Chapter 19
Management, Pharmacotherapies, and Precision Medicine for Smoking Cessation

Abstract Although 70% of smokers want to quit, only 4–7% are successful in the long term. Cigarette smoking persists because of both the addictive propensity of nicotine and the low success rates of existing treatments. Smoking cessation outcomes are influenced by both smoking cessation medications and genetic factors which include variations in the enzymes that metabolize nicotine and in nAChR subunit genes that are the primary targets of nicotine and of treatment medications. Identifying subjects with appropriate variants is an essential element in improving smoking cessation outcomes. In this chapter, we highlight recent progress in our understanding of how genetic variants in the pharmacological targets of nicotine and smoking cessation medications could be used to tailor cessation therapy and increase the success rate.

Keywords Smoking dependence · Consulting · Smoking cessation · Quitting · DSM-V · Genetic markers · Fagerström Test for Nicotine Dependence · FTND · Intervention · 5As · Biomarkers · SNPs · *Bupropion hydrochloride* · *Zyban* · *Varenicline tartrate* · Chantix · Nicotine replacement therapy · *CYP2A6* · *CYP2B6* · Tobacco dependence · *CHRNA5/A3/B4*

1 Clinical Diagnostic Criteria for Nicotine Dependence (ND)

The DSM-V (APA 1994) defines tobacco use disorder as a problematic pattern of tobacco use leading to clinically significant impairment or distress, as manifested by at least two of the following criteria during a 12-month period: (1) using tobacco in larger amounts or for a longer period than intended; (2) a persistent desire or unsuccessful effort to reduce or control tobacco use; (3) a great deal of time spent in activities necessary to obtain or use tobacco; (4) craving or a strong desire or urge to use tobacco; (5) recurrent tobacco use resulting in a failure to fulfill obligations of major roles at work, school, or home; (6) continued tobacco use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of tobacco; (7) important social, occupational, or recreational activities given up or reduced because of tobacco use; (8) recurrent tobacco use in situations in which it is physically hazardous; (9) tobacco use being continued despite knowledge of

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Table 19.1 Fagerström Test for Nicotine Dependence (FTND)

Question	Selections	Score
1. How many cigarettes a day do you usually smoke?	1–10	0
	11–20	1
	21–30	2
	31 or more	3
2. How soon after you wake up do you smoke your first cigarette?	Within 5 min	3
	6–30 min	2
	31–60 min	1
	More than 60 min	0
3. Do you smoke more frequently during the first 2 h of the day than during the rest of the day?	Yes	1
	No	0
4. Which cigarette would you most hate the most to give up?	The first cigarette in the morning	1
	Any other cigarette	0
5. Do you find it difficult to refrain from smoking in places where it is forbidden, such as church, at the movies, etc.?	Yes	1
	No	0
6. Do you still smoke even when you are so ill that you are in bed most of the day?	Yes	1
	No	0
Total		0–10

having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by tobacco; (10) tolerance; and (11) withdrawal symptoms.

There are some concerns about the DSM criteria for ND, one of the primary ones being that they do not measure the degree of dependence. Thus, other instruments have been used as a supplement or replacement in both clinical and research settings. The Fagerström Test for Nicotine Dependence (FTND) is one of the most popular questionnaires to characterize the degree to which the patient is physically dependent on cigarette smoking (Heatherton et al. 1991) (Table 19.1).

Another questionnaire for measuring ND is the Wisconsin Inventory of Smoking Dependence Motives (WISDM) (Piper et al. 2004), which provides greater information regarding various domains of smoking motivation. This is a relatively new scale but with accumulating evidence suggesting its utility. Other scales are used less frequently and tend to be restricted to research applications. However, only limited direct research has evaluated the appropriateness of these new criteria.

2 Clinical Characteristics of ND

Patterns of tobacco use differ considerably in different users. Individuals may consume tobacco sporadically or daily, in small to large amounts, and in single vs. multiple forms. The degree to which an individual's pattern of tobacco use is

elicited by exposure to tobacco stimuli (e.g., others smoking, distressing circumstances) is variable, as is the type, intensity, and duration of the particular withdrawal symptoms experienced. The general characteristics of the tobacco-using population are changing, with higher prevalence rates now evident among those of lower socioeconomic status and educational attainment and those with psychiatric diagnoses or symptoms. Overall, the risk of relapse post-cessation is high, particularly for those who quit without professional assistance or among certain subgroups (e.g., pregnant women). Patients who have used tobacco products for an extended period often present with signs of compromised health, generally related to the length of their smoking history. Depressive or anxiety symptoms or both are relatively common, and the clinician should be aware that the suicide rate for smokers is substantially higher than that for the general population; the risk for former smokers falls in between.

3 Genetic Screening for ND

Although there is substantial evidence for the involvement of genetic factors in ND and smoking cessation, no major Mendelian genes or variants have been identified. Familial clustering is common but not universal. Nevertheless, many variants have been implicated in ND and its treatment. Further validation is greatly needed in order to use this genetic information clinically.

Currently, there is a lack of clear and robust evidence supporting genetic testing for ND or ability to quit smoking. Even though some markers appear to be promising, most of those tests have not yet been validated clinically. Although many SNPs in various candidate genes have been associated with ND or smoking cessation, only a few of them have been replicated in multiple independent samples, and most of these findings await further replication. So far, the most convincing example is variants in the nicotinic receptor subunit *CHRNA5/A3/B4* gene cluster on chromosome 15 (see Chap. 5); a risk variant rs1051730 in this cluster has been used to predict the potential genetic risk for ND in individuals of European origin. However, the SNPs that have been investigated account for a very small proportion of the variance (e.g., <5%), and thus, their predictive clinical validity would be low.

4 Management and Pharmacotherapies for ND

Healthcare-based interventions for tobacco dependence that include both counseling and pharmacologic evidence-based components are the most effective treatment approach. In general, interventions that incorporate higher levels of effort/resources increase the likelihood of success. With respect to counseling, this means longer treatment times/more sessions, as well as input from providers from a variety of

fields. When considering medications, recent evidence indicates that higher doses (as appropriate), some combination regimens, longer duration of therapy, and initiating prior to quit date (for nicotine replacement, similar to accepted protocols for other medications) generally are associated with higher success rates.

4.1 Psychosocial Interventions

Counseling for ND greatly improves long-term success. Although intervention can be delivered in many forms, emphasis on two factors appears to be key: practical skills/problem solving and intra-treatment support. The delivery of services can differ with respect to intensity and modality. "Intensity" refers to the amount of time/number and spacing of sessions. The depth to which issues are dealt with and the extent of patient participation are likely correlated features. "Modality" is the manner in which treatment is delivered. The following is a brief overview of current options.

(a) *Brief interventions in the primary care setting*: Primary care physicians and their staffs operate in an environment that offers many advantages regarding the delivery of a standardized, brief intervention. The use of health information by experts to motivate patients, along with the capacity to counsel and provide prescription medications, is a highly effective combination. The major barriers are the limited time available to deliver these services, as well as inadequate reimbursement.

Brief interventions can be developed in light of the usual operations in the outpatient clinic. They require little money or staff time, with interventions as short as 3 min substantially increasing cessation rates. One widely employed option is the "5As" method, which involves the following: (1) asking about tobacco status at each visit, (2) advising all tobacco users to quit, (3) assessing the patient's willingness to quit, (4) assisting the patient in quitting, and (5) arranging for follow-up contact. Finally, if the intervention is unsuccessful or the provider believes a more potent intervention is necessary, patients can be referred to more intensive counseling programs.

(b) *Specialty tobacco clinic interventions*: This treatment option represents the highest end of the intensity dimension. Such programs generally are delivered by individuals who have received Tobacco Treatment Specialist training to conduct a multi-session, face-to-face program (group or individual based) that addresses numerous issues related to achieving cessation. These programs often employ aggressive pharmacotherapy and more sophisticated counseling techniques and provide extended follow-up services.

(c) *Quitelines*: Telephone-based services have the advantages of broad reach and somewhat more sophisticated counseling services, as well as easy access and relative anonymity. Pharmacotherapy options tend to be more limited, relying on patients working with their own physicians for complex options, and thus are not as

tailored or closely monitored as specialty clinic options. Overall, they may be considered of moderate intensity and represent a good option for many patients.

(d) *Other options*: Recently, other delivery modalities have emerged, including web- and cellular telephone text-based options. Although available data are limited, early findings suggest the utility of these treatments.

4.2 Approved Treatment for ND

National guidelines recommend that pharmacologic therapy be considered for all smokers attempting to quit unless it is medically contraindicated. The US Food and Drug Administration (FDA)-approved pharmacologic interventions are nicotine replacement therapies (NRTs), bupropion hydrochloride, and varenicline tartrate, all of which enjoy extensive published support for their effectiveness. Behavioral counseling is an important adjunct to any pharmacologic intervention for smoking cessation (Faessel et al. 2010).

A large proportion of the ability to quit smoking is heritable, with an estimated heritability of 50–60% (Broms et al. 2006). During recent years, genetic variation in the major pathway of nicotine metabolism has been shown to alter the quantity of cigarettes smoked. Genetic variation in nicotine metabolism and receptor genes, and in the dopaminergic pathway genes, has been implicated in the ability to quit smoking.

(a) *Nicotine replacement therapies* deliver nicotine to ease withdrawal and craving while allowing the smoker to break the behavioral habits associated with tobacco use. Withdrawal symptoms are experienced by many when attempting to quit and can reduce the likelihood of achieving and maintaining abstinence.

There are five FDA-approved nicotine replacement options. Nicotine polacrilex gum and lozenges are available in 2 mg and 4 mg doses and are sold without a prescription. Patients must be instructed as to their proper use (e.g., "chew and park" routine for the gum, avoiding ingestion of anything that alters the oral pH). The primary advantage of these products is the ability to adjust administration as needed for changing circumstances. Nicotine transdermal patches (also over-the-counter) have the advantage of maintaining steady blood nicotine concentrations over the course of the day. Both the nicotine nasal spray and the inhaler require a prescription. All NRTs may produce side effects, although these often can be reduced or eliminated with proper use tailored to the individual. The usual duration of use is approximately 3 months, although evidence is accumulating of better long-term abstinence with longer use.

(b) *Bupropion* hydrochloride (Zyban) is an atypical antidepressant with noradrenergic and dopaminergic effects. Mechanisms of action include inhibition of dopamine reuptake in the nucleus accumbens, as well as nicotine antagonism in the ventral tegmental area. The recommended and maximum dose for smoking cessation is 300 mg per day, usually taken as 150 mg twice daily. Dosing should begin at 150 mg a day, the drug being given daily for the first 3–7 days, followed by an

increase to the recommended 300 mg a day as tolerated. Typically, therapy is begun 1–2 weeks before the patient's determined smoking quit date. Treatment should continue for at least the recommended 12 weeks.

(c) *Varenicline* tartrate (Chantix) was approved by the FDA in 2006 for the treatment of ND. This medication appears to function as a partial agonist at α4β2 and full agonist at α7 nicotinic cholinergic receptors that binds with high affinity to these receptors. Nicotine stimulation of this particular receptor, with which varenicline binds with high specificity, is associated with significant mesolimbic dopamine release, which reinforces nicotine use. The high affinity with which varenicline binds to this receptor, in conjunction with its long half-life, reduces nicotine's capacity to stimulate the receptor, thereby attenuating the reinforcing properties of nicotine ingestion while providing sufficient stimulation to counter withdrawal symptoms. Dosing is up-titrated from 0.5 mg per day to 2 mg per day over the first week; 3–6 months of use is recommended.

5 Precision Medicine for ND

Almost all approaches to human genetic studies have been used to search for susceptibility genomic regions and genes for ND, including genome-wide linkage analysis and candidate gene-based or genome-wide association (GWA) studies. Although there is a great variability in the detected linkage peaks among studies, primarily because of the small samples, variations in measures of smoking behavior, and differences in ethnic backgrounds and environmental factors, genetic variants in the following three groups have received much attention:

(a) *Nicotine metabolism genes*: One of the most investigated genes of this type is *CYP2A6*, which encodes the enzyme cytochrome P450 CYP2A6. In humans, about 70–80% of nicotine is converted to cotinine by this liver enzyme, with minor contribution from CYP2B6. Nicotine is metabolized to minor compounds by additional enzymes, including FMO3 and UGT2B10. The majority of cotinine undergoes further metabolism to 3′-hydroxycotinine (3HC) in a reaction mediated exclusively by CYP2A6 (Fig. 19.1). The 3′-hydroxycotinine/cotinine ratio, known as the nicotine metabolite ratio (NMR), is an established and validated phenotypic indicator of CYP2A6 activity in daily smokers; faster CYP2A6 activity is reflected by a higher NMR (Allenby et al. 2016). Approximately 33–40% of cotinine is converted to its primary metabolite, 3HC, also by *CYP2A*6.

The *CYP2A6* gene is highly polymorphic, with many variants altering the protein's function. Variants in *CYP2A6* have been associated with several smoking-related phenotypes. Individuals can be genotyped for these variants and grouped into CYP2A6 activity groups (e.g., faster and slower metabolizers) on the basis of the predicted metabolic impact of their *CYP2A6* genotype on nicotine clearance (Benowitz et al. 2006). Smokers with reduced- or null-activity *CYP2A6* alleles (i.e., *CYP2A6*9*, *CYP2A6*12*, *CYP2A6*2*, or *CYP2A6*4*) smoke fewer cigarettes and

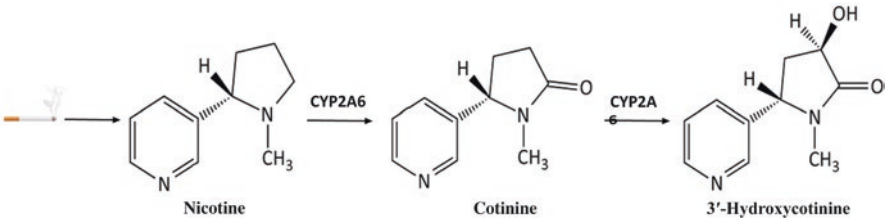

Fig. 19.1 Metabolism of nicotine to cotinine and *trans*-3′-hydroxycotinine

tend to be less nicotine dependent and more likely to quit than smokers with normal or increased enzyme activity. Several smoking cessation studies have reproducibly indicated that the nicotine metabolism rate predicts quitting success.

Given the large number of *CYP2A6* alleles, as well as the influence of environmental factors on nicotine metabolism, a phenotypic biomarker of CYP2A6 activity (3HC/cotinine) appears to be a more robust predictor of cessation than genotype. Similar to genotype-based activity groupings, smokers can be dichotomized as faster or slower metabolizers on the basis of NMR. However, there currently is no single optimized NMR cut-point to distinguish slower from faster metabolizer for cessation optimization. Different investigators have selected NMT cut-points based on sensitivity and specificity analyses of smoking cessation outcomes. Slower nicotine metabolizers have lower cigarette consumption, dependence, nAChR availability, and brain response to smoking cues than do faster nicotine metabolizers. Slower nicotine metabolizers also display higher smoking cessation rates in the absence of pharmacotherapy.

In smokers randomized to treatment based on NMR, varenicline was more efficacious than were nicotine patches in faster metabolizers but showed no or little difference in value for slower metabolizers, suggesting that varenicline is more suitable for faster metabolizers, whereas the patch is more suitable for slower metabolizers (Lerman et al. 2015).

Like *CYP2A6*, *CYP2B6* is highly polymorphic. The CYP2B6 protein is expressed in the liver and in extrahepatic tissues, including the brain, and degrades bupropion to its pharmacologically active metabolite hydroxybupropion (Kharasch et al. 2008). Thus, variation in CYP2B6 activity that alters the hydroxybupropion concentration could influence the success of bupropion-assisted smoking cessation. The common CYP2B6*6 haplotype (e.g., about 25% in Caucasians) comprises the VYP2B6*4 (rs2279343) and CYP2B6*9 (rs3745274) non-synonymous variants and is associated with lower hepatic CYP2B6 protein expression and reduced metabolism of bupropion.

In addition to its role in bupropion metabolism, CYP2B6 is believed to act in the central metabolism of nicotine. In rats, the selective inhibition of brain CYP2B, which is thought to mimic genetically slow CYP2B6 metabolism in humans, is associated with high brain nicotine concentrations and a need for a greater number of sessions to extinguish nicotine self-administrative behavior. In placebo-treated Caucasian heavy smokers, those with one or two copies of *CYP2B6*6* had lower

end-of-treatment quit rates than those with no copies of the variant (Lee et al. 2007). Thus, slow CYP2B6 activity may be associated with a higher relapse risk in subjects receiving placebo and possibly those taking bupropion.

(b) *Nicotinic receptor subunit genes*: Variation in nAChR genes, particularly in the *CHRNA5/A3/B4* cluster, located on chromosome 15q25, has been examined for association with smoking cessation success either in the absence of treatment or with active pharmacotherapy. Although variants in the *CHRNA5/A3/B4* cluster are robustly associated with small differences in cigarette consumption and ND (see Chap. 5), the association between these variants and smoking cessation outcomes has differed in various studies.

Of the SNPs in this cluster that have been investigated, rs16969968, located in *CHRNA5*, has been studied most frequently. In a meta-analysis of 24 studies in nontreatment-seeking Caucasian smokers, those with the AA genotype of rs16969968 quit a median of 4 years later than smokers with the GG genotype (Chen et al. 2015b). In a separate analysis of community-based Caucasian smokers, a high-risk haplotype, defined by rs16969968 (A allele) and rs680244 (C allele), delayed self-reported smoking cessation by a median of 2 years compared with lower-risk groups (Chen et al. 2012). In contrast, rs16969968 does not appear to be associated with quitting with the aid of pharmacotherapy. A meta-analysis in smokers receiving NRT showed no associations between rs16969968 or rs1051730 and end-of-treatment or 6-month quit rate (Leung et al. 2015). Furthermore, in several studies of treatment-seeking individuals, including those using the nicotine patch, bupropion, or varenicline, variant rs16969968 showed no association with smoking cessation or the end-of-treatment quit rate (Chen et al. 2015a; Tyndale et al. 2015). Two other SNP tagging loci, rs588765 and rs578776, in the *CHRNA5/A3/B4* cluster that have been robustly associated with minor influences on cigarette consumption and dependence in Caucasians, likewise, were not associated with cessation outcomes (Tyndale et al. 2015). Taken together, the lack of replicated findings for nAChR gene variants and smoking cessation outcomes reduces the likelihood that this genomic region will be useful in precision medicine action for smoking cessation.

Beyond the *CHRNA5/A3/B4* cluster, variation in other nAChR subunit genes also has been associated with smoking cessation. The A allele of rs2072661 in *CHRNB2* was associated with lower quitting rates in both bupropion- and placebo-treated smokers (Conti et al. 2008). Analyses in three separate placebo-controlled clinical trials revealed additional SNPs, rs3811450 and rs4292956 in *CHRNB2*, rs3787138 and rs2236196 in *CHRNA*4, and rs6494214 in *CHRNA7*, which influenced abstinence in response to varenicline (King et al. 2012). Whether these findings will be replicated in other varenicline-treated smokers or extended to other treatments remains to be determined.

(c) *Dopamine and other relevant neurotransmitter systems*: Variation in the genes involved in the dopamine system has been investigated as a potential source of differences in smoking cessation outcomes. In general, functional polymorphisms that lead to reduced dopaminergic activity are thought to contribute lower smoking cessation success (David et al. 2008).

Although the VNTR polymorphism in exon 3 of *DRD4* was not associated with overall abstinence in Caucasian smokers receiving placebo or bupropion, bupropion increased the cessation rate in smokers with one or more copies of the long allele (seven or more repeats) and showed no benefit in smokers with two copies of the short allele (fewer than seven copies) compared with placebo-treated controls (Simpson et al. 2010). In a separate study, Bergen et al. (2013) observed a larger, albeit nonsignificant, benefit of bupropion in those with the long allele than in those homozygous for the short allele. Together, these data suggest that bupropion is a more suitable treatment for smokers with the long allele of exon 3 of *DRD4*.

Genetic variants in the dopamine transporter (*SLC6A3*) and *DRD*2 genes also have been examined as potential modulators of smoking cessation outcomes. At the end of treatment, neither the 3′-VNTR polymorphisms in *SLC6A3* nor the *Taq*1A2 RFLP polymorphism located in about 10 kb of the 3′ end of *DRD2* was found to be associated with abstinence in Caucasian smokers randomized to receive either placebo or bupropion (David et al. 2007). However, the *Taq*1A2 polymorphism was associated with bupropion-assisted quitting at 6-month follow-up. In those with the *DRD2 Taq*1A2/A2 genotype, quit rates were higher for subjects taking bupropion than those on placebo. By contrast, bupropion was not associated with a greater cessation rate in *Taq*1A1 individuals. These findings highlight the potential importance of assessing multiple genes and gene–gene interactions, as opposed to single genes, to identify subgroups of smokers who are more likely to benefit from a certain treatment.

6 Concluding Remarks

The recent and current genetic studies of ND and smoking cessation have already provided a wealth of knowledge regarding the etiology of ND and its successful treatment. Insights into the molecular mechanisms underlying ND and other smoking-related behaviors should provide new biological targets for developing novel treatment drugs. Although none of the susceptibility variants is a definitive genetic screening tool for the diagnosis of ND and its treatment, many susceptibility variants have been suggested. For example, smokers with faster rates of nicotine metabolism, as determined by the NMR, have higher quit rates when taking varenicline than with the nicotine patch. On the other hand, for the slower metabolizers, varenicline is not superior to the patch. Thus, appropriate determination of variants influencing *CYP2A6* activity is an important element in implementing precision medicine for smoking cessation. Although the genetic variants in nAChRs and the dopaminergic systems also have been associated with smoking cessation, the results from different studies have been less consistent. Further investigation is needed to improve personalized treatment. The development of treatment approaches that consider multiple genetic and environmental factors may provide important new options for the prevention and treatment of and population screening for ND. Finally, pharmacogenetic research may identify the individuals most susceptible to ND and those who may benefit maximally from certain medications.

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