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Biomarkers to optimize the treatment of nicotine dependence

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Abstract

The application of genomic medicine to the treatment of nicotine dependence holds great promise for revitalizing the steady decline in smoking rates witnessed in the USA over the past several decades. This paper examines the current knowledge base concerning the use of biomarkers to guide the selection of nicotine dependence treatments. First, we review the neurobiology of nicotine dependence and present evidence that supports its heritability. We then discuss the various studies of pharmacokinetic and pharmacodynamic genes related to therapeutic response. Current evidence suggests that biomarkers of genetic variability in both nicotine metabolism, referred to as the nicotine metabolite ratio, and dopamine genotypes may be useful for guiding treatment selection for nicotine dependence. Barriers to the translation of this research to clinical practice are discussed, as are directions for future research.

Keywords

CYP2A6; dopamine; nicotine dependence; nicotine metabolite ratio; pharmacogenetic; smoking; tobacco

Tobacco use is the single greatest cause of preventable death and disease in the USA, accounting for close to 450,000 deaths each year [1]. Smoking is responsible for 80–90% of lung cancers, and is causally linked to laryngeal, oral, pharyngeal, esophageal, gastric, pancreatic, renal, bladder and cervical cancers. It causes cardiovascular and respiratory diseases, and results in numerous perinatal conditions [2]. Indeed, tobacco use is responsible for more deaths than alcohol, AIDS, car accidents, illegal drugs, murders and suicides combined [2]. As a consequence, the economic costs of tobacco use are enormous. Between direct healthcare costs due to tobacco-related diseases and indirect costs due to tobacco use (i.e., lost productivity, absenteeism, and recruitment, retention or replacement of workers), the US economy loses almost US$200 billion each year [1].

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Nevertheless, one of the greatest public health achievements in US history was the substantial reduction in tobacco use over the past 50 years. A combination of enhanced public awareness, the advent of new medications and the implementation of broad public health policies led to the lowering of US adult tobacco use rates from over 50% in 1965 to approximately 20% today [3,4]. Yet, the public health community was not able to meet the 12% prevalence target set for the USA in Healthy People 2010, and recent epidemiological surveys of tobacco use show that the rates of smoking in the USA have remained constant over the past 5 years [3,4]. It is now widely accepted among experts in the fields of public health and nicotine dependence treatment that further innovations in treatment approaches are needed in conjunction with more forceful public policies if we are to see additional reductions in tobacco use in the USA in the coming decades [5,6].

There are several reasons for the stalled progress in reducing US smoking rates. First, remarkably few smokers interested in giving up utilize formal treatment programs and US FDA-approved medications for nicotine dependence. Studies show that less than half of smokers who are screened for cessation treatment programs go on to attend [7,8], and upwards of 60% of smokers prefer to try to give up on their own without any form of cessation product or behavioral treatment [9]. However, only 3–5% of smokers who try to give up smoking without formal treatment are successful [10]. Second, there are comparatively few treatment options available for smokers interested in giving up. Currently, there are only three classes of medications to choose from: nicotine replacement therapy (NRT; patch, gum, lozenge, inhaler or nasal spray), bupropion and varenicline. This is a relatively small number of treatment options compared with the variety of medications available to treat many other medical conditions. Finally, only one out of three smokers who utilize FDA-approved medications for nicotine dependence are successful in their attempt to give up [11]. For these reasons, it is critical that public health researchers continue to identify ways to increase utilization of efficacious treatments for nicotine dependence while national investment is made in the development of new treatment approaches for smoking, with a major priority given to identifying methods to improve the efficacy of existing treatments for nicotine dependence.

Advances in human genomics may offer just such an important step forward. A genetic biomarker model to guide treatment selection for nicotine-dependent smokers interested in giving up offers the promise of significantly improving treatment response rates. Guided by studies that have associated outcomes with variability in both genes that influence the pharmacokinetics and pharmacodynamics of medications, researchers and clinicians may soon be poised to individualize the treatment of nicotine dependence in order to enhance the probability of giving up, maximize cost–effectiveness and prevent exposure to unnecessary treatment-related side effects. In this paper, we discuss the evidence for the heritability of nicotine dependence, summarize the current literature concerning the links between individual genetic variation and nicotine dependence treatment response, and highlight barriers to the translation of research into clinical practice. While we may be several years away from a time when smokers will provide DNA to their physicians or to their local pharmacy to ascertain immediate personalized treatment recommendations, there is good reason to be hopeful that advances in the pharmacogenetic treatment of nicotine dependence will eventually stimulate the next wave of reductions in the rate of smoking in the USA.

Neurobiology of nicotine dependence

Advances in our knowledge concerning the underlying neurobiology of nicotine dependence have been critical to guiding research to identify sources of genetic variation in nicotine dependence treatment response. Nicotine, the addictive ingredient in tobacco, binds to the neuronal nicotinic acetylcholine receptors (nAChRs), primarily the α4β2 subtype, located on

the dopaminergic cell bodies in the ventral tegmental area (VTA) [12,13]. When these receptors are stimulated by nicotine, there is a shift from tonic firing of the neurons to burst firing, which increases levels of dopamine (DA) in both the nucleus accumbens (NAC) [14] and the prefrontal cortex [15]. As with other drugs of abuse, this increase in DA levels is experienced as rewarding and pleasurable, and is believed to be a critical mechanism that perpetuates drug dependence [16]. Animal studies using the intracranial self-stimulation paradigm, for instance, have yielded results that support the addictive properties of nicotine [17,18].

The neurobiology of nicotine dependence involves other neurotransmitter systems besides DA as well. Indeed, it would be an oversimplification to characterize the neurobiology of nicotine as solely involving DA. Nicotine affects GABA interneurons within the VTA, GABA neurons in the NAC, and GABAergic afferents to the VTA, which, in turn, influence DA concentrations and the acute rewarding effects of nicotine [19]. Nicotine also stimulates nAChRs on glutamatergic terminals, provoking the release of glutamate which, in turn, stimulates DA release in the NAC and frontal cortex and affects the acute reinforcing effects of nicotine [20,21]. The nAChRs located on the GABAergic neurons are of the α4β2 subtype [22], whereas the presynaptic nAChRs located on the glutaminergic terminals have α7 nAChR subunits [23]. These findings have been further supported by studies showing that compounds which reduce glutamate or enhance GABA influence smoking phenotypes, including reduction in the reinforcing effects of nicotine [24].

In addition, chronic nicotine exposure (but not acute nicotine administration) reduces monoamine oxidase A and B activity, thereby increasing DA concentrations and influencing the maintenance of nicotine addiction [25]. Chronic nicotine exposure also leads to adaptations to the effects of nicotine through a change in the number and function of nAChRs [24]. The exact nature of the relationship between chronic nicotine exposure and neuroadaptations of nAChRs remains to be elucidated, and there is variability in the rate of desensitization and upregulation across the receptor class [24]. Nevertheless, chronic nicotine use results in receptor desensitization and upregulation, processes that are believed to underlie nicotine tolerance and dependence [24].

Nicotine reward is also influenced by the endogenous opioid system. Nicotine administration causes an increase in endogenous opioid peptides such as enkephalins and β-endorphin [26], which subsequently bind to the μ-opioid receptors located on the GABA interneurons in the VTA [27]. Activation of these μ-opioid receptors produces disinhibition of the GABAergic inter-neurons and, thus, further increases DA release in the NAC [28].

More recently, researchers have begun to use neuroimaging technologies to identify brain regions and receptors involved in nicotine dependence [29,30]. While this area of research is in an early stage, findings to date have supported the role of nAChRs as a mechanism through which nicotine exerts its reinforcing effect, demonstrated the stimulatory effects of nicotine on DA release and identified several brain areas underlying nicotine dependence [29].

Genetics of nicotine dependence

While environmental factors are clearly important for determining risk for smoking initiation and progression to regular use, it is now widely acknowledged that the risk of developing nicotine dependence is influenced by genetic factors as well [31,32]. Numerous studies of the smoking behavior of monozygotic and dizygotic twins have been conducted, and meta-analyses of these studies suggest that 50–60% of the variability in smoking initiation is attributable to genetic factors [32–34]. The heritability estimate for smoking initiation might be greater for males than for females [35], but contradictory data have

emerged [32]. Likewise, researchers have examined the relationship between adoptees' smoking behavior and that of both their adopted and biological parents and siblings in order to examine the genetic contributions to smoking behavior. Osler *et al.* found that adoptees raised in separate environments had a greater likelihood of being a current smoker if their biological siblings were smokers or ex-smokers and were more likely to be a heavy smoker if their biological sibling was also a heavy smoker [36]. Genetic factors may also explain upwards of two thirds of the variability in smoking rate and level of nicotine dependence [34,37,38], with greater heritability among men [31]. Meta-analyses of twin studies that have examined the variability in measures of smoking cessation behaviors have concluded that as much as two thirds of the variability in the ability to give up smoking may be attributable to genetic factors [33,35,39], including the results of cessation attempts, the duration of cessation [40] and the self-reported level of withdrawal symptoms [39]. The heritable underpinnings of cessation have also been suggested by adoption studies, which have also shown that a person's ability to give up smoking is strongly associated with their biological sibling's ability to give up [36].

Identifying genes related to response to treatments for nicotine dependence

A greater understanding of the neurobiology of nicotine dependence, and a growing recognition of the genetic influences on nicotine dependence and the ability to give up smoking, have prompted researchers to identify specific genetic polymorphisms, or groups of genetic polymorphisms, linked with smoking-related phenotypes. Previous reviews have identified specific genes or groups of genes, from case–control candidate gene studies, from genome-wide association studies or from linkage analysis, related to smoking initiation and measures of smoking behavior, such as amount smoked and level of nicotine dependence [41–43]. Strong evidence has emerged that associates number of cigarettes smoked per day with genetic variation in both the CYP2A6 enzyme, responsible for 70–80% of the metabolism of nicotine [44,45], and in a cluster of nicotine receptor subunits [44–47]. The results from genome-wide association studies are robust in their consideration of numerous genes and control of statistical error in determining a positive association between a mutation and a smoking phenotype. However, for the purposes of the present article, we will focus on studies that have examined genetic variability associated with response to treatment for nicotine dependence (as done previously [48,49]) despite the fact that the same criteria for determining the significance of the association between a mutation and treatment response may not be as rigorous as for the genome-wide association studies of other smoking phenotypes (e.g., control of statistical error). Below, we provide a more detailed account of the present literature on pharmacogenetic studies of nicotine dependence treatments (Table 1).

Potential biomarkers of NRT activity

There are currently five NRTs approved by the FDA for the treatment of nicotine dependence: the transdermal patch, gum, nasal spray, inhaler and lozenge. NRTs treat nicotine dependence by:

- Ameliorating withdrawal symptoms that characterize initial physical and psychological reactions to cessation, such as irritability, restlessness, depressed mood and poor concentration;
- Reducing the experience of nicotine craving upon cessation and limiting possible weight gain;

- Providing a safer way to experience the neuro-biological and psycho-physiological effects of nicotine.

NRTs are safe for smokers to use, and generally double cessation rates versus placebo [50,51]. Yet, only one in five individuals who use an NRT to give up smoking are successful [51]. Several genetic characteristics of the smoker may serve as useful biomarkers of NRT response.

Nicotine metabolism

A number of studies have focused on examining the relationship between genetic variability in nicotine metabolism and response to NRT. The vast majority of nicotine is metabolized by the liver enzyme CYP2A6 and several genetic alleles that influence CYP2A6 activity have been identified [52]. In addition, rate of nicotine metabolism is a highly heritable trait [53]. Initial studies concerning genetic variants of *CYP2A6* reported that individuals with reduced activity alleles – indicating that they are slower metabolizers of nicotine – are more likely to give up smoking [54] and are less likely to experience severe withdrawal symptoms following smoking cessation [55]. However, work in this area has concentrated more on using a phenotypic biomarker that represents *CYP2A6* genetic variation and rate of nicotine metabolism since:

- All of the alleles for *CYP2A6* have yet to be identified;
- Reduced activity alleles have relatively low frequency;
- The frequency of these alleles varies considerably across racial/ethnic groups;
- Rate of nicotine metabolism is influenced by environmental factors, such as gender and use of oral contraceptives, which are not accounted for solely by the alleles;
- There is substantial individual variation in nicotine metabolism within those who possess the wild-type genotype [52].

The phenotypic biomarker for *CYP2A6*, referred to as the nicotine metabolite ratio, is highly correlated with *CYP2A6* genotypes (higher values for the nicotine metabolite ratio reflect faster nicotine metabolism [56]), can be reliably measured in saliva and plasma [57], is independent of time since last cigarette [58] and day of time assessed [59], and can account for environmental factors that influence rate of nicotine metabolism, including race and gender [60].

The first study to examine the effect of the nicotine metabolite ratio on response to treatments for nicotine dependence used data from a clinical trial that randomized smokers to either transdermal nicotine patches or nicotine nasal spray [61]. Cessation rates were assessed at the end of treatment and 6 months after the target cessation date. Among smokers randomized to nicotine patch, individuals with a lower nicotine metabolite ratio (slower metabolizers) reported a significantly higher cessation rate (46%), compared with individuals with a higher nicotine metabolite ratio (faster metabolizers; 27%). This effect persisted at the 6-month follow-up (30 vs 11% for slow vs fast metabolizers). No effect of the nicotine metabolite ratio on cessation rates was observed for the nasal spray group since these participants could titrate their doses of nicotine to match their rate of nicotine metabolism. This relationship between the nicotine metabolite ratio and cessation rates for individuals using the nicotine patch was replicated subsequently in an independent sample [62].

Nicotine receptors

Researchers have examined the association between genetic variability in nicotinic receptors and response to NRTs. A functional polymorphism in the *CHRNA4* gene (rs2236196),

which can increase receptor binding and increase sensitivity to the acute effects of nicotine, was examined for its potential association with differential response to nicotine patch or nicotine nasal spray [63]. Compared with participants with a TT genotype at this single nucleotide polymorphism (SNP) locus, participants with the TC genotype were significantly more likely to have given up smoking with the nasal spray compared with the nicotine patch, suggesting that smokers who are more sensitive to the effects of nicotine may respond better to NRTs that have faster absorption and reach the CNS more quickly. A second trial examined the effect of genetic variability in the *CHRNB2* gene (rs2072661) on response to nicotine patch [64]. In this placebo-controlled crossover study, individuals who were homozygous for the G allele for *CHRNB2* reported a greater number of days abstinent and were more likely to have given up on the designated cessation date if they received nicotine patch versus placebo. There was no significant difference between nicotine and placebo patch for the AA or AG genotype groups. While the functional significance of this polymorphism is unknown, the data suggest that the nicotine patch may be more effective for carriers of the GG allele of *CHRNB2*. A recent study examined a panel of genes that affect nAChRs in the endogenous cholinergic system for associations with abstinence following transdermal nicotine treatment [65]. While smoking cessation was not associated with SNPs in any of the nAChR genes, a cluster of SNPs in one of the haplotypes for the *ChAT* gene was significantly associated with smoking cessation. While the functional significance of the *ChaT* SNP is currently unknown and replication of this finding is needed, there are plausible biological mechanisms to link the *ChaT* gene with smoking cessation outcomes [65].

Dopaminergic system

A relatively larger number of studies have examined the effect of genetic variability in genes that influence DA on response to NRTs. Initial studies in this area focused on the *Taq1A* polymorphism (rs1800497), which was originally believed to be in the *DRD2* gene, but later determined to be in the neighboring *ANKK1* gene. In a large placebo-controlled trial of nicotine patch, Yudkin *et al.*, first reported that women who were carriers of the A1 allele, which decreases D2 receptor binding [66], showed higher cessation rates on nicotine patch versus placebo, compared with women who were carriers of the A2 allele [67]. No genotype X treatment effect was identified among men enrolled in this trial. In a separate analysis of data from this trial, carriers of the A1 allele who were also carriers of a nonfunctional *DBH* variant (1368A), had a significantly higher cessation rate with nicotine patch versus placebo, compared with participants with other genotypes [68]. However, more recently, the relationship between the *TaqA1* allele and a greater response to transdermal nicotine patches was not replicated in a clinical trial where smokers were randomized to different behavioral smoking cessation treatments and all participants received NRT [69].

Two other dopaminergic functional polymorphisms have been identified in *DRD2* and have been examined in pharmacogenetic trials with NRT. The *DRD2* -141C Ins/Del allele (rs1799732), which influences transcriptional efficiency [70], and the C957T allele, which affects mRNA stability [71], were examined as a factors related to response to transdermal nicotine versus nicotine nasal spray [72]. While no genotype X treatment effect was detected, cessation rates at the end of treatment were significantly greater for smokers who were carriers of the Del C allele or carriers of the CC/CT genotype for C957T (vs TT genotype). In separate analyses, the effect of an interaction on abstinence between -141C Ins/Del alleles and variation in a gene encoding the neuronal calcium sensor-1 protein (*FREQ*), which functions to regulate D2 receptor desensitization, was examined [73]. Individuals with at least one copy of the Del C allele and two copies of the *FREQ* (rs1054879) A allele were significantly more likely to be abstinent following NRT treatment compared with smokers with other genotypes.

Two functional polymorphisms on the DRD4 receptor have been examined for their potential effect on response to nicotine patch in a large placebo-controlled clinical trial [74]. The study examined the seven-repeat polymorphism in the variable number of tandem repeats and the C to T transition polymorphism at position -521 (C-521T) in the *DRD4* gene, polymorphisms that effect ligand binding, gene expression, or transcriptional efficacy [75,76]. Smokers with one or more copies of the seven-repeat polymorphism for a variable number of tandem repeats were more likely to be abstinent at the end of treatment, but for both placebo and nicotine patch. Furthermore, there was no effect of the *DRD4* C-521T on cessation rates for either treatment arm.

COMT is the primary enzyme that degrades and inactivates DA located extrasynaptically in the brain and a functional polymorphism, referred to as the Val108/Met158 (rs4680), has been identified [77]. This polymorphism converts a Val high-activity allele to a Met low-activity allele, resulting in a three- to fourfold reduction in COMT activity and an increase in DA [77]. Initially, a case–control study suggested that there was no association between *COMT* genotypes and smoking cessation [78]. However, more recently, accumulated data from several studies indicate a consistent relationship between the Met/Met allele for COMT and a greater likelihood for smoking cessation following NRT. Collila *et al.* found that a higher proportion of former versus current smokers in a case–control study were *COMT* Met allele carriers and carriers of the Met/Met allele were significantly more likely to have given up smoking following treatment with either nicotine patch or nicotine spray, compared with individuals with the Val allele [79]. Likewise, Johnstone *et al.* [80] and Munafò *et al.* [81] found that individuals with the Met/Met allele were significantly more likely to have given up smoking following nicotine patch treatment, compared with those with a Val allele. More recently, the relationship between the *COMT* Met/Met allele and greater responsiveness to NRT was validated in an analysis of data pooled from several NRT randomized clinical trials [82]. Based on accumulated data, David *et al.* hypothesized that individuals with the Met/Met genotype respond more favorably to NRT because they are more sensitive to adverse symptoms of nicotine abstinence and are more responsive to the reinforcement yielded from NRT's effects on DA [82].

Opioid system

Given the role of the opioid system in affecting the reinforcing effects of nicotine, researchers have also examined variability in genes within this system as possible correlates of response to treatments for nicotine dependence. Research in this area has focused on the *OPRM1* gene, which includes a functional polymorphism, Asn40Asp in exon 1 (rs561720), related to mRNA expression and protein levels [83] and receptor binding potential [84]. The first study of this polymorphism evaluated the relationship between *OPRM1* alleles and response to transdermal nicotine and nicotine nasal spray [85]. In this study, participants with the Asp40 variant of the *OPRM1* gene were significantly more likely to have given up smoking at the end of treatment than participants with the Asn40 variant but this was only true for those undergoing transdermal nicotine treatment. The second study observed an opposite finding, in that participants with the common Asn40 variant were more likely to have given up smoking using the nicotine patch versus placebo [86]. A third trial examined the possibility that *OPRM1* alleles interact with two additional genes that encode μ-opioid receptor-interacting proteins, namely *ARRB2*, which encodes β-arrestin 2, and HINT-1 [87]. Neither of these genes predicted abstinence and no interaction effect with *OPRM1* at either time point was detected.

Other pathways

Researchers have examined the effect of genetic variability in the serotonergic pathway on abstinence rates following nicotine dependence treatment. To date, studies have found no

relationship between the serotonin transporter repeat polymorphism (*5-HTTLPR*), which influences serotonin transporter transcription, and response to NRT [88,89]. Likewise, a recent analysis of pooled data from several NRT clinical trials found no relationship between abstinence rates and alleles in *5-HTTLPR*, or two other serotonergic pathway genes, namely tryptophan hydroxylase (*TPH1* A779C) and *5-HT1A* (HTR1A C-1019G) [90].

Biomarkers of bupropion activity

Bupropion is an antidepressant used to treat nicotine dependence, originally marketed as both Wellbutrin® and Zyban® (GlaxoSmithKline, Brentford, UK). While the mechanism through which bupropion effectively treats nicotine dependence is not fully understood, it is generally believed to act by augmenting DA and norepinephrine levels, and by acting as a partial antagonist at particular nAChRs in the brain [91]. Bupropion doubles cessation rates, compared with placebo [50,92]. However, only one out of four smokers who use bupropion to give up smoking will succeed in their attempt to give up [92], underscoring the need to identify biological characteristics that relate to treatment response.

Nicotine & bupropion metabolism

One study has examined the effect of the nicotine metabolite ratio phenotypic biomarker of *CYP2A6* activity on response to bupropion [93]. In this placebo-controlled clinical trial, the interaction between nicotine metabolite ratio and treatment arm was significant; in the placebo arm, there was a dose–response effect of nicotine metabolite ratio on cessation rates, with slow metabolizers showing a 32% abstinence rate at the end of treatment, compared with 10% for the fast metabolizers. By contrast, there was no significant difference across the nicotine metabolite ratio quartiles among those in the bupropion group, with the fastest metabolizers showing a cessation rate of 34%. Similar results were found at the 6-month follow-up, indicating that bupropion may be a potential efficacious treatment for fast metabolizers of nicotine who respond poorly to the nicotine patch.

Bupropion is primarily metabolized by the P450 enzyme *CYP2B6*, for which several genetic variants have been identified [52]. Lerman *et al.* examined the effect of the *CYP2B6**5 (C1459T) variant (rs3211371) on response to bupropion in a placebo-controlled clinical trial [94]. Smokers with the *CYP2B6**5 CC allele, which yields normal metabolic activity, were more likely to be abstinent at the end of treatment compared with smokers with T alleles. Among female smokers, however, bupropion significantly increased abstinence rates among T allele carriers versus placebo. In a separate placebo-controlled bupropion trial, David *et al.* examined the interaction between *CYP2B6* and *ANKK1* Taq1A alleles [95]. While there was no detectable effect of allele on the effectiveness of specific treatments, the alleles did seem to have a significant impact on the outcomes of treatment in general. Specifically, at 6 months after the cessation day, individuals with at least one *CYP2B6* T allele and two *ANKK1* A2 alleles exhibited significantly higher rates of abstinence than individuals with other *CYP2B6* or *ANNK1* alleles. Lastly, a separate variant allele of *CYP2B6* was examined as a moderator of response to bupropion in a placebo-controlled clinical trial [96]. The *CYP2B6*6* allele was examined since it is believed to decrease bupropion metabolism [97], thereby yielding an enhanced therapeutic response. Among carriers of the *CYP2B6*6* allele, those treated with bupropion reported a significantly higher cessation rate, compared with those on placebo, an effect that persisted out to 6 months after the cessation date. However, participants in this trial with *CYP2B6*1* alleles showed the same therapeutic response to placebo and bupropion and showed similar cessation rates on bupropion as those with the *CYP2B6*6* allele. As such, the *CYP2B6*6* allele does not necessarily enhance response to bupropion, but may facilitate greater maintenance of abstinence once treatment is completed.

Nicotine receptors

Relatively few studies have examined the effect of variability in nicotine receptor genes on response to bupropion. In the context of a placebo-controlled bupropion clinical trial, Conti *et al.* examined the relationship between abstinence rates across treatment arms and variability in SNPs within candidate nAChRs genes [98]. The results indicated that a SNP (rs2072661) in the β2 nAChR gene (*CHRNB2*) was related to end of treatment and 6-month follow-up abstinence rates. Specifically, individuals with the GG allele for *CHRNB2*, compared with those with AA or AG alleles, were significantly more likely to have given up smoking and were more likely to maintain abstinence for at least 6 months. However, this genetic effect was evident in the placebo group as well. Lastly, a novel Bayesian model statistical method was used to screen numerous potential genetic markers of response to bupropion using data from a randomized placebo-controlled bupropion clinical trial [99]. By this method, several SNPs located in the *CHRNA5*, *CHRNA2* and *CHaT* genes were nominated for subsequent examination within pharmacogenetic analyses of therapeutic response to bupropion.

Dopaminergic system

A relatively large number of studies have examined the relationship between genetic variability in dopaminergic genes and response to bupropion treatment. As with NRT, researchers have evaluated the role of the Taq1A polymorphism of the *ANKK1* gene in influencing response to bupropion treatment. The first study in this area examined the effect of both *ANKK1* Taq1A and *SLC6A3*, a DA transporter gene, on cessation rates in a placebo-controlled bupropion study [100]. While there were no main effects for genotype on cessation rates and no gene–treatment interaction effect, a significant gene–gene interaction effect was detected; among those with the A1 genotype for *ANKK1*, there were no differences in cessation rates between those with *SLC6A3* nine-repeat allele versus other alleles for this gene. By contrast, among participants with *ANKK1* A2 genotypes, cessation rates were significantly higher for those with the *SLC6A3* nine-repeat genotype versus other *SLC6A3* alleles. A second study examined the effect of the *ANKK1* Taq1A gene on cessation rates from data pooled from two placebo-controlled bupropion clinical trials [101]. A significant genotype–treatment arm effect emerged whereby, among individuals homozygous for the *ANKK1* A2 allele, cessation rates were significantly higher for bupropion treated participants versus placebo, but no treatment arm differences were detected for those with *ANKK1* A1 genotypes. Carriers of the A2 allele for *ANKK1* were more likely to have given up smoking in a separate open-label bupropion study, although this effect was detected only among women [102]. In this same trial, Swan *et al.* examined the *ANKK1*–*SLC6A3* interaction effect on abstinence following bupropion treatment [102]. The results diverged from those reported by Lerman *et al.* in that the effect of the nine-repeat allele for *SLC6A3* was present only among A1 allele carriers for *ANKK1*, not among those homozygous for the A2 allele of this gene [100]. In particular, individuals with the nine-repeat allele were more likely to be abstinent if they possessed the *ANKK1* A1 allele, but *SLC6A3* genotype was not related to abstinence among A2 allele carriers. Lastly, a study of individuals treated with either open-label NRT or bupropion found that cessation rates were significantly higher among those possessing the nine-repeat allele for *SLC6A3*, versus other alleles for this gene [103].

Within a placebo-controlled bupropion clinical trial, the effect of the *DRD2* 141C Ins/Del allele and the C957T allele on abstinence was examined [72]. A significant interaction of genotype with treatment arm was detected, whereby, in the placebo group, end of treatment abstinence rates were lower among those with the CC genotype, versus those with CN/NN genotypes. However, in the bupropion arm, carriers of the CC allele were more likely to have given up smoking versus carriers of the CN/NN alleles. The interaction effect for 6-

month follow-up was not significant, but the pattern of cessation rates by treatment arm and genotype were the same. There was no effect of the C957T allele on cessation rates across treatment arms. The effect of variation in the *DRD4* gene (the variable number of tandem repeats polymorphism in exon III) on response to bupropion in a placebo-controlled trial has also been examined [104]. The analyses yielded a significant gene–treatment arm interaction, whereby participants with at least one copy of the long allele (or seven-repeat) showed greater cessation rates on bupropion, compared with placebo, but there were no differences in abstinence rates across treatment arms for the short allele carriers (six or fewer).

Lastly, the *COMT* Val/Met allele and two additional *COMT* SNPs were examined for their effect on response to bupropion treatment in a placebo-controlled clinical trial. While the Val/Met allele was not associated with bupropion response, a haplotype comprising two *COMT* SNPs (rs165599 and rs373865) was associated with higher cessation rates with bupropion compared with placebo [105]. For rs165599, individuals with GG alleles experienced higher cessation rates on placebo when compared with individuals with the AA or AG genotypes, who experienced significantly higher cessation rates on bupropion. These results varied by time of follow-up and the racial composition of the sample.

Biomarkers associated with varenicline effect

Varenicline, approved by the FDA in 2006, is currently the most efficacious FDA-approved medication for nicotine dependence, yielding cessation rates that significantly exceed those produced by bupropion [106,107] and the nicotine patch [108–110]. Randomized clinical trials and meta-analytic reviews of varenicline indicate that 6-month abstinence rates for varenicline are approximately 30% [106,107,111]. Varenicline is an α4β2 nAChR partial agonist. As such, varenicline binds to the α4β2 nAChRs, preventing nicotine from binding, and simultaneously providing a moderate amount of stimulation of nAChRs and DA release. These processes reduce the rewarding effects of smoking and reduce abstinence-induced withdrawal symptoms [112]. Varenicline's efficacy is also believed to be due to the drug's effects on abstinence-induced psychological distress and cognitive impairment. In fact, several studies now show that varenicline mitigates adverse psychological effects and cognitive impairment associated with giving up smoking [112–116]. To date, no published studies have examined the effect of genetic variability on response to varenicline.

Conclusion

Overall, replicating genetic associations with response to treatment across studies has been difficult. This said, relatively consistent pharmacogenetic effects on therapeutic response to treatments for nicotine dependence have been identified for the nicotine metabolite ratio biomarker, representing genetic variability in rate of nicotine metabolism. Slow metabolizers of nicotine based on the nicotine metabolite ratio may be appropriate candidates for NRT. However, other treatments may be more effective for faster metabolizers of nicotine. For example, while replication is needed, initial evidence suggests that faster metabolizers of nicotine based on the nicotine metabolite ratio may be better candidates for bupropion. In addition, several biomarkers of DA handling have also shown relatively consistent pharmacogenetic predictive capacity. Carriers of the Met/Met allele of the *COMT* gene, which affects DA release, appear to fair better with NRT compared with other treatments. By contrast, carriers of the long allele of *DRD4* appear to be good candidates for bupropion. However, there are several limitations: much of the literature in this area is based on a small number of randomized clinical trials and no studies have examined pharmacogenetic effects for varenicline. It is worth noting that, even when statistically significant associations have been detected, the variance in treatment outcome

that is explained by the allele or SNP is relatively small. This not only indicates that cessation treatment outcome is polygenic and/or influenced by environmental factors as well, but this also indicates that developing cost-effective procedures to screen smokers and match them to treatments will be challenging. Future studies are needed to:

- Confirm the positive results determined thus far in independent and large clinical trial populations;
- Examine pharmacogenetic effects for varenicline;
- Develop panels of multiple genotypes that can explain larger proportions of variance in nicotine dependence treatment response.

Barriers to translating pharmacogenetic results to practice

The promise of individualizing treatment for nicotine dependence based on an individual's genetic profile may become a reality in the coming years. The integration of a pharmacogenetic treatment model for nicotine dependence may increase cessation rates, thereby lowering the US rate of smoking, and reduce costs and spare smokers from unnecessary medication side effects by identifying smokers who could effectively give up without the use of medications. Undoubtedly, we are probably several years away from being able to have smokers provide a DNA sample to a health-care professional in order to receive empirically based treatment recommendations that provide smokers with the best chance for cessation. However, when this evolution occurs, capitalizing on the potential benefits of a pharmacogenetic treatment model for treating nicotine dependence may depend on how prepared the physician is to incorporate genetic testing into their clinical practice [117].

Primary care physicians (PCPs) can be the entry point for many smokers to initiate treatment for nicotine dependence. Each year, nearly 80% of smokers see a physician [118] and patients generally respect and adhere to their physician's healthcare advice [119]. Initiating treatment for nicotine dependence in the context of discussing general health issues may increase motivation to give up [120] and can be a cost-effective treatment approach [121]. Government agencies and public health organizations have advocated for physicians to play a larger role in disseminating treatments to smokers and physician-based treatments for nicotine dependence can significantly reduce smoking rates [50].

Yet, PCPs appear reluctant to adopt genetic testing to individualize smoking cessation treatment. Only 4% of PCPs report that they are prepared to address genetic testing with their patients [122] and a third of physicians indicate that they are reluctant to use genetic testing to guide smoking cessation treatment with their patients [123]. In fact, more than a third of PCPs have never ordered a genetic test for their patient for any condition and a quarter have never referred their patient for any sort of genetic test [122]. Physicians may be reluctant to incorporate genetic testing into treatment for nicotine dependence because genetic tests can be difficult to interpret and communicating test results can be complicated and challenging. The outcome of genetic testing involves probabilities and requires consideration of environmental factors, which can undermine the PCP's ability to convey test results, especially given the limited training that physicians receive in clinical genetics [124]. Indeed, many physicians report that they lack the qualifications to interpret and convey genetic information to patients [124]. PCPs reluctance to incorporate genetic testing into treatment for nicotine dependence may also be driven by their recognition of the potential dangers associated with genetic testing for nicotine dependence. Many genes linked to nicotine dependence are also associated with a greater risk for other addictions and psychiatric conditions. Physicians may worry that genetic information related to the tailoring of treatments for nicotine dependence could be used to discriminate against their patients in

insurance or employment settings [125]. In addition, practical barriers to incorporating genetic testing into routine medical practice should not be underestimated. PCPs have concerns about the burden that genetic testing procedures and feedback protocols will present to their busy practices [124]. Small clinic practices, which comprise half of all PCP practices in the USA, may have particular difficulty establishing the infrastructure needed to personalize treatment for nicotine dependence based on genetic testing results [124].

Thus, efforts are needed to bolster PCP education in clinical genetics to increase physician competence and confidence in interpreting and conveying test results, and using test results to guide treatment selection. Medical school curricula should include coursework on clinical genetics for future physicians, and innovative education models need to be utilized to enhance knowledge and skills among established physicians. In addition, physician awareness of legislation to prevent the misuse of genetic information is needed. The passage of the US Genetic Information Nondiscrimination Act will reduce fears among many physicians and will likely bolster use of genetic tests. Solutions to physician time and economic constraints are also needed. Treatment for nicotine dependence, including potential genetic testing, requires reimbursement, and smaller PCP practices need access to cost-effective procedures for testing and treating patients for nicotine dependence. Surveys of PCPs indicate that they are more willing to use a nongenetic test to guide treatment decisions versus a genetic test [123]. This suggests that the potential uptake of the nicotine metabolite ratio biomarker to personalize treatment for nicotine dependence may be greater than tests for genetic polymorphisms.

Future perspective

Tobacco use continues to be the leading cause of death in the USA and a major source of economic drain from the US economy. Unfortunately, the steady decline in smoking rates witnessed in the USA over the past several decades has recently stalled. A greater understanding of the neurobiology of nicotine dependence and advances in genomics has led to the possibility of individualizing the treatment for nicotine dependence based on genetic variability across smokers. This advance holds great promise for increasing treatment response and ushering in a new wave of reductions in the US rate of smoking in the coming few years.

While additional research is needed to identify genetic variants linked to response to nicotine dependence treatments, a genetically informed biomarker that represents variation in the rate of nicotine metabolism shows particular promise as a tool for individualizing treatment decisions for nicotine dependence. Slower metabolizers of nicotine exhibit relatively higher cessation rates on transdermal nicotine [61,62] and counseling [93], whereas fast metabolizers of nicotine show relatively higher cessation rates on bupropion compared with placebo. Determining if varenicline is efficacious for treating nicotine dependence among fast metabolizers of nicotine is a critical priority for future research. In addition, this biomarker has several advantages over using genotyping of *CYP2A6* alleles to assess rate of nicotine metabolism, including incorporation of environmental factors that influence rate of nicotine metabolism and ease of assessment and interpretation. Uptake of use for this biomarker among physicians may be greater, compared with use of genetic alleles, since probabilities are not required for interpretation and the risk for misuse of information is reduced.

Further replication and extension of the literature concerning the nicotine metabolite ratio and response to nicotine dependence treatment may pave the way for the first genetically informed biomarker for use in individualizing treatment for nicotine dependence. Such a development could substantially improve nicotine dependence treatment response rates and

help initiate a new round of reductions in the rate of tobacco use in the USA. Nevertheless, capitalizing on this achievement may require the reduction of barriers to physician uptake of genetically informed tests. In addition, demonstrating that pharmacogenetic models for treating nicotine dependence can be costeffective may be critical for eventual uptake into standard clinical care. There are some data to suggest that, under certain circumstances, a pharmacogenetic model of treating nicotine dependence with NRT and bupropion can be cost effective [126]. In addition, the use of a biomarker rather than a gene or multiple genes to tailor nicotine dependence treatment may be more cost effective, since less clinician time would be needed for explaining the test results. However, cost–effectiveness data from prospective clinical trials using the nicotine metabolite ratio are needed to facilitate the translation of the findings in this area to clinical care. With the broadening and strengthening of anti-tobacco public policies such as a comprehensive ban on smoking in public places and enhanced efforts to prevent the initiation of smoking among youth, the advent of a pharmacogenetic treatment model for nicotine dependence holds great promise for reducing tobacco-related morbidity and mortality in the USA in the coming years.

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Executive summary

- Tobacco use is the leading cause of death in the USA and has enormous financial costs. Almost 500,000 deaths in the USA each year are attributable to tobacco use and almost US$200 billion each year is spent on tobacco-related diseases.
- Smoking continues to be highly prevalent in the USA. The steady decline in the US smoking rate over the past few decades has stalled and the current rate of adult smoking is approximately 20%, far above the Healthy People 2010 objective of 12%.
- Novel methods are needed to increase response rates to treatments for nicotine dependence. At best, only one out of three smokers who try to give up smoking using US FDA-approved medications for nicotine dependence are successful.
- Genomic medicine may offer the potential for improving cessation rates following pharmacotherapy for nicotine dependence. The ability to give up smoking is influenced by genetic variability and physiological mechanisms underlying nicotine dependence involve nicotinic receptors, dopamine, GABA, glutamate and endogenous opioids.
- Pharmacogenetic analyses of smoking cessation clinical trials have identified biomarkers and genetic alleles related to treatment response.
- The nicotine metabolite ratio, representing variation in the rate at which nicotine is metabolized, the *COMT* Val/Met allele, which affects dopamine release, and the *DRD4* long allele, which affects dopamine release, influence response to treatments for nicotine dependence.
- Slow metabolizers of nicotine show high cessation rates with counseling alone or with nicotine patch, while fast metabolizers of nicotine show high rates with bupropion.
- Carriers of the Met/Met allele for *COMT* show high cessation rates with NRT, while Val allele carriers do not.
- Those with the long allele of *DRD4* show higher cessation rates on NRT and bupropion compared with short allele carriers for *DRD4*.
- Additional research is needed before a pharmacogenetic model can be integrated into the framework of treatment for nicotine dependence. Many findings concerning the relationship between genetic alleles and response to treatment for nicotine dependence have not been replicated and have emerged from a small number of smoking cessation clinical trials. No studies have examined pharmacogenetic effects for varenicline, the most efficacious treatment for nicotine dependence.
- The integration of a pharmacogenetic model within the framework of treating nicotine dependence may depend on physician willingness and ability to integrate genetic or biomarker analyses into clinical care.
- Nearly 80% of smokers see a primary care physician each year and most patients are receptive to physician treatment recommendations.
- Many physicians are unwilling to integrate genetic testing procedures into their clinical care often because of: a lack of training in clinical genetics, concerns over the complexity of interpreting and conveying results, worries about the

possible misuse of genetic information, and lack of time and financial reimbursement for testing and feedback.

- Initiatives are needed to address barriers to the integration of pharmacogenetic treatment into primary care in order to capitalize on the potential benefits of genomic medicine to reduce smoking rates in the USA.
- Advances in genomic medicine hold great promise for reigniting the steady decline in US smoking rates seen over the past several decades, but research is needed to confirm biomarkers related to treatment response and translate such findings into clinical practice.

Table 1

Summary of results from pharmacogenetic studies of nicotine dependence treatments.

Gene	Polymorphism	Treatment	Main finding	Ref.
CYP2A6	3-HC/cotinine	NRT (patch vs spray)	Slower nicotine metabolizers showed higher cessation rates with patch but 3-HC/cotinine had no effect for nicotine spray	[61]
	3-HC/cotinine	NRT (patch)	Slower nicotine metabolizers showed higher cessation rates with patch	[62]
	3-HC/cotinine	Bupropion	An interaction effect was noted with cessation rates lower for fast metabolizers on placebo vs slow metabolizers, but there was no difference across metabolizer groups in the bupropion condition	[93]
CYP2B6	C1459T (rs3211371)	Bupropion	Participants with the **5* CC allele were more likely to be abstinent than participants with T alleles but, among females, bupropion increased cessation rates for T allele carriers	[94]
	C1459T (rs3211371)	Bupropion	Participants with at least one copy of T allele and two copies of *ANKK1* A2 alleles were more likely to have given up smoking	[95]
	**6*, **1*	Bupropion	Participants with **6* allele showed higher cessation rates on bupropion vs placebo, but there was no difference between placebo and bupropion for participants with **1* allele	[96]
CHRNA4	rs2236196	NRT (patch vs spray)	Participants with TC genotype were more likely to have given up smoking with nasal spray vs patch	[63]
CHRNB2	rs2072661	NRT (patch)	Participants homozygous for the G allele were more likely to have given up on the target cessation date on patch vs placebo, but there was no effect for those with AA or AG alleles	[64]
	rs2072661	Bupropion	Participants with the GG allele were more likely to have given up smoking vs those with the AA or AG allele	[98]
	rs2565065	Bupropion	Participants with the rare allele showed little difference between placebo and bupropion but the cessation rate was significantly greater for those with the more common allele in the bupropion condition	[99]
CHRNA5	rs871058	Bupropion	Participants with the rare allele showed little difference between placebo and bupropion but the cessation rate was significantly greater for those with the more common allele in the bupropion condition	[99]
ChAT	rs4838547, rs6537546, rs1917810, rs11101202 and rs867687	NRT (patch)	Participants with AAACG and ATACA haplotypes were less likely to have given up smoking	[65]
	rs1917810	Bupropion	Participants with the rare allele showed little difference between placebo and bupropion, but the cessation rate was significantly greater for those with the more common allele in the bupropion condition	[99]
	rs2269338	Bupropion	Participants with the common allele showed a higher cessation rate on bupropion vs placebo but there was no difference between treatment arms for those with the rare allele	[99]
ANKK1	Taq1A (rs1800497)	NRT (patch)	Female participants with the A1 allele showed higher cessation rates, but no effect was seen for men	[67]
	Taq1A (rs1800497)	NRT (patch)	Participants with the A1 allele who were also carriers of the dopamine β-hydroxylase variant (1368A) had significantly higher cessation rates on patch vs placebo	[68]
	Taq1A (rs1800497)	NRT (patch)	There was no effect of A1 allele on cessation rates following patch treatment	[69]
	Taq1A (rs1800497)	Bupropion	Participants homozygous for the A2 allele had higher cessation rates with bupropion vs placebo, but no treatment effect was evident for those with A1 genotypes	[101]

Gene	Polymorphism	Treatment	Main finding	Ref.
SLC6A3	3′UTR VNTR	Bupropion	Among participants with the A1 allele, there were no differences in cessation rates between participants with the *SLC6A3* nine-repeat allele vs other alleles, but among those with A2 genotypes, cessation rates were higher for those with the *SLC6A3* nine-repeat allele	[100]
	3′UTR VNTR	Bupropion	Participants with the nine-repeat allele for *SLC6A3* were more likely to have given up smoking if they possessed the A1 allele, but no effect was found for A2 carriers	[102]
	3′UTR VNTR	Bupropion or NRT	Participants with the nine-repeat allele for *SLC6A3* were more likely to have given up smoking	[103]
DRD2	-141C Ins/Del (rs1799732)	NRT (patch vs spray)	Participants with the Del C allele were more likely to have given up smoking	[72]
	-141C Ins/Del (rs1799732)	NRT (patch vs spray)	Participants with one copy of the Del C allele and two copies of the *FREQ* (rs1054879) A allele were more likely to have given up smoking	[73]
	C957T	NRT (patch vs spray)	Participants with CC/CT genotype were more likely to have given up smoking versus those with the TT genotype	[72]
	-141C Ins/Del (rs1799732)	Bupropion	Participants with the CC allele were more likely to have given up smoking vs those with the CN/NN alleles in the bupropion arm, but the opposite was found in the placebo arm	[72]
	C957T	Bupropion	There was no effect of genotypes on cessation rates	[72]
DRD4	Seven-repeat of VNTR	NRT (patch)	Participants with one or more copies of the seven-repeat allele were more likely to give up smoking for patch and placebo	[74]
	C-521T	NRT (patch)	No relationship between alleles and cessation rate	[74]
	Seven-repeat of VNTR	Bupropion	Participants with at least one copy of the seven-repeat allele had a higher cessation rate on bupropion vs placebo, but there was no effect of treatment for the short allele carriers (six or fewer)	[104]
COMT	Val108/Met158 (rs4680)	NRT (patch vs spray)	Participants with the Met/Met allele were more likely to have given up smoking vs those with the Val allele	[79]
	Val108/Met158	NRT (patch)	Participants with the Met/Met allele were more likely to have given up smoking vs those with the Val allele	[80]
	Val108/Met158	NRT (patch)	Participants with the Met/Met allele were more likely to have given up smoking vs those with the Val allele	[81]
	Val108/Met158	NRT (patch)	Participants with the Met/Met allele were more likely to have given up smoking vs those with the Val allele	[82]
	rs165599, rs373865	Bupropion	Participants with the GG allele for rs165599 had a higher cessation rate on placebo vs AA and AG genotypes who showed higher cessation rates on bupropion	[105]
OPRM1	Asn40Asp (rs561720)	NRT (patch vs spray)	Participants with the Asp40 variant were more likely to have given up smoking with the nicotine patch vs those with the Asn40 variant	[85]
	Asn40Asp	NRT (patch)	Participants with the Asn40 variant were more likely to have given up smoking versus those with the Asp40 variant	[86]
	Asn40Asp	NRT (patch vs spray)	No interactions between Asn40Asp and variants of *ARRB2* and *HINT-1* were found for response to treatment	[87]
5-HTT	5-HTTLPR	NRT (patch)	No effects of variants on response to treatment	[88]
	5-HTTLPR	NRT (patch)	No effects of variants on response to treatment	[89]
	5-HTTLPR	NRT (patch)	No effects of variants on response to treatment, including no interactions with TPH1 and 5-HT1A	[90]

3-HC: 3-hydroxycotinine; NRT: Nicotine replacement therapy; UTR: Untranslated region; VNTR: Variable number of tandem repeats.