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Factors influencing the impact of pharmacogenomic prescribing on adherence to nicotine replacement therapy: A qualitative study of participants from a randomized controlled trial

Alison J. Wright,[1] Stephen Sutton,[2] David Armstrong,[3] Paul Aveyard,[4] Ann Louise Kinmonth,[2] Theresa M. Marteau[2]

[1]Centre for Behaviour Change, University College London, London, WC1E 7HB, UK

[2]Department of Public Health and Primary Care, University of Cambridge, Cambridge, CB2 0SR, UK

[3]School of Population Health Sciences, King's College London, London, SE1 1UL, UK

[4]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, OX2 6GG, UK

Correspondence to: AJ Wright, alison.j.wright@ucl.ac.uk

Abstract

Pharmacogenomics may improve health outcomes in two ways: by more precise and therefore more effective prescribing, tailored to genotype, and by increasing perceived effectiveness of treatments and so motivation for adherence. Little is known about patients' experiences of, and reactions to, receiving pharmacogenomically tailored treatments. The aim of this study was to explore the impact of pharmacogenomic prescribing of nicotine replacement therapy (NRT) on smokers' initial expectations of quit success, adherence, and perceived important differences from previous quit attempts. Semi-structured interviews were conducted with 40 smokers, purposively sampled from the Personalized Extra Treatment (PET) trial (ISRCTN 14352545). Together with NRT patches, participants were prescribed doses of oral NRT based on either mu-opioid receptor (OPRM1) genotype or nicotine dependence questionnaire score (phenotype). Data were analyzed using framework analysis, comparing views of participants in the two trial arms. Although most participants understood the basis for their prescribed NRT dose, it little influenced their views. The salient features of this quit attempt were the individualized behavioral support and combined NRT, not pharmacogenomic tailoring. Participants' initial expectations of success were mostly based on prior experiences of quitting. They attributed taking medication to nurse advice to do so, and attributed reducing or stopping it to side effects, forgetfulness, or practical difficulties. Intentional nonadherence appeared very rare. Pharmacogenomic NRT prescribing was not especially remarkable to participants and did not seem to influence adherence. Where services already tailor prescriptions to phenotype and provide individualized behavioral support for treatment adherence, pharmacogenomic prescribing may have limited additional benefit.

Keywords

Precision medicine, Pharmacogenetics, Smoking cessation, Nicotine replacement therapy, Psychological impact, Patient compliance

INTRODUCTION

Pharmacogenomics, the study of how genetic factors influence an individual's response to medication, offers the promise of "enabling the provision of the right drug at the right dose to the right patient" [1], increasing treatment effectiveness and reducing side

Implications

Practice: Pharmacogenomic tailoring of medication dose cannot be relied on to improve motivation for treatment adherence.

Policy: Policymakers should note that the benefits of pharmacogenomics are more likely to be realized via optimized treatment effectiveness or reduced likelihood of side effects rather than by motivating increased medication adherence.

Research: Further research is needed to examine patients' understanding of pharmacogenomic prescribing and its effects across a range of conditions.

effects. Treating nicotine dependence provides one potential clinical application of pharmacogenomics with broad population relevance and potential benefit. Tobacco smoking was the second leading risk factor for disability-adjusted life years lost worldwide in 2015 [2]. In 2015, age-standardized prevalence of daily smoking was 18.1% for women and 19.9% for men in the UK, and 11.7% for women and 14.4% for men in the USA [2].

There is evidence that responses to pharmacological smoking cessation therapies can vary across individuals based on their genotype. Tailoring smoking cessation therapies to smokers' genotypes could enhance their effectiveness [3–5]. However, little is known of how smokers might respond to pharmacogenomic tailoring of their cessation medications in clinical contexts. In particular, do smokers understand the rationale for their recommended dose, how does pharmacogenomic tailoring affect beliefs about quitting and is there any behavioral impact on medication adherence? Given there is evidence that greater adherence to cessation medications enhances the likelihood of quit attempt success [6,

7], there is a strong rationale to explore the impact of pharmacogenomic prescribing on beliefs about treatment and adherence.

Commentators point to several potential impacts of pharmacogenomic tailoring on beliefs and medication adherence [8, 9]. Treatment recommendations based on genomic factors may be seen as more personalized than recommendations based on phenotypic factors. Increased perceived relevance of a medication recommendation may increase perceived medication effectiveness and expectations of treatment success, leading to higher adherence. Secondly, a number of studies have suggested that when genomic factors are described as influencing a health problem, treatments with biological mechanisms of action, such as medications, may be perceived as more effective [9−11]. Given greater perceived effectiveness of medication is associated with increased adherence [12], this could be another mechanism by which pharmacogenomic prescribing increases adherence. However, one concern is that patients may not understand pharmacogenomic tailoring and therefore such interventions may not influence their motivation for medication adherence. A second concern regards how patients may react if pharmacogenomic tailoring suggests they need a larger than average dose, or a stronger medicine. Such information might reduce expectations of treatment success, or this effect could be offset by the benefit of knowing one's prescription is tailored to maximize the likelihood of effective treatment.

To assess the impact on adherence to nicotine replacement therapy (NRT) of informing smokers that their dose of medication is tailored to their genotype, a randomized trial (ISRCTN 14352545) was conducted, comparing the impact of pharmacogenomic tailoring of NRT dose size versus tailoring based on nongenomic information, that is, phenotype [13, 14]. In the trial, informing smokers their oral dose of NRT was tailored to genotype had a small, statistically nonsignificant effect on 28-day adherence to NRT. To better understand this finding, a qualitative process evaluation was undertaken. This paper presents the findings from semi-structured interviews with trial participants, exploring how they made sense of pharmacogenomic versus phenotypically based tailored prescriptions and how this affected their views about, and experiences of, smoking cessation.

Aims and objectives
To conduct semi-structured interviews with participants from both arms of the trial to explore:

- How they understood the pharmacogenomic or non-pharmacogenomic basis for their NRT dose.
- Their initial expectations regarding the likely impact of their tailored NRT dose.
- Their explanations for their level of adherence to NRT and the extent which pharmacogenomic tailoring appeared to influence this.

- What they felt were the notable differences between this and previous quit attempts and the extent to which pharmacogenomic tailoring was salient.

METHODS

The intervention and the study setting
The trial was prospectively registered (ISRCTN 14352545) and procedures are described in detail elsewhere [14], so an overview is provided here. Ethical approval for the trial was secured from Hertfordshire 1 Research Ethics Committee (reference 06/Q0201/21). The trial took place in two large UK cities, in the context of UK National Health Service (NHS) stop smoking services, which provide behavioral support and smoking cessation medication. To be eligible for the trial, individuals had to smoke at least 10 cigarettes a day. All participants were offered behavioral support and NRT. Behavioral support was based on withdrawal-orientated therapy [15] and provided for all participants twice prior to quit day and weekly thereafter until 4 weeks after quitting and then once more 8 weeks after quitting. All nurses were trained to give individual behavioral support to NHS standards [16]. The support lasted 10−30 min, depending upon progress and stage of the quit attempt.

Smoking cessation medication
NRT was prescribed according to the intervention protocol at the second clinic visit and a quit date agreed. All participants were prescribed two types of NRT: patches and an oral type of "top-up" NRT, because this combination is more effective than NRT patch alone [17]. NRT patch strength was based on cigarettes smoked per day for all participants. Participants were randomly assigned to have their top-up NRT dose tailored based on genotype or phenotype information. The aim of the trial was to examine the behavioral impact of pharmacogenomic tailoring. In order to isolate the impact of pharmacogenomic tailoring specifically, we provided tailored top-up doses to both groups, and explained the dose to the control group in a manner analogous to that used in the pharmacogenomic group. We term the approach used in the control group as phenotypic tailoring.

Pharmacogenomic tailoring
The trial used testing for the Asp40 variant in the mu-opioid receptor (*OPRM1*) gene as its paradigm. During the design of the trial, the *OPRM1* gene was a promising candidate, with a reported association with smoking cessation [18]. Moreover, in that original study, abstinence rates at follow-up among the group receiving the nicotine transdermal patch were ∼31% in those with one or more copies of the Asp40 variant, and ∼16% in those with two copies of the

Asn40 variant. The rates among the group receiving the nicotine nasal spray were ∼15% and ∼13%, respectively. Therefore, Asp40 carriers appeared to have double the short-term quit-rates when using the patch (a form of NRT with higher levels of nicotine replacement), compared with the spray (NRT resulting in lower levels of replacement.) However, it should be noted that the genotype × treatment interaction effect was not statistically significant in this study, and a subsequent study failed to replicate this finding [19]. Nevertheless, for present purposes, whether individuals' genotype influences smoking cessation is not directly relevant. The focus here is rather the impact of communicating to smokers that their medication has been tailored on a genetic basis. One day before quit day, participants were given their patches and oral NRT and told the basis (pharmacogenomic or phenotypic) for the dose of oral NRT by the research nurse. Participants in the genotype arm were informed that,

> Your extra NRT is based on the results of a genetic test. We did a genetic test on the blood/saliva sample that you gave last week. People have different versions of the 'OPRM1' gene. This gene influences how dependent you are on nicotine. There is more information on genes in the leaflet. Based on the results of your genetic test, you are more likely to be successful in stopping smoking if you have a (standard dose/higher dose) of extra NRT.

Participants with the Asn variant were advised to take oral NRT to deliver 6 mg NRT/day ("standard dose"), while those with the Asp variant were advised to take oral NRT to deliver 12 mg/day ("higher dose").

Phenotypic tailoring

Participants in the phenotype arm had their oral NRT dose tailored on the basis of their Fagerström Test for Nicotine Dependence (FTND) [20] responses. They were informed,

> Your extra NRT is based on the results of the questionnaire you completed last week. The questionnaire shows how dependent you are on nicotine. Based on the results of this questionnaire, you are more likely to be successful in stopping smoking if you have a (standard dose/higher dose) of extra NRT.

Participants scoring less than eight on the FTND were advised to take a "standard dose" of top-up NRT (6 mg/day) while those scoring eight or above were advised to take a "higher dose" of top-up (12 mg/day). Participants were requested to take their NRT as prescribed for 4 weeks after their quit date. The primary outcome was the proportion of all NRT prescribed that was consumed, averaged over the 28 days after the quit date.

All participants were given a personalized booklet, describing their daily NRT dose and giving reasons for that dose, including the physiological mechanisms by which taking their NRT, including their personalized top-up dose, would increase their chances of quitting. The research nurses followed a clinical protocol that asked them to emphasize the importance of adherence and the pharmacogenomic or phenotypic rationale for the NRT dose, using wording similar to:

> You should wear a new patch for 24 hours each day for at least four weeks. The patch works by releasing a steady dose of nicotine into your blood stream. You have also been given a standard/high dose of extra NRT. Please use this as well as wearing the patch. You may wish to take it when you get a craving, but you can also take it at other times of the day. Even if you feel you don't need the extra NRT, you should take it. Many quit attempts fail because people don't take enough NRT or stop taking it before they have beaten their withdrawal symptoms. Remember that this dose has been calculated to suit your individual needs − try to stick to this amount each day in addition to wearing the patch.

Sessions in which the basis for tailoring of oral NRT was communicated were audio-recorded. Assessment of a subsample of randomly selected recordings was conducted to assess the fidelity to the clinical protocol. This was deemed acceptable in all cases, with delivery of all key components [13]. Participants were also given a wallet-sized appointment card summarizing their top-up dose of NRT and its rationale.

At each of the four, subsequent weekly visits, the nurses assessed the amount of NRT patients used by doing a "pill count". The intervention manual instructed nurses to stress the importance of adherence as follows:

> Check that the participant is using their NRT as prescribed, and also that they are using it correctly. Emphasize that the oral product should be used regularly and that they should keep taking it, even if they feel that they don't need it. If the participant does not wear a patch for 24 hours reiterate the importance of doing so. However, if the participant states that they are unable to wear the patch for 24 hours (e.g. at night due to nightmares) instruct them to wear the patch for at least 16 hours and take more extra NRT as stated below to make up for the NRT not taken

The manual also instructed nurse to repeat the genotypic or phenotypic rationale for the NRT dose, as follows:

> Reiterate the rationale for the prescription. Emphasize that the extra NRT has been personalized to their individual requirements, and should be uniquely suited

to their needs. Be sure to highlight that it has been prescribed according to the results of their DNA test or their smoking habits questionnaire.

Qualitative data collection

Semi-structured telephone interviews collected data about the experiences of trial participants. Interviews took place at least 28 days after the quit date but before the 6-month follow-up assessment, so that participating in the interviews (which involved discussing one's level of adherence to NRT) would not bias the primary outcome, but participants would have made their quit attempts recently enough to be able to recall their experiences in detail. All interviews were conducted by the first author, who at the time was a postdoctoral research associate with a PhD in Health Psychology. The interviews were conducted using a semi-structured topic guide. Participants were asked about their understanding of the basis for their top-up NRT dose, their initial expectations upon learning about their tailored dose, their experiences of taking NRT including factors they felt influenced their adherence and what they felt were the differences between this and previous quit attempts. The latter was asked in order to gauge the extent participants spontaneously mentioned dose tailoring as an important difference from their perspectives.

Participants

Participants for this qualitative study were purposively sampled from the trial participants, aiming to represent all four trial arm/top-up dose size combinations, and then within each arm/dose group a range of ages, genders, and study nurses seen. Notes were made of all contacts with potential participants, including those who declined to be interviewed. After interviewing 10 participants for each combination of trial arm/dose size it was decided that no major new themes were emerging, so no further data were collected. Interview duration ranged from 15 to 35 min.

Analysis

All interviews were transcribed verbatim and anonymized using participant numbers. Data were analyzed using framework analysis [21]. Framework analysis has five stages: familiarization, identifying a thematic framework, indexing, charting, and mapping and interpretation. NVivo11 software was used to manage the data. We explored similarities and differences in the accounts of participants in the genotype and phenotype trial arms and those receiving higher or standard doses of top-up NRT. Internal validity was enhanced by using the "constant comparative method" and deviant case analysis. To ensure that constructions placed on the data by the lead analyst (first author) had been consistently and rigorously derived, a second, independent analyst (second author) reviewed the data to verify the interpretations. Disagreements were resolved through discussion, often resulting in refinements to the categories and explanations.

RESULTS

Participants interviewed

Table 1 shows the characteristics of the participants interviewed. The interviewees are similar to the full trial sample in terms of age and gender. However, their mean NRT adherence is somewhat better than for the full trial sample (which was 66.0%) but similar to the mean adherence level for the subsample who completed the 4-week behavioral support program (88.7%) [6].

How did participants understand the basis for their dose?

Genotype arm

Most participants in the genotype arm described their dose as tailored based on either a genetic test or a "blood test." The genetic test was viewed as indicating the dose of NRT required or as indicating how heavily participants smoked or how susceptible they were to addiction,

> I had the genes suggestion, which was, as I say, the six tablets and the patches (Participant 11, genotype standard)

> The genetic thing suggested that I was an average sort of smoker. (participant 12, genotype standard)

Table 1 | Qualitative study participants' demographic characteristics and NRT adherence

Characteristic	Genotype	Phenotype
Prescribed dose of top-up NRT (% (*n*))		
Higher	50 (10)	50 (10)
Standard	50 (10)	50 (10)
Gender (% (*n*))		
Male	40 (8)	25 (5)
Female	60 (12)	75 (15)
Age (mean (*SD*))	48.0 (10.8)	51.9 (14.6)
Proportion of all prescribed NRT consumed over 28 days (mean (*SD*))	84.4 (23.8)	80.9 (29.5)

NRT nicotine replacement therapy; *SD* standard deviation.

Interviewer: Did you know what they were looking for in your saliva sample?

Pt: Well they, they were looking for genetic markers for addiction. (participant 14, genotype standard)

A few participants described their dose as based on blood test results, but did not state that the blood test examined genetic factors. There was only one participant who explicitly described the genetic test results in terms of their implications for quit attempt success, and this person had the lower risk genotype.

[I] didn't have the, erm, the affected gene, erm, that meant that I was more susceptible to, to not giving up, as I remember. (participant 16, genotype standard)

Many of the genotype arm participants who knew their dose was based on a genetic or blood test, especially those prescribed a higher dose of top-up, also described their dose as influenced by how heavily they smoked.

Interviewer: Why is it that they recommended that [dose] ... what do you think that was based on? ... Participant: Probably because of my blood test which stated that I had that terrible gene. Erm, and also that. . . . I had been having about ten to 12 roll ups a day (participant 1, genotype higher)

This may reflect all participants' NRT patch doses being tailored to their nicotine dependence. Participants perhaps did not distinguish between how their patch dose was determined and how their top-up dose was determined. Alternatively, this may result from the pharmacogenomic rationale describing the gene as influencing nicotine dependence. Nevertheless, two genotype arm participants explained the basis for their top-up dose only in terms of heaviness of smoking.

There was little evidence that the genetic information had caused comprehension problems and only two participants could not recall the basis for their NRT dose. Another was adamant he had not been recommended a set top-up dose and so was not asked about the basis for its size. He had multiple health issues, which may have affected his information processing ability, and so may have had particular difficulty with the study information.

Phenotype arm
Most participants in the phenotype arm understood their prescribed dose as based on their heaviness of smoking or level of nicotine dependence, with a sense that NRT dose was designed to replicate the nicotine intake from smoking. A minority of participants were more specific, describing their NRT dose as based on their questionnaire responses,

I filled in a questionnaire, and the patches and the amount of lozenges were suggested from the results of the questionnaire. (participant 21, phenotype higher)

Only one phenotype arm participant was unable to recall the basis for their dose. In contrast to the genotype arm, phenotype arm participants prescribed higher and standard doses of top-up NRT described the basis for their dose size in similar fashions.

Initial expectations of the quit attempt after receiving tailored NRT prescribing

Participants' early expectations for their quit attempt, having been informed about their tailored dose, were largely positive. The influences on these expectations were varied, including prior quit experiences, perceived benefits of NRT, the basis for the prescribed dose and study information. There was no clear patterning of expectations according to the basis of NRT prescribing. Participants often drew on their experience of their own or others' previous quit attempts to judge the likely usefulness of the NRT offered. One of the most common explanations for positive initial expectations was previous failures to quit using a single type of NRT.

It was more than what I'd had previously from the GP [family physician] and the smoking clinic, because they just gave you either the patches or the gum. And I just thought the more replacement I was having, the less chance I was likely to smoke. (participant 22, phenotype higher)

One participant drew on others' experiences of using NRT patches, saying

I've never used patches, but lots of people I know have tried the patches... and, you know, they've nearly all said, 'Oh they're useless, you know', so I ... felt that, probably, for me anyway, I did need something to boost them up (participant 31, phenotype standard)

For another participant, vicarious experience of NRT's benefits came via a relative who worked in smoking cessation who reported seeing even very heavy smokers quit successfully using NRT. Only two participants, both in the genotype arm and receiving a standard dose of NRT, mentioned the basis for the prescribed top-up dose as an influence on their expectations. One felt positive, saying,

Well it was explained to me, as I say, the results on the genetic sort of ((thing?)) was that if I took the two I would stand more of a better chance of, you know, staying, staying off it really, which I think is how it works. (participant 13, genotype standard)

In contrast, the other participant who mentioned the basis of her dose explained she was uncertain what to expect because she was uncertain how her dose compared to other people's and how it had been tailored.

While some participants based their expectations on previous experiences, others focused on aspects of the NRT recommended in the trial. They felt positive due to having the two types of NRT to use or being prescribed a larger dose of nicotine replacement than in their previous quit attempts. However, one participant considered their recommended dose too large to decrease their nicotine dependence as quickly as they desired.

The size of the prescribed NRT dose was not the only aspect of the top-up NRT that informed positive expectations. Participants from both trial arms had anticipated that the top-up NRT would help them deal with cravings and, in the case of those using the inhalator, provide a useful substitute for actions associated with smoking.

The recommendation to use a fixed, minimum quantity of NRT each day informed some participants' positive expectations. One thought this more directive approach to NRT use was likely to work better than the less structured way he had used it in the past. The other participant reported positive expectations due to the importance ascribed to NRT adherence in the study materials.

NRT dose size and expectations

One concern was that participants prescribed higher doses of oral NRT might interpret this as suggesting a lower likelihood of quit attempt success. However, this was not borne out. Having a way to deal with cravings informed positive initial expectations for participants prescribed both standard and higher top-up doses. Participants prescribed a higher dose of top-up had positive expectations due to knowing they were getting a larger replacement dose of nicotine than in previous quit attempts or were not solely reliant on one form of NRT. Participants prescribed higher top-up doses did not seem to view this as indicating that they had less chance of quitting successfully. Participants prescribed a standard top-up dose expected benefits from using of top-up as a substitute for the actions of smoking more often. They explicitly referred to study information about NRT other than the basis for their prescribed dose more often as influencing their initial expectations than did participants prescribed a higher dose.

Explaining NRT adherence

Participants' explained variation in their adherence to their prescribed NRT as due to multiple factors. Their accounts encompassed both intentional and unintentional (non)adherence. Deliberately not taking one's prescribed dose of NRT was very rare. The only genotype arm participant who did so wanted to test whether he had overcome his nicotine dependence,

> If you have an operation and you're in some pain thereafter, you take loads of painkillers. . . . After a while you might stop taking the painkillers to see how well you feel, because while you're taking painkillers

it doesn't hurt, right? So, if you stop taking the painkillers and it still doesn't hurt then you know you're healing up nicely. . . . So, on some days I wasn't using the patches to see . . . whether I could manage without using the patches. (participant 2, genotype higher)

However, according to the participant, the trial nurse strongly advised against this, explaining that varying one's dose, "Sort of ... interferes with your brain and you've, you've got to wean yourself off it gradually, gradually and consistently" (participant 2, genotype higher).

Two participants in the phenotype group mentioned deliberately varying their NRT dose. In both cases, the participants felt that their prescribed dose of nicotine replacement was too large.

> They say, don't they, on the pack [of NRT patches], it's like twenty or more cigarettes a day to have the highest dose of the patch. So then I was thinking, well if I have four of these [inhalator cartridges] I might as well smoke my cigarettes. . . . I thought, 'I'm trying to be cutting down not taking more' (participant 23, phenotype higher)

Participants in the phenotype group appeared to be deliberately nonadherent because they understood the basis for their dose and felt that the prescribed dose did not match that basis well enough.

The fact that trial nurses recommended NRT adherence as key to quit attempt success, both in general and after participants had been nonadherent, was one of the most common explanations for adherence.

> Participant: I've took exactly what [the nurse] said.
> Interviewer: Okay. And why was it that you decided to do that?
> Participant: Because she told me to. Because she told me that I'd got to take a patch and two inhalators every day. (participant 16, genotype standard)

> Some days I wasn't taking as many and she said, 'Please take what we prescribe would you?' That was fine. (participant 24, phenotype higher)

Genotype arm participants were somewhat more likely to note the trial nurses' advice as an influence on their NRT use than phenotype arm participants. Another positive influence on adherence was the NRT use diary, which formed one of the trial outcome measures. A few participants felt that recording their daily NRT consumption in the diary had increased their adherence.

Participants' experiences while taking NRT heavily influenced their adherence. The positive impact of oral NRT on cravings encouraged further adherence, as well as validating the trial nurses' advice.

> [The nurse] kept saying to me every week, 'Just keep saying no. And if you feel like a cigarette pop a chewing

gum in.' And I did, and it worked every time. (participant 3, genotype higher)

Side effects, such as mouth and throat pain, nausea, or headaches, were key obstacles to NRT adherence for participants in both trial arms. Participants, particularly those in the genotype arm, noted that using top-up NRT correctly was time-consuming. They described lozenges or microtabs taking up to an hour to dissolve in the mouth, interfering with enjoying one's food, drinking and talking with others.

> Those things can take up to an hour to dissolve under your tongue, about six hours a day. When do you find time to have a cup of tea, eat a meal without the taste of a nasty thing in your mouth, talk to somebody? (participant 14, genotype standard)

Other participants explained that, in their workplaces, sucking "sweets" (candy) or chewing gum were deemed inappropriate, deterring their adherence. Some participants, particularly in the genotype arm, reported sometimes forgetting to use their NRT. The time required to use top-up correctly could exacerbate the impact of forgetting to use it earlier in the day,

> I couldn't remember to take twelve in a day. And if I would forget for, you know, four hours or something and then think, 'Oh ****! I've got to have nine in the next hour before I go to bed.' (participant 1, genotype higher)

Reasons for adherence and size of prescribed top-up dose
Only participants prescribed higher doses of top-up NRT were deliberately nonadherent to their medication. They also more commonly used top-up according to when they experienced the urge to smoke. Side effects seemed to deter adherence more for participants prescribed a standard size dose. However, the most commonly expressed factors influencing adherence, following the trial nurses' recommendations, finding time to take the whole dose and experiencing practical difficulties were noted as often by those prescribed a standard dose as those prescribed a higher dose.

Perceived differences between this and previous quit attempts

Participants who reported prior quit attempts were asked what they felt were key differences between this attempt and their previous ones, in order to gauge how often tailored dosing was spontaneously mentioned as an important difference. Responses fit into five broad categories: quitting in the context of a research study, NRT, support from study staff, psychological factors, and the environment in which the quit attempt occurred. There was little evidence that size of top-up NRT dose affected the types of

differences noted. For one participant, from the phenotype arm, the quit attempt occurring in the context of a trial was important, as

> You have to take it seriously. . . . I can't imagine going and not being serious about quitting smoking. (participant 32, phenotype standard)

There was no mention of the tailoring of NRT dose, apart from one participant, who stated,

> Having that, that test and being told that 'yes, you did have the gene,' made me forgive myself a bit more for smoking in the first place. (participant 1, genotype higher)

Genotyping seemed to allow her to be less self-critical about smoking. The genotype information may have been notable for her because she had a relative who worked in smoking cessation, and so perhaps was more familiar with what these services typically offer.

Participants often noted differences related to NRT. A few participants, all prescribed standard doses of top-up, had not used NRT before and so noted using NRT as a key difference. In contrast, many participants, from both trial arms, had used NRT before and felt that having top-up NRT, or a particular kind of top-up NRT, was important

> The inhaler that's the thing that, that makes the difference. That's the one product that they've brought out which works (participant 2, genotype higher)

Participants across both trial arms commonly emphasized support available from the trial nurses as an important difference, typified by this comment,

> Last time I tried, although I did have a little bit of support from the . . . clinic at the doctor's, it wasn't anything like as comprehensive as this help. (participant 33, phenotype standard)

Aspects of the support that were noted as particularly helpful included having a regular weekly appointment and preferring one-to-one support to smoking cessation groups because,

> It was more personal and you could, you know, ask questions, that sort of thing. (participant 34, phenotype standard)

Participants also stressed differences in their own psychological resources for quitting. Some reported that they had more willpower, more motivation or were fully ready to quit.

> I'd kind of got to a point where I didn't want to be a smoker (participant 25, phenotype higher)

Others felt their previous quit attempts were in response to pressure from significant others, whereas this time it was, "Me, I wanted to stop" (participant 15, genotype standard). Reporting positive psychological differences was more common among participants in the genotype arm. A minority of participants remarked on differences in the wider environment that influenced their quit attempts, such as more restrictions on where one could smoke and greater perceived social pressure not to smoke than during previous attempts.

DISCUSSION

This study explored the experiences of smokers receiving either pharmacogenomically or phenotypically individualized smoking cessation treatment, as part of the first fully powered trial to investigate whether pharmacogenomic prescribing could promote medication adherence [13]. The majority of participants could describe the basis upon which their NRT dose had been individualized. However, the strongest positive influences on adherence were following study information and the nurses' advice, while key negative influences were side effects, forgetting, and practical difficulties. Participants in the genotype arm did not remark upon the pharmacogenomic personalization of the NRT as a key difference from previous quit attempts, instead noting the use of oral NRT and individualized nurse support as important.

Implications for the impact of pharmacogenomic prescribing on patients' adherence

The data reported here help illuminate why the trial found no significant advantage of pharmacogenomic prescribing on adherence to NRT over the first 28 days of the quit attempt. They also have implications for whether pharmacogenomic tailoring of medications for other health problems might promote medication adherence. Firstly, in contrast to concerns that pharmacogenomic test results might cause comprehension difficulties [22], most participants in the genotype arm could report the gist of how their dose had been tailored. As part of the trial, effort was made to develop the accessible written information materials explaining the rationale for participants' recommended NRT dose. Study nurses also provided repeated explanations at each study visit. Future pharmacogenomically tailored interventions may benefit from taking a similar approach.

Being prescribed a higher dose of NRT, based on one's genotype or phenotype, did not seem to lead to doubts about treatment effectiveness or one's ability to quit. Instead, drawing on their experiences of previous quit attempt failures, participants prescribed higher top-up NRT doses felt positive due to having a larger dose of NRT than in previous attempts or because they expected to better cope with cravings.

Thus, feeding back pharmacogenomic test results suggesting that larger than average doses of the medication are required need not have a discouraging effect on patients receiving these results. The study information framed the pharmacogenomic NRT dose recommendation positively, as that which would maximize the likelihood of quit attempt success. Only one of the genotype arm participants appeared to connect this information with susceptibility to quit attempt failure. Participants instead spoke of the genetic marker in terms of their susceptibility to addiction or dependence and/or their need for a particular NRT dose. Framing the pharmacogenomic information differently, for example, describing *OPRM1* as a marker of reduced ability to quit smoking and the recommended NRT dose as required to lessen the risk of quit attempt failure, might have had a different, potentially more adverse, psychological impact.

With a couple of exceptions, reasons participants gave for their level of NRT adherence were similar in the two trial arms. Although pharmacogenomic prescribing might have influenced initial views about NRT, it seemed that experiences while quitting had a stronger influence on adherence. In particular, side effects deterred adherence, while the need to deal with cravings prompted participants to use their NRT. Side effects and perceiving medication as effective at treating symptoms are likely to be influences on medication adherence across a wide variety of health problems that might be addressed by pharmacogenomically tailored medications. On the basis of this study, we might expect that such factors will have more influence on adherence than pharmacogenomic tailoring to maximize the likelihood of positive treatment response. In contrast, if a pharmacogenomic intervention instead tailored treatments to reduce the likelihood of adverse effects, then any resultant reduction in experienced side effects might serve to promote medication adherence. Finally, it should be noted that oral NRT requires multiple doses per day and thus engenders both practical problems and memory demands. Therefore, these findings may not transfer to the impact of pharmacogenomic prescribing on adherence to medications taken once or twice a day.

Implications for using pharmacogenomics to tailor treatments for smoking cessation

Together with the results of the trial, this study suggests that benefits of pharmacogenomic prescribing of smoking cessation treatment are more likely to be via increasing the likelihood of a positive treatment response or reducing risks of adverse effects, rather than simply by motivating smokers to be more adherent to smoking cessation medication. It remains possible that providing a more extensive pharmacogenomic rationale, based on a genetic marker more strongly predictive of medication response, might better motivate adherence. The intervention

was delivered in primary care in a universal coverage health care system, which is free at point of use. This constrained the number of sessions that could be offered. An intervention devoting more time to expanding on the pharmacogenomic rationale might have stronger effects on adherence, but may be harder to later implement into routine clinical care if found effective. The setting for the present study also meant participants came from a range of backgrounds. Therefore, the findings should have high transferability to other contexts in which pharmacogenomic tailoring of smoking cessation medication may be implemented.

The one-to-one psychological support for quitting provided by the trial nurses was highly valued by participants and perceived by them as an effective form of treatment personalization. The apparent influence of nurses' advice on adherence may be somewhat inflated if social desirability concerns led some interviewees to present themselves as valuing the advice more than they did. However, there was evidence that participants experienced positive consequences of following the nurses' advice, such as finding that use of oral NRT enabled better coping with cravings, which may have served to enhance the perceived credibility of, and further attention to, the nurses' recommendations.

The behavioral support program provided in both arms was mostly typical of those provided within the NHS Stop Smoking Service in England, albeit with extra attention to adherence, explaining the rationale explicitly and assessing it every week. This extra focus on adherence may have led to the high levels of adherence seen in both arms of the trial [6]. Increasing the emphasis on NRT adherence in behavioral support provided to smokers during a quit attempt may be a simple change that could be adopted by many smoking cessation programs.

Implications for using pharmacogenomics to tailor treatments for other conditions

Participants in the present study had typically smoked for many years and often tried to quit previously, sometimes using medication to do so. As a result, their previous smoking cessation treatment experiences clearly informed their reactions to the NRT dose recommendation. Our findings suggest that, when treating a chronic health problem where patients have considerable prior experience of treatments, expectations of a new treatment are likely to be more informed by patients' prior treatment experiences than by whether the treatment has been individualized according to phenotypic or pharmacogenomic factors. In contrast, the present study's findings might not transfer to patients' reactions to pharmacogenomic prescribing for a condition with which they have been newly diagnosed, such as cancer. In the present study, pharmacogenomic testing informed dosage, rather than the choice of

therapeutic agent. The impact of this second type of pharmacogenomic prescribing on medication adherence remains to be determined.

All participants had accepted an invitation to make a pharmacologically assisted quit attempt in a medical setting. Evidence suggests that only a small proportion of British smokers who attempt to quit make use of such services [23]. Therefore, participants may have had more positive initial expectations of, and willingness to use, NRT than do the broader population of smokers, who tend to be chary of using medication [24, 25]. The impact of pharmacogenomic tailoring may be different for health conditions where there is no viable alternative to using medication and so treatment may be offered to individuals with a wider range of initial willingness to take medication.

Strengths and limitations

This study is one of the first to use qualitative methods to explore the experiences of patients undergoing pharmacogenomic tailoring to determine medication dose size in a clinical and trial context. The sampling strategy enabled us not only to contrast those whose dose was determined by genotype against those whose dose was determined by phenotype, but also to explore how views and experiences differed for those prescribed higher and standard doses. The ideal trial design for contrasting the behavioral effects of pharmacogenomic and phenotypic prescribing would have been to use the same dosing algorithm in both arms but to randomize each arm to receive different information on the method employed to tailor dose. However, as this would have required deceiving participants, it was regarded as unacceptable [13].

It is possible that pharmacogenomic prescribing may have had a larger influence if greater time had been spent explaining it to participants. However, when rolling out pharmacogenomics into the smoking cessation clinic, the time available to explain a pharmacogenomic dosing rationale is likely to be limited. Therefore, it is valuable to examine how smokers understand this type of rationale when it is presented as part of an intervention of feasible length.

Participants interviewed for this study were, on average, slightly more adherent to NRT than the full sample of trial participants. While intention to treat principles were used when calculating mean adherence in the trial, only participants who remained engaged with the trial and were willing to be interviewed could contribute data to the present study. Therefore, we do not know how individuals who dropped out of the trial soon after their quit date and who may have had very low NRT adherence perceived pharmacogenomic tailoring. Participants' stated reasons for their NRT adherence may have been influenced by social desirability concerns.

Attempts were made to minimize this by prefacing interview questions about adherence with a statement to suggest that nonadherence was common, expected and occurred for a wide range of reasons. Individuals may lack awareness of the full range of psychological factors influencing their behavior [26], and so tend to overestimate the importance of cognitive, rational factors while having less awareness of the impact of more automatic influences such as habits, prompts, and emotions. Therefore, reported reasons for adherence may not encompass all factors that in fact influenced adherence.

It should be noted that evidence has emerged since this trial was conducted [19] suggesting that *OPRM1* genotype does not predict response to smoking cessation therapy, and so this particular genomic marker is unlikely to be applied clinically in the future. However, this does not change the value of the present study in providing a paradigm in which to explore smokers' adherence responses to pharmacogenomic prescribing of NRT and how patients in general may behaviorally respond to pharmacogenomic testing to determine optimum medication dosage.

CONCLUSION

This study suggests that pharmacogenomic tailoring of NRT dose was not especially remarkable to participants and did not seem to influence adherence better than prescribing tailored to phenotype, consistent with the trial's results. Where smoking cessation services already tailor NRT prescriptions to nicotine dependence and provide behavioral support for treatment adherence, pharmacogenomic prescribing may have limited additional benefit. The benefits of pharmacogenomics are more likely to be realized via optimizing treatment effectiveness or reducing the likelihood of side effects rather than simply through motivating increased medication adherence.

Compliance with Ethical Standards

Conflict of Interest: P.A. is the chief investigator of a publicly funded trial of nicotine patches, where the patches have been donated to the National Health Service by Glaxo Smith Kline. There was no direct benefit to him or his employer. A.J.W., S.S., D.A., A.L.K., and T.M.M. declare they have no actual or potential conflicts of interest.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Primary data: The findings reported have not been previously published and the manuscript is not being simultaneously submitted elsewhere. A very early, partial version of the data analysis reported in this manuscript was presented as an oral presentation at the European Health Psychology Society Conference, Pisa, Italy, 2009. The main results of the trial from which participants were drawn are reported in Marteau et al. [13]. The authors have full control of all primary data and they agree to allow the journal to review their data if requested.

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