicline has been linked to depression, but a number of studies suggest that the drug does not significantly worsen depression nor increase risk of suicidal behaviours.\textsuperscript{18,19}

Compared to nicotine replacement therapies, bupropion and varenicline have proven to be more effective in smoking cessation. Short-term smoking cessation rates were reported to be higher using varenicline than nicotine replacement therapies, but incidences of adverse side effects were higher with varenicline use.\textsuperscript{20} However, the study reported that the side effects were well tolerated by the smokers. Randomized, double-blind clinical trials comparing bupropion and varenicline revealed higher abstinence rates and overall smoking cessation with varenicline.\textsuperscript{21,22} The trials also noted a reduced severity of withdrawal symptoms and cravings and lowered satisfaction with smoking. This is consistent with varenicline’s suggested mechanism for attenuating nicotine’s effects and symptoms from smoking cessation. Genes encoding nicotinic acetylcholine receptors (nAChR) subunits have previously been investigated for smoking cessation response with varenicline.\textsuperscript{23} A randomized multicentre clinical trial examining the effectiveness of combination of varenicline and bupropion SR in prolonging the abstinence from smoking was conducted with a 12-week treatment period and 52-week follow-up from 2009 to 2013. The study showed that combined use of varenicline and bupropion among cigarette smokers increased the prolonged abstinence but not 7-day prevalence at 12 and 52 weeks.\textsuperscript{24} The study has limited generalizability to the general population due to exclusion of patients with serious medical and
psychiatric illnesses including those with active substance abuse. Another limitation of the study was that 38% of the participants did not complete the study resulting in overestimating or underestimating the true treatment outcomes.24 However, a most recent double-blind, randomized, parallel-smoking cessation clinical trial showed that combination treatment of bupropion and varenicline does not increase smoking abstinence rates as compared to that of varenicline alone.25

### 3.1.3 Bupropion

Bupropion, a pharmacologic agent that is generally used as an antidepressant, has also been used as a smoking cessation aid. A number of studies have shown bupropion to double the rate of smoking cessation among the smoking population.7,10 Although bupropion and varenicline have more or less similar efficacy as smoking cessation aids, bupropion is more cost effective and has better known side-effect profile.26 Bupropion’s mechanism of action is not entirely clear; the most agreed upon mechanism is that the bupropion and its metabolites enhance dopaminergic and noradrenergic transmission through the blockage of neurotransmitter reuptake at the synapse.27,28 Bupropion is also known to act as nicotine receptor antagonist by inhibiting the stimulant effect of nicotine on the nicotine acetylcholine receptor.29,30 Metabolism of this pharmacologic agent is reportedly mediated by the cytochrome P450 2B6 enzyme (CYP2B6). This enzyme is responsible for the hydroxylation bupropion to form an active metabolite called hydroxybupropion as illustrated in Figure 1. Bupropion also undergoes metabolism to form erythrohydrobupropion (EB) and theohydrobupropion (TB) in the presence of carbonyl reductase.31 CYP2B6-mediated pathway is the predominant metabolic pathway for bupropion. This review will be focusing on variations due to polymorphism of CYP2B6 on bupropion metabolism and therapeutic activity.

As a smoking cessation medication, a study found bupropion to be effective with abstinence rates of 23 per cent in groups that received 300 mg of bupropion per day for 7 weeks compared to 12 per cent in the group that received a placebo.32 This study also demonstrated that a higher dosage of bupropion had greater effect initially after 6 weeks, but after 12 months, the 100, 150 and 300 mg bupropion groups displayed a similar percentage of subjects that did not smoke. Few recent studies have shown that bupropion in combination with varenicline has shown to be well tolerated and efficacious. The reasoning for these effects is as the varenicline and bupropion have additive therapeutic effects.33,34 The combination therapy is proposed for patients in whom nicotine replacement therapy was ineffective. Bupropion’s therapeutic activity is the combination of the parent drug and the active metabolites. Inter-patient variation in expression of CYP2B6 will affect the effectiveness of bupropion in various population.

### 3.2 CYP2B6 gene and common mutations in CYP2B6

The CYP2B6 gene is located on chromosome 19 and encodes for the CYP2B6 enzyme involved in the metabolism of several therapeutically important drugs, in particular, bupropion. Multiple polymorphisms of this gene exist, and the variant alleles are commonly associated with diminished hepatic CYP2B6 expression and catalytic activity compared to the wild type.35,36 The most common mutations in CYP2B6 involves single nucleotide polymorphisms that define the 2B6*6 variant allele and summarized in Table 1.37 This allele leads to lower expression of CYP2B6 enzymes due to erroneous splicing. Other known alleles include CYP2B6*11, *15 and *18, with a large number of uncharacterized variants being discovered as part of the 1000 Genome Project.38 Given the genetic variability in CYP2B6 activity, there may be a potential role...
for CYP2B6 genotype to guide smoking cessation treatment with bupropion.

### 3.3 Influence of CYP2B6 genetic variation on pharmacokinetics of bupropion

Hydroxylation of bupropion is mediated selectively by CYP2B6, and a number of studies reported allelic variants of this gene affect the catalytic activity of this enzyme. Zhang et al conducted a study on CYP2B6*4-CYP2B6*9 polymorphic variants and reported reduced catalytic efficiency in hydroxylation of bupropion in variants compared to the wild type. The study also reported the amino acid substitution in the CYP2B6*8 variant exhibits a charge-reversal mutation that results in loss of function enzyme.

Of these variants, the CYP2B6*6 variant is the most studied. This variant is characterized by Q172H and K262R amino acid substitutions that have been reported to affect enzyme binding affinity. This mutation does not affect bupropion clearance but does affect the generation of the active metabolite hydroxybupropion and a resultant lower hydroxybupropion serum concentration in patients administered with bupropion compared to the wild type.

### 3.4 Influence of CYP2B6 genetic variation on pharmacodynamics of bupropion

CYP2B6 pharmacogenomic-guided bupropion therapy has the potential to identify individuals who are most likely to achieve continuous abstinence for the treatment of nicotine dependence. The presence of at least one CYP2B6*6 allele can be found in approximately 45%, 50% and 25% of Caucasians, African Americans and Asians, respectively, which could substantially impact a large proportion of patients that

### TABLE 1 Known amino acid substitutions and mutations that characterize known CYP2B6 polymorphic variants

<table>
<thead>
<tr>
<th>CYP2B6 Polymorphic variant</th>
<th>Amino acid substitution</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2B6*4</td>
<td>K262R</td>
<td>39</td>
</tr>
<tr>
<td>CYP2B6*5</td>
<td>R487C</td>
<td>39</td>
</tr>
<tr>
<td>CYP2B6*6</td>
<td>Q172H/K262R</td>
<td>39</td>
</tr>
<tr>
<td>CYP2B6*7</td>
<td>Q172H/K262R/R487C</td>
<td>39</td>
</tr>
<tr>
<td>CYP2B6*8</td>
<td>K139E</td>
<td>39</td>
</tr>
<tr>
<td>CYP2B6*9</td>
<td>Q172H</td>
<td>39</td>
</tr>
<tr>
<td>CYP2B6*18</td>
<td>I328T</td>
<td>40</td>
</tr>
<tr>
<td>CYP2B6*22</td>
<td>Promoter</td>
<td>40</td>
</tr>
<tr>
<td>CYP2B6*27</td>
<td>M198T</td>
<td>38</td>
</tr>
</tbody>
</table>

### TABLE 2 Functional effects and metabolic changes due to known CYP2B6 polymorphic variants

<table>
<thead>
<tr>
<th>CYP2B6 Polymorphic variant</th>
<th>Functional effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2B6*4</td>
<td>↑Enzyme expression</td>
</tr>
<tr>
<td>CYP2B6*5</td>
<td>↓Enzyme expression</td>
</tr>
<tr>
<td></td>
<td>↑Specific activity</td>
</tr>
<tr>
<td>CYP2B6*6</td>
<td>↓Enzyme expression</td>
</tr>
<tr>
<td></td>
<td>↓Reduced HB concentration</td>
</tr>
<tr>
<td>CYP2B6*18</td>
<td>↓Enzyme expression</td>
</tr>
<tr>
<td></td>
<td>↓Enzyme activity</td>
</tr>
<tr>
<td></td>
<td>↓Reduced HB concentration</td>
</tr>
<tr>
<td>CYP2B6*22</td>
<td>↑Enzyme expression</td>
</tr>
<tr>
<td></td>
<td>↑Induction in vitro</td>
</tr>
</tbody>
</table>

### TABLE 3 Enzyme kinetics of CYP2B6 variants

<table>
<thead>
<tr>
<th>CYP2B6 Variant</th>
<th>System</th>
<th>$K_{\text{m}}$ (µmol/L)</th>
<th>$K_{\text{cat}}$ (min$^{-1}$)</th>
<th>$K_{\text{cat}}/K_{\text{m}}$</th>
<th>$V_{\text{max}}$ (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2B6*1</td>
<td>E coli</td>
<td>95</td>
<td>6.8</td>
<td>0.072</td>
<td>100</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>COS-1</td>
<td>87</td>
<td></td>
<td></td>
<td></td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Sf9</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>CYP2B6*4</td>
<td>E coli</td>
<td>162</td>
<td>4.1</td>
<td>0.025</td>
<td>35</td>
<td>39</td>
</tr>
<tr>
<td>CYP2B6*5</td>
<td>E coli</td>
<td>134</td>
<td>4.5</td>
<td>0.034</td>
<td>66</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>COS-1</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>CYP2B6*6</td>
<td>E coli</td>
<td>380</td>
<td>11.9</td>
<td>0.031</td>
<td>175</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>COS-1</td>
<td>72</td>
<td></td>
<td></td>
<td>81</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Sf9</td>
<td>63</td>
<td></td>
<td></td>
<td>139</td>
<td>47</td>
</tr>
<tr>
<td>CYP2B6*7</td>
<td>E coli</td>
<td>83</td>
<td>4.7</td>
<td>0.057</td>
<td></td>
<td>39</td>
</tr>
<tr>
<td>CYP2B6*9</td>
<td>E coli</td>
<td>244</td>
<td>6.7</td>
<td>0.027</td>
<td></td>
<td>39</td>
</tr>
</tbody>
</table>
Bupropion is metabolized by CYP2B6 to the active metabolite 4-hydroxybupropion. Although the 4-hydroxybupropion metabolite exhibits only half of the pharmacological activity of bupropion, its concentration in plasma is 20-fold higher than that of the parent compound under steady-state conditions. Therefore, 4-hydroxybupropion is considered to be the major active principle in vivo and the predominant pharmacodynamic entity contributing to the smoking cessation effects of bupropion. In a study of 270 participants treated with bupropion for smoking cessation, individuals with higher hydroxybupropion levels (700 ng/mL or higher) were more likely to achieve abstinence 3, 7 and 26 weeks compared to individuals with CYP2B6*6 allele (carriers of the CYP2B6*6 allele) may require 320 and 420 mg, respectively, to attain hydroxybupropion concentrations of 700 ng/mL representing the minimum concentration within a good bupropion response tertile. Moreover, a significant relationship was identified between participants with the low activity variant of CYP2B6 (CYP2B6 1459C>T) were less likely to be abstinent and more vulnerable to relapse compared to wild type. In contrast to variants that decrease the function of CYP2B6, the CYP2B6*4 allele is associated with increased CYP2B6 activity. One study has suggested that carriers of the CYP2B6*4 allele have lower smoking cessation success rates (35.5%) compared to wild type (48%).

4 | WHAT IS NEW AND CONCLUSIONS

The literature shows a strong correlation between polymorphic variants of CYP2B6 and the effects of these mutations on CYP2B6 pharmacogenomics. The variants are responsible for altered pharmacokinetics and pharmacodynamics of bupropion, affecting smoking cessation outcomes. There is potential for pharmacogenomics-guided treatment with bupropion to improve treatment efficacy. Individuals interested in using bupropion can be pre-emptively genotyped to determine their CYP2B6 metabolic traits. Information about CYP2B6 metabolic status can enable a physician to select an optimal dose and or treatment plan with bupropion. The personalized therapy will potentially increase the success of bupropion-mediated smoking cessation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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34. Rose JE, Behm FM. Combination varenicline/bupropion treatment benefits highly dependent smokers in an adaptive smoking cessation paradigm. *Nicotine Tob Res*. 2017;19(8):999-1002.


