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Tailoring Nicotine Replacement Therapy

Rationale and Potential Approaches

Jennifer B. McClure[1] and *Gary E. Swan*[2]

1 Group Health Cooperative, Center for Health Studies, Seattle, Washington, USA
2 SRI International, Center for Health Sciences, Seattle, Washington, USA

Abstract

Nicotine replacement therapy (NRT) is an effective treatment for smoking cessation, but as with all such pharmacotherapies, the majority of smokers who use NRT products do not stop smoking or remain abstinent long term. Treatment outcome is affected by a range of individual-specific factors, as well as the pharmacokinetic profile of each NRT formulation. This has led to speculation that abstinence rates could be improved if NRT treatments were individually tailored to best match each individual's needs and preferences. There are also populations for whom special product and dosage considerations are warranted to maximise treatment safety.

This paper reviews the rationale for NRT treatment, standard dose recommendations and recommendations for how to best match NRT treatment to the specific needs of individual smokers. We also review emerging evidence that genetic profiling may one day be a useful consideration for tailoring NRT treatment.

Two medications are currently approved for smoking cessation: nicotine replacement therapy (NRT) and bupropion sustained release (SR). Both have been shown to approximately double the odds of long-term smoking cessation;[1,2] however, their effects are relatively modest. NRT results in abstinence rates of approximately 18–31% after 6 months in clinical trials,[1] and 5–15% in over-the-counter (OTC) simulation studies.[3] Comparable abstinence rates have been reported for bupropion SR.[4] Current practice guidelines recommend both medications be combined with behavioural treatment for maximum intervention effectiveness.[1,5]

Individually tailoring behavioural smoking cessation materials increases their efficacy compared with generic materials.[6-8] Similarly, choices about medication type, formulation and dose are commonly based on individual characteristics and altered as necessary to improve outcome. Given the modest effects of NRT, experts have speculated that the effectiveness of this medication could also be enhanced by tailoring its form, dose and duration to each individual's needs and preferences. Tailoring may further increase treatment safety. In this article, we discuss the rationale and evidence for individually tailoring NRT use. We explore the relevant expert opinion and empirical evidence for this practice, examine populations for whom special treatment considerations may be warranted, and discuss genetic factors that may prove to be important for tailoring NRT in the future. Based on the available evidence, we also present a decision tree to aid clinicians in making decisions about NRT.

1. Overview of Nicotine

1.1 Nicotine and Tobacco Dependence

Nicotine is the most important compound in the initiation and maintenance of tobacco dependence.[9-11] Once tobacco smoke is inhaled, it travels to the small airways and alveoli of the lungs, where nicotine is absorbed rapidly into the blood. The average nicotine intake per cigarette is 2.3mg, but it has been shown to be as high as 3.5mg.[12] The exact amount absorbed depends on puff volume, inhalation depth, the extent of dilution with ambient air, puff rate and puff intensity. Within 10–20 seconds after inhalation, nicotine reaches the brain. This rapid absorption speed and its related consequences make smoking a highly reinforcing and dependence-producing form of nicotine administration.[13]

Nicotine is thought to create dependence by activating the mesolimbic dopaminergic reward pathway. Nicotine stimulates neural nicotinic acetylcholine receptors (nAChRs), which are present presynaptically in the CNS and post-synaptically in the autonomic nervous system.[14] nAChRs modulate the release of neurotransmitters such as dopamine.[14] As nicotine exposure increases, the number of nAChRs increases and tolerance develops. Factors that decrease the bioavailability of nicotine are thought to increase an individual's cravings and decrease the likelihood of cessation because more of the drug is needed to achieve a given level of dopamine.[15] When nicotine self-administration stops, physiological withdrawal symptoms occur.[15,16]

1.2 Relevant Pharmacokinetics of Nicotine

There is considerable individual variation in the rate and pattern of nicotine metabolism.[17] In general, 70% of nicotine is eliminated from the blood in each pass through the liver, and approximately 70–80% of absorbed nicotine is converted to cotinine.[18] The plasma half-life of nicotine after smoking averages about 2 hours, while the half-life of cotinine is about 16 hours.

A number of environmental and genetic factors affect nicotine metabolism, but the relative contribution of each is unknown. Eating, posture, exercise and ingestion of drugs alter hepatic blood flow and, therefore, are likely to alter the rate of nicotine metabolism. Menthol, grapefruit juice and increasing age can also inhibit nicotine metabolism.[13] An emerging literature suggests that sex hormones may induce liver enzyme cytochrome P450 (CYP) 2A6 activity, which could explain recent findings that pregnancy and the use of oral contraceptives are associated with faster clearance of nicotine in women.[19] This could also explain why some studies have found that NRT is less effective in women than in men.[20,21]

Genetics also play a role in nicotine metabolism. While the entire nicotine metabolic pathway remains to be fully elucidated, several genes, particularly *CYP2A6*, are clearly implicated.[22-24] There are many allelic variants of *CYP2A6*. These variants range in frequency from 0% to 22.3%, depending on the ethnicity of the population under study, and can be associated with reduced or no metabolism of nicotine.[13] In a recent investigation of nicotine metabolism in Caucasian twins, metabolism heritability was substantial (~60%), but the variation in *CYP2A6* genotype accounted for only a small portion of the total twin covariation.[25] These results suggest that there are other unaccounted-for sources for genetic variation in nicotine metabolism, in addition to *CYP2A6*. Currently, we do not have a complete understanding of all relevant genes in the metabolic pathways (e.g. *CYP2B6*,[26] *CYP2D6*,[27,28] *CYP2E1*,[29] *CYP2A13*[30] and flavin-containing mono-oxygenase-3 gene [*FMO3*])[31] or of several of the genes responsible for glucuronidation.[32,33] In time, however, we will have a more complete understanding of how genetics influence nicotine metabolism and the subsequent treatment implications of these findings.

2. Nicotine Replacement Therapy (NRT)

2.1 Current Formulations and Pharmacokinetics

NRT is currently available in six different formulations, but the availability of each varies by country.

Nicotine gum is available without a prescription in most countries and comes in 2mg and 4mg doses. The 4mg gum is recommended for heavier smokers (>25 cigarettes per day). The gum may be used in response to nicotine cravings, but a fixed interval schedule (e.g. 1–2 pieces an hour) for 1–3 months is recommended. Gum use is associated with mild adverse effects, including hiccups, upset stomach or sore jaw. These effects tend to diminish if the gum is used correctly.[1]

The transdermal nicotine patch is also commonly available without a prescription. There are four different patch formulations on the market. Each varies in its design, pharmacokinetics and duration of wear (e.g. 24 or 16 hours).[34] All are available in a similar range of patch doses. For example, the NicoDerm® CQ® [1] patch (marketed in the US by GlaxoSmithKline Consumer HealthCare) and the Habitrol® patch (marketed in the US by Novartis) come in three dosing strengths (21, 14 and 7mg). The Nicotrol® patch (marketed in the US by Pfizer) comes in two doses (15 and 5mg). All are designed to be tapered over time, but the tapering schedule also varies by brand.

Patch use may be associated with mild adverse effects including headache, upset stomach, nausea and dizziness. These effects generally subside within a few days.[35] Sleep disturbance and a mild rash at the site of placement are also common.[36] Many smokers prefer the patch because it requires administration only once a day; however, its relatively slow rate of nicotine delivery and low level of peak absorption have raised questions about whether its effectiveness could be improved.

Transdermal nicotine patches were designed to alleviate symptoms of withdrawal from abstinence.[37] Following administration, venous nicotine concentrations slowly increase and then plateau within 4–6 hours.[38] This slow, stable delivery results in desensitisation of nicotine receptors and eventual tolerance to the reinforcing effects of nicotine,[38,39] but transdermal nicotine delivery does not completely alleviate cigarette cravings.[40,41] This led to the development of other forms of NRT which deliver nicotine in a way that more closely resembles smoking.

The nicotine nasal spray is available by prescription in most countries,[34] but is not currently available in France (Le Houezec J, personal communication). Each dispenser contains 10 mg/mL of nicotine, which is dispensed at a rate of 0.5mg per spray. A single dose equals one spray per nostril. It is recommended that one to five doses be used per hour, but no more than 40 per day, for 3–6 months. Adverse effects are common and include nasal and throat irritation, a runny nose, watery eyes, sneezing and coughing. These effects may subside with continued use.[42,43] A comparative advantage of the nasal spray is its speed of nicotine delivery to the brain, which is faster than with each of the other formulations. Peak plasma concentration is reached within 11–13 minutes after administration;[44] however, compliance with the nasal spray is lower than with other forms of NRT.[45]

The nicotine inhaler is marketed as a prescription medication in the US and the UK, but is available without prescription in some countries. The recommended dose is 6–16 cartridges per day, each of which delivers 4mg of nicotine in 80 inhalations. Treatment duration is 6 months, with use tapering after the third month. Like the nasal spray, use of the inhaler can result in mouth and throat irritation and can cause a cough. These effects usually resolve with continued use, but compliance is lower than with the patch or gum.[46]

The nicotine lozenge is available without a prescription. The lozenge comes in 1, 2 or 4mg doses, but the 1mg lozenge is available only in some European countries and there are no efficacy data available for this dose.[34] The pharmacokinetic properties

1 The use of trade names is for product identification purposes only and does not imply endorsement.

of the lozenge are similar to those of nicotine gum, but nicotine absorption is 25–27% higher than with the gum.[47] The adverse effects are generally moderate and transient, the most common being insomnia (reported in <5% of users), nausea, hiccups, coughing, heartburn, headache and flatulence. Dosage is based on how soon after waking the first cigarette of the day is smoked. In the US and UK, a 4mg dose is indicated for most smokers.[34]

The nicotine sublingual tablet is available in many European countries.[34] The 2mg tablet is held under the tongue, where the nicotine is absorbed sublingually. The pharmacokinetic profile of the sublingual tablet resembles that of the 2mg gum. Adverse effects are also similar to those of nicotine gum and are generally mild, tolerable and transient.[48] People who smoke <20 cigarettes per day are instructed to use one tablet per hour. Those who smoke >20 cigarettes a day are advised to use two tablets per hour and not to exceed 40 tablets per day. After 12 weeks, it is recommended that the number of tablets be gradually tapered.[34]

Each NRT formulation is buffered to alkaline pH to facilitate the absorption of nicotine through cell membranes. Of all the formulations, the nasal spray most closely approximates the rate of nicotine delivery from smoking, but with all formulations, absorption is slower and the increase in nicotine blood concentrations more gradual than with smoking. NRT also fails to achieve complete replacement of plasma nicotine concentrations from smoking. Plasma nicotine concentrations from NRTs tend to be in the range of those observed in low-level cigarette smokers. *Ad libitum* use of NRTs results in one-third to two-thirds the concentration of nicotine that is achieved by cigarette smoking.[13]

2.2 Effectiveness

Based on systematic reviews of the literature, NRT increases the likelihood of giving up smoking by a factor of 1.5–2.0 compared with placebo.[1,49] Of all the formulations, the nicotine nasal spray performed best in clinical trials, but its advantage was small. Overall, each formulation is considered to be as effective as the other[1,49] and the effectiveness of each is increased by the use of adjunctive behavioural counselling.[14]

3. Tailoring NRT

3.1 Rationale

NRT treatment outcome may be affected by a range of factors including treatment adherence, adverse effects, nicotine dependence, individual differences in nicotine metabolism and the kinetic profile of each NRT formulation. Although NRT is effective compared with placebo, experts speculate that outcomes could be enhanced by tailoring treatment to match individuals' needs and preferences. To date, there are limited empirical data to inform these types of decisions, and current treatment guidelines and product information offer little guidance on how to individualise NRT to maximise effectiveness. Much of what is known is based on expert clinical opinion. Product choice and timing of use also have important safety implications for some populations. In this section, we discuss several basic considerations that should be taken into account when initiating NRT treatment, review the evidence for enhancing NRT doses and discuss several populations for whom special tailoring considerations may be warranted (figure 1). Finally, we examine the emerging evidence that individual genetic variation may be an important consideration for tailoring NRT pharmacotherapy in the future.

3.2 Basic Tailoring Considerations

The first decision in tailoring NRT is product choice. Initial NRT product choice should take the individual's medical condition into account. NRT is generally not recommended in persons who have had a myocardial infarction within the last 2 weeks, serious arrhythmias or serious angina. It should also be used with caution during pregnancy or in breastfeeding women. These issues are discussed further in section 3.5. Other use precautions are specific to each type of NRT. For example, nicotine gum should be used with caution in patients with dental prosthetics; the patch may aggravate existing skin conditions; and the nasal spray should be used

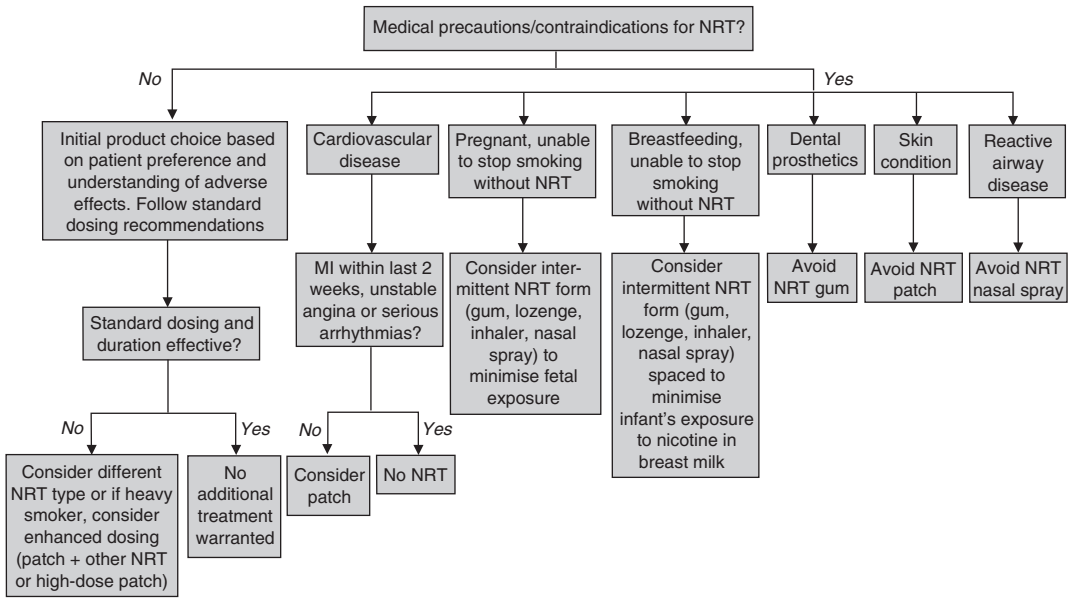

Fig. 1. Decision tree for tailoring nicotine replacement therapy (NRT) for adult smokers. **MI** = myocardial infarction.

with caution in persons with severe reactive airway disease.[1]

In the absence of medical precautions or contraindications for a particular NRT type, initial product choice can be informed by patient preference. Preference should take into account the administration requirements and adverse effect profile of each product. However, it is unclear to what extent patient preference is clinically important. In one study, smokers who chose their NRT form were more likely to reduce their smoking over a 2-week period compared with those randomly assigned to treatment,[50] but a separate study[51] failed to find any difference in outcome at 15 weeks when smokers were randomly assigned to NRT type.

Once a product type is chosen, dose should be based on pretreatment level of nicotine dependence, which is typically determined by the number of cigarettes smoked per day. Instructions for dosage and administration are included with each product. More complicated algorithms have also been recommended. Haustein[52] suggests an algorithm based on a combination of each smoker's Fagerström Test of Nicotine Dependence score, pretreatment smoking rate and expired carbon monoxide level. While this algorithm may provide a more accurate proxy of nicotine dependence, to date there are no empirical data to show that more elaborate measures of dependence improve NRT treatment matching or outcomes; moreover, such measures may be more complicated than is practical for the average smoker or clinician.

3.3 Enhanced NRT Dosing

Given the overall modest effectiveness of NRT, it has been proposed that enhancing NRT dose or duration could increase long-term abstinence success, particularly in heavier smokers. The maximum standard patch dose (21 or 22mg, depending on brand) provides a steady-state concentration of venous nicotine that is well below the concentrations obtained by heavy smoking (>20 cigarettes per day). In one study, only one-third of abstinent smokers wearing a daily 22mg patch were found to have steady-state nicotine concentrations equalling their pretreatment smoking concentrations.[53] Since a higher patch dose (44 mg/day) results in better nicotine replacement and overall withdrawal management,[54] increasing serum nicotine concentrations

through use of a higher NRT dose could promote greater cessation in heavier smokers.

There are two ways to enhance NRT dosing: (i) by increasing the dose of a single NRT form; or (ii) by combining NRTs. Three studies have evaluated the efficacy of enhanced monotherapy, i.e. a 44mg patch compared with a standard patch.[55-57] Three additional studies have compared a 25mg, 16-hour patch with a 15mg, 16-hour patch.[40,58,59] Pooling data from all six studies, Silagy and colleagues[49] concluded that higher patch doses may provide a small overall benefit compared with standard patch doses (odds ratio [OR] 1.21; 95% CI 1.03, 1.42).

Seven studies have examined the use of combination NRT (patch + gum, patch + nasal spray, patch + inhaler) versus standard dose monotherapy.[60-66] The patch provides a steady state of nicotine replacement, which is augmented with a faster-acting NRT to address breakthrough cravings.[67] The results of these trials are mixed, but when their outcomes were pooled for meta-analysis, there was a clinically modest, but statistically significant benefit for combining the patch with another form of NRT (OR 1.42; 95% CI 1.14, 1.76).[49] Consistent with this evidence, both the US and UK tobacco dependence treatment guidelines recommend that smokers who are not successful using monotherapy should be encouraged to try combination therapy (i.e. patch + other).[1,68] However, NRT manufacturers have not sought regulatory approval for combination therapy and their labeling in the US and most countries warn against such use. More safety data will be needed before regulatory approval is sought, but even so, this may not occur as it is not a priority for manufacturers who do not market more than one NRT product.[67]

NRT dosing may also be enhanced by extended treatment duration. Current clinical guidelines recommend an 8-week course of the nicotine patch, although some manufacturers recommend up to 10 weeks. Several studies have evaluated the benefit of extending patch therapy beyond 8 weeks, but have failed to provide strong support that this significantly increases the treatment effect.[49,59,69-72] In contrast, in a recent analysis that pooled data from 21 NRT trials published between 1984 and 1999, Medioni and colleagues[73] used mathematical modeling to demonstrate that stopping NRT increased the risk of smoking relapse compared with the risk associated with stopping placebo treatment. The authors estimated that among 1000 smokers who stop smoking while using NRT, 310 will be abstinent at 5 months. If abstainers stop using NRT after 5 months, an estimated 140 will be abstinent at 24 months. If abstainers continue to use NRT, an estimated 175 will be abstinent at 24 months. If this model is confirmed in future clinical trials, treatment recommendations may be modified to include extended NRT.

3.4 Combination NRT and Bupropion

Bupropion (SR formulation) is the first non-nicotine medication shown to be effective for smoking cessation. Its exact mechanism of action is unknown, but it is thought to block the reuptake of dopamine and/or noradrenaline (norepinephrine).[1] While bupropion can be used in combination with NRT, to date there is little research on the combined effect of NRT and bupropion and no empirical support for this practice. Jorenby et al.[74] found that combined NRT and bupropion resulted in clinically and statistically higher 1-year continuous abstinence rates than NRT patch alone (23% vs 10%; $p < 0001$), but there was no difference when this treatment was compared with bupropion alone (18%). In a separate trial of adolescent smokers, abstinence rates at 26-week follow-up were no different for patch plus 150mg bupropion versus patch alone (8% vs 7%).[75]

3.5 Tailoring for Special Populations

3.5.1 People with Cardiovascular Disease

Randomised clinical trials have failed to support an association between acute myocardial events and NRT use, even when individuals continue to smoke.[76-80] Despite the general safety of NRT, some authorities recommend it not be used for at least 2 weeks post-myocardial infarction,[78] or by persons with severe arrhythmias or unstable angi-

na.[81] NRT is considered to be well tolerated and is recommended for other cardiac patients.[82]

Of the different forms of NRT, some experts believe the patch is preferable for particularly high-risk cardiac patients because of its slow delivery and low concentration of nicotine. Other forms of NRT deliver nicotine more quickly and may pose more risk for already high-risk cardiovascular patients.[81] Ultimately, however, continued smoking poses the greatest risk to persons with acute cardiovascular disease and the clinical appropriateness of all forms of NRT should be considered.[82]

3.5.2 Pregnant Women

Nicotine is responsible for many adverse outcomes during pregnancy (e.g. loss of the fetus, premature labour or delivery, placental abruption and toxic effects to the fetus) and a range of post-natal outcomes (e.g. sudden infant death syndrome, mental retardation, childhood cancer, and behavioural and cognitive problems during childhood).[83] As a result, NRT is classified as a Pregnancy Category D drug by the US FDA. This rating acknowledges the fetal risk, but implies that the health benefits to the pregnant woman may be acceptable despite the risks. Continued smoking during pregnancy results in fetal exposure to nicotine and a host of carcinogenic toxins. If pregnant women are unable to stop smoking without pharmacological aid, exposure to NRT may pose less risk to the fetus than continued smoking.

Funding agencies have generally been hesitant to support research on NRT use during pregnancy.[83] As a result, there is no direct evidence of the safety and effectiveness of NRT during pregnancy.[84] However, expert consensus and leading practice guidelines support the use of NRT among pregnant women who are unable to stop smoking without pharmacotherapy.[1,68]

To date, there is no empirical evidence to inform decisions regarding tailoring the type, dose or timing of NRT in pregnant smokers. Because it appears that sustained exposure to nicotine can cause fetal neurotoxicity, it is most prudent not to use nicotine patches during pregnancy, but rather to use more rapid-release forms of nicotine intermittently or, if patches are used, to use them for only 16 hours and not 24 hours in order to minimise fetal exposure.[83]

3.5.3 Breastfeeding Women

Nicotine adminstered via NRT passes into breast milk and infants who are breastfed in this setting are exposed to nicotine. This low level of exposure is unlikely to be hazardous to the child and any potential risks are outweighed by the benefits of not smoking to both the mother and child.[1,83] There is no empirical basis for choosing one form of NRT over another for the breastfeeding mother, but it is theoretically possible that the type of NRT formulation used could impact on the concentration of nicotine present in breast milk. Transdermally administered nicotine provides a steady state of venous nicotine and is likely to result in a steady concentration of nicotine in breast milk. In comparison, intermittent NRT use, as can be achieved with other NRT formulations, may minimise nicotine exposure in breast milk if the duration between nicotine administration and breastfeeding is prolonged.[83] More research is needed, but breastfeeding women may consider use of lower-dose, intermittent forms of NRT while breastfeeding.

3.5.4 Adolescents

The effectiveness of NRT in adolescents is largely unknown. Two open-label[85,86] and three randomised trials[75,87,88] have evaluated the impact of NRT use in this population. Only Moolchan et al.[88] found evidence that the patch was more efficacious than placebo (18% vs 2.5% abstinent at 3 months). Nicotine gum was also examined in this study, but not found to be more effective than placebo.

In the absence of evidence that NRT use is harmful to adolescents, experts recommend that it be offered to youths who are trying to stop smoking, provided there is evidence of nicotine dependence or there is evidence that nicotine withdrawal symptoms were present during previous attempts to give up.[1,89] NRT is not recommended for adolescents who smoke <10 cigarettes per day or as a first-line treatment for adolescents.[90] Adolescents should first be encouraged to attempt to quit smoking without pharmacological aid. If NRT is subsequently

used, there is no empirical data to indicate which form is preferable in this patient population.

3.6 Genetic Tailoring

Although it is too early to make recommendations for NRT tailoring based on genotype, current pharmacogenetic research is attempting to elucidate the role of genes in pharmacological treatment outcome. One placebo-controlled study found that variations in the dopamine receptor *DRD2* and dopamine β-hydroxylase *DBH* genes were associated with the likelihood of abstinence following use of the patch.[91] Specifically, individuals with the A1 allele of *DRD2* and the A allele of *DBH* were much more likely to be abstinent at 1 week and at 12 weeks following treatment initiation. Subsequent analysis revealed that these associations may be mediated by sex. Women with the *DRD2* A1 allele were more likely to be abstinent at the 6- and 12-month follow-ups, whereas this effect was not observed in men.[92] An open-label trial of patch and nasal spray found that variation in the μ-opioid receptor (*OPRM1*) gene was also predictive of treatment response.[93] Smokers with the Asp* variant were more likely to be abstinent than those who were homozygous for the Asn* variant, with the effect being most pronounced in individuals who received the patch. It is important to further note that the effect of genotype diminished as the nicotine dose of the patch was tapered, and was entirely absent following the end of treatment in this trial.

In another published report, Lerman and colleagues[94] examined the role of two functional genetic variants of the *DRD2* gene in response to NRT and bupropion among participants in two randomised clinical trials. At the end of treatment, there was a significant interaction between the *DRD2 – 141 C Ins/Del* genotype and treatment that indicated a more favourable response to bupropion among smokers who were homozygous for the *Ins C* allele compared with those with a *Del C* allele. By contrast, smokers with the *Del C* allele had significantly higher cessation rates while using NRT patch compared with those homozygous for the *Ins C* allele. The results suggest that NRT may be more beneficial for smokers with the *DRD2 – 141 Del C* allele and bupropion may be preferential for smokers homozygous for the *DRD2 – 141 Ins C* allele.

The accumulating literature makes it clear that an individual's genotype accounts for some variation in the effectiveness of NRT, but the association between genotype and treatment outcome is complex. The association appears to depend not only on genes, but also on the type of medication. For NRT, it also depends on form and dose, sex and time of follow-up. Finally, the role of any single candidate gene is likely to be small. Gene/gene interactions are expected to provide better predictors of treatment outcome than single gene effects.[95,96]

More research is needed before treatment recommendations can be based on genetic profile. First, a true prospective pharmacogenetic trial of sufficient size is needed so that individuals with different genotypes can be assigned to different treatments in order to test *a priori* hypotheses.[97] Secondly, it is likely that responsiveness to NRT is at least a two-pathway process, with one involving the nicotine metabolic pathway and the other involving a receptor pathway.[98] To date, no studies involving more than one pathway have been published. Another area in need of further research is the cost effectiveness of treatment tailoring based on genotype relative to that for tailoring based on a less invasive proxy for genotype, such as family history of smoking, or to no tailoring at all.[99] Finally, it should be noted that substantial variation in the frequency of alleles associated with slower nicotine metabolism has been reported across samples of different ethnic origin.[13,100] This strongly suggests the need for caution in extrapolating findings from NRT clinical trials based on Caucasian participants to the treatment of individuals in other ethnic groups, especially with regard to dose and duration of NRT.

4. Conclusion

Current leading practice guidelines recommend NRT use for smokers trying to quit.[1,2,68] This treatment has been demonstrated to be effective in numerous clinical trials;[1,49] however, abstinence rates with NRT are less than ideal and there are some

populations for whom NRT use involves special considerations to minimise risk. NRT may not be the pharmacotherapy of choice for all smokers, and there is clear evidence that its effectiveness is enhanced when paired with comprehensive behavioural counselling,[1,2] but individually tailoring NRT type and dose to match smokers' needs and preferences may also enhance treatment outcome and maximise safety. These assumptions are based largely on expert clinical opinion, but there are some empirical data to support them. Special tailoring considerations are recommended with more nicotine-dependent smokers, particularly those who do not respond to standard NRT treatment, pregnant and breastfeeding women, persons with significant cardiovascular disease and adolescents. There are also emerging pharmacogenetic data to suggest that individual genotypes may alter NRT response and that treatment may one day be tailored to an individual's genetic profile. More empirical evidence is needed in each of these areas. In the meantime, clinicians are advised to consider whether their patients may benefit from a tailored NRT treatment regimen which takes into account smokers' individual characteristics, needs and preferences.

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Correspondence and offprints: Dr *Jennifer B. McClure*, Center for Health Studies, Group Health Cooperative, 1730 Minor Ave, Suite 1600, Seattle, WA 98101, USA.
E-mail: McClure.J@GHC.org