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The effect of nicotine dependence and withdrawal symptoms on use of nicotine replacement therapy: secondary analysis of a randomized controlled trial in primary care

Abstract

Introduction: Nicotine replacement therapy (NRT) is effective for smoking cessation, but the optimal method of using NRT to maximize benefit is unclear. We examined whether nicotine dependence was associated with consumption of NRT, whether this was mediated by withdrawal symptoms, and the impact of these factors on cessation, in a population advised to use as much NRT as needed.

Methods: Secondary analysis of data from an open label, parallel group randomized controlled trial. Participants (n=539) attended a smoking cessation clinic in primary care and remained engaged with treatment for at least one week following a quit attempt. Baseline dependence was measured by the Fagerström Test for Cigarette Dependence (FTCD), with tobacco exposure assessed via an exhaled carbon monoxide test. At one week after quit day, mean daily consumption of NRT was measured for all participants; withdrawal (Mood and Physical Symptoms Scale (MPSS)) was also assessed in the subsample who reported being completely abstinent to that point (n=279). Abstinence was biochemically assessed at four weeks for all participants as the principal smoking cessation outcome.

Results: Each point higher on the FTCD was associated with 0.83mg/day more NRT consumption, controlling for tobacco exposure. This relationship was diminished when withdrawal was controlled for, and withdrawal was associated with NRT consumption, with each point higher on the MPSS associated with a 0.12mg/day increase. Increased consumption of NRT directly predicted subsequent smoking cessation.

Conclusions: Higher dependence appears to lead to greater withdrawal, which appears to drive greater use of NRT. This effect may partly offset lower abstinence rates in people with higher dependence. Advice to use sufficient NRT to suppress withdrawal may increase abstinence rates.

Keywords: withdrawal; dependence; nicotine replacement therapy; adherence; abstinence; smoking cessation

Introduction

Nicotine replacement therapy (NRT) is considered to be a safe and effective pharmacological intervention for smoking cessation, with increases in consumption directly increasing the likelihood of sustained smoking cessation (Hollands et al., 2013; Raupach et al., 2014). A Cochrane review of the effectiveness of NRT found all forms to be significantly more effective than placebo in aiding abstinence from smoking, with participants using NRT over 1.5 times more likely to be abstinent (Hartmann-Boyce et al., 2018). Another Cochrane review found evidence that using higher doses of NRT may increase abstinence (Lindson et al., 2019), including using fast-acting NRT on top of nicotine patches compared with patches alone, using 25mg compared with 15mg nicotine patches, and using 4mg rather than 2mg gum. Thus, for people seeking help to quit smoking, increasing adherence to prescribed doses and achieving higher doses may improve the success of aided quit attempts.

While higher doses of nicotine replacement may increase abstinence, there is some evidence that this may only apply to people with higher dependence. For example, the Lindson et al review (Lindson et al., 2019) reported a risk ratio for abstinence for 4mg versus 2mg gum of 1.85 [1.36, 2.50] in people with higher dependence, and 0.77 [0.49, 1.21] in people with lower dependence. Thus it appears particularly imperative to increase the amount of nicotine used in people with higher dependence. One approach that may enable this is to advise individuals to use as much NRT, both from a patch as well as supplemental ('top-up') oral NRT, as they feel that they need to stave off cravings and other symptoms of withdrawal. This approach is commonly advocated in practice, and is consistent with studies finding that providing moderate or heavy

smokers with substantially more NRT (e.g., 40mg and above) than a standard dose, increases quit rates, at least in the short-term (Hughes et al., 1999; Jorenby et al., 1995). Prescribing high levels of NRT may also reduce urges and withdrawal symptoms (Rohsenow et al., 2007). These findings reflect that standard NRT doses generate only around half of the cotinine concentrations achieved through smoking. As a result, the nicotine replacement needs of heavier smokers are frequently unmet and require better tailoring accounting for dependence and related smoking characteristics (Hurt et al., 2009). However, there are few data available to show directly whether advising people to use as much NRT as they need is an effective strategy. In the current study, we exploit a randomized controlled trial (Marteau et al., 2012) that gave this instruction to participants to examine whether higher nicotine dependence was associated with higher consumption of NRT when ad libitum dosing was encouraged and, second, whether this effect was mediated by experience of withdrawal symptoms.

Although there is some prior evidence to suggest that greater dependence predicts greater use of medications for cessation, and NRT specifically, this is inconsistent (Pacek et al., 2018). The current study has the potential to better clarify this relationship, with the data collected including a high-quality objective measure of NRT consumption, and allowing for key factors to be controlled for, such as the prescribed dose. We examine the relationship between NRT use and both a commonly-used marker of nicotine dependence, the Fagerström Test for Cigarette Dependence (FTCD) (Fagerström, 2012; Heatherton et al., 1991), and baseline carbon monoxide (CO) concentration in expired air, a commonly administered marker of tobacco intake or exposure. Prior studies that have both measured dependence using the FTCD as well as objectively assessed NRT use via pill counts of returned products, have found that more dependent smokers consume more NRT (Hood et al., 2013); have found the converse relationship (Alterman et al., 1999); or have identified no clear association between dependence and use (Hollands et al., 2013). Regarding carbon monoxide concentration, it has been found that higher levels of tobacco exposure are associated with increased NRT use, albeit informed solely by less reliable self-reported NRT data (Okuyemi et al., 2010).

The second principal aim of this study is to test the hypothesis that higher levels of nicotine dependence could drive a person to consume more NRT because more dependent patients experience withdrawal more strongly and hence need to consume more nicotine. There is existing complementary evidence that higher dependence leads to more severe withdrawal (Pomerleau et al., 2000; Shiffman et al., 2006), and that in highly dependent smokers NRT use reduces withdrawal symptoms, with this explaining long-term abstinence (Shiffman, 2008). Here we examine directly whether withdrawal symptoms mediate any observed association between nicotine dependence and consumption of NRT. We anticipate that any mediation will be determined mainly in relation to, and thus effects may be stronger for, the consumption of the supplemental oral NRT component within a combination regimen, than for consumption of total NRT (patch plus supplemental oral NRT). This is because there is evidence that people are able to titrate their needed dose of short-acting NRT more effectively than for patches and are able to consume medication immediately when they experience urges to smoke or acute withdrawal symptoms (Fagerström & Hughes, 2002). Finally, while the primary focus of this study was on the use of NRT, reflecting the aim of the original trial, we also examined impact of these factors on smoking cessation.

Materials and Methods

Design

This study is a secondary analysis of data from an open label, parallel group randomized controlled trial (ISRCTN: 14352545). Full details of the trial and methods are published elsewhere (Marteau et al., 2010, 2012). Ethical approval was granted by the Hertfordshire 1 Research Ethics Committee, reference 06/Q0201/21.

Recruitment

We conducted a randomized controlled trial in National Health Service (NHS) smoking cessation clinics in primary care, with participants recruited from 29 primary care practices in two English cities. These clinics provide a combination of weekly behavioral support and pharmacotherapy to assist smokers to quit. Eligible

participants were patients smoking an average of at least 10 cigarettes a day, who wanted to quit and were 18 years or older, and 633 people were randomized. Participants did not receive financial compensation for taking part. We confined this analysis to the 539 participants who remained engaged with treatment – by attending their clinic appointment in person or, occasionally, if unable to attend, over the telephone - for the first week of the behavioral support programme. Although there is also evidence that NRT use is effective even in people not intending to quit (Carpenter et al., 2004), people in smoking cessation support programmes typically use NRT only until they abandon an attempt to stop smoking. As such, assessing usage during the period of engagement with treatment gives a more meaningful picture of consumption and what predicts consumption beyond failing to quit. We note that the 94 participants excluded did not significantly differ from those that were included in this analysis in respect to any sociodemographic or tobacco use variables assessed at baseline (age, gender, socio-economic status, cigarettes per day, CO level, FTCD). For example, baseline nicotine dependence was very similar (excluded group FTCD = 5.66; included group FTCD = 5.54, p=.64).

Pharmacotherapy

All participants were prescribed a nicotine patch. Those who smoked 15 or more cigarettes a day were prescribed 21mg patches while those smoking 10-14 cigarettes a day were prescribed 14mg patches. Participants also received an additional prescribed dose of supplemental oral NRT, with this dose, and the corresponding rationale given to the participant, tailored either on their genotype (presence/absence of OPRM1 mutation) or their level of nicotine dependence (FTCD), as determined by randomization. The dose of supplemental oral NRT was of either 6mg or 12mg a day, where the dose reflected typical levels of absorption, delivered by their preferred means (inhalator, gum, lozenge, or sublingual tablet). Thus a 2mg gum typically delivers about 1mg of nicotine and as such a 6mg dose comprised six 2mg pieces of gum. Where the daily dose of supplemental oral NRT was determined by genotype, those with the specified mutation received 12mg, and those without this mutation received 6mg. Where this was determined by level of dependence, those with a FTCD score ≥8 received 12mg, and those with a FTCD score <8 received 6mg. Differences in prescribed doses of NRT were controlled for in the analysis (*see 'Analysis'*).

Behavioral support and follow up

Participants in the trial attended seven weekly clinic appointments with a research nurse. In the first clinic, participants completed baseline measures of dependence and tobacco exposure. Participants started their quit attempt either immediately following the third clinic visit or the following morning. At this third appointment, the rationale for participants' doses, based on the group to which they had been randomized, was given. Participants were encouraged to use the total dose described above but also that "you may wish to take it when you get a craving, but you can also take it at other times of the day." At the fourth clinic appointment, one week after quitting, we assessed NRT consumption, smoking cessation, as well as nicotine withdrawal where relevant (*see 'Outcomes and measures'*). At the seventh clinic appointment (four weeks after quitting) smoking cessation was again assessed.

Outcomes and measures

Nicotine dependence. At baseline, this was assessed using the Fagerström Test for Cigarette Dependence (FTCD) (Fagerström, 2012; Heatherton et al., 1991), scored 0-10 with higher scores representing greater dependence.

Tobacco exposure. At baseline, this was assessed using an exhaled carbon monoxide (CO) test reading.

Nicotine withdrawal. This was assessed one week into the quit attempt using the Mood and Physical Symptoms Scale (MPSS) (West et al., 1984; West et al., 2006; West & Hajek, 2004) with participants rating their experiences over the previous weekly period. This scale is used routinely in many smoking cessation services in the UK and has adequate psychometric properties (West & Hajek, 2004). The measure comprises seven five-point ratings of depressed mood, anxiety, irritability, restlessness, hunger, difficulty concentrating, and difficulty sleeping, and two seven-point ratings of strength of urges to smoke and time spent with these urges. We used the composite scale score that incorporates all items, scoring a total of 9 to 49 (MPSS Total). This measure was assessed only in those participants who reported complete abstinence from smoking (i.e., withdrawal was not assessed in those reporting any smoking since their quit attempt), reflecting the recommendation of the SRNT Subcommittee that this group should be the primary focus when assessing withdrawal (Shiffman et al., 2004).

Consumption of NRT at one week. Mean daily consumption of NRT (in milligrams) was assessed at the fourth clinic appointment i.e., after the first week of the treatment programme. Consumption was ascertained using 'pill counts' of NRT consumed (i.e., recording the number of patches, gums, lozenges, inhalator cartridges, or sublingual tablets that were dispensed, and then asking the participant to return with their remaining supplies) and participants' daily diary recordings corroborated by a research nurse.

Validated abstinence from smoking at four weeks. This was assessed using the Russell standard procedures counting participants lost to follow up as being smokers (West et al., 2005). Abstinence was defined as smoking fewer than five cigarettes in the past two weeks verified by CO<10ppm.

Analysis

We used linear regression models to examine whether nicotine dependence, tobacco exposure, and withdrawal symptoms predicted mean daily consumption of total combination NRT over the first week of the treatment programme. Model 1 comprised the baseline measures of nicotine dependence (FTCD) and tobacco exposure (CO level) as predictors, with consumption as the dependent outcome variable. Collinearity statistics were examined and were satisfactory (all tolerance values were >0.80; all VIF values were <1.3). For Model 2 we additionally entered MPSS score, and for Model 3 we introduced potentially confounding variables relating to the study design and therefore adjusted for trial arm, participant genotype (OPRM1 mutation absent/present), baseline heaviness of smoking (cigarettes per day), and two binary variables of prescribed NRT dosage (high/low patch; high/low supplemental oral NRT). Because MPSS was only assessed for those who reported abstinence at one week (n=279), Models 2 and 3 were run on this smaller subgroup of participants. Collinearity statistics were examined for Models 2 and 3 and were satisfactory for both (all tolerance values were >0.50; all VIF values were <2). Because genotype and FTCD were used to tailor the prescribed dose in each trial arm, we intended to also include multiplicative interaction terms in Model 3 (trial arm x FTCD; trial arm x genotype), but these were discarded as they led to multicollinearity of an unacceptable degree (VIF values >16) suggesting that they did not add further unique explanation. As the FTCD was found to be associated with NRT consumption, we then ran a series of mediation models in AMOS 26, using a bias-corrected bootstrap of 10,000 samples, to assess whether withdrawal symptoms mediated

the effect of this dependence measure on consumption of i) total NRT (i.e., patch and supplemental oral NRT) and ii) supplemental oral NRT only. In an exploratory analysis, we added smoking cessation to the final mediation model. The models are described in the Results section. Analyses were registered on the Open Science Framework (https://osf.io/k2nvq).

Missing data were excluded listwise whereby participants were not included in the respective regression models if there were missing data for any of the included variables. We did not attempt to impute missing data given the small proportions involved, with between 0% and 2.4% of data missing for the specified analyses. Specifically, Model 1 was run for only 526 of 539 eligible participants (2.4% missing), because one participant had missing baseline FTCD data and 12 participants had missing CO level data. No data were missing for Model 2, which was run for 279 participants. Model 3 was run for 277 of those 279 participants as genotype group data were missing for two participants (0.7% missing).

Results

In terms of participant characteristics, 54% of participants were female, mean age was 47.4 (SD 13.3) years, and there was a wide range of educational backgrounds (with 16% having a university degree, and 28% having no qualifications). Participants consumed a mean (SD) of 23.4 (8.2) mg combination NRT daily, comprising 16.5 (5.4) mg from NRT patches plus 6.9 (4.6) mg from supplemental oral NRT. For nicotine dependence, mean (SD) baseline FTCD score was 5.5 (2.2). CO level was 19.2 (8.7) ppm.

Dependence as a predictor of mean daily NRT consumption (*Table 1*)

In Model 1, participants who were more dependent on cigarettes consumed an additional 0.8mg in mean daily NRT per point on the FTCD scale. In Model 2, adding MPSS score slightly weakened the association with FTCD, to 0.6mg per FTCD point. Each point rise in MPSS score was associated with a 0.1mg increase in mean daily NRT consumed. In Model 3, a similar association with MPSS was seen, and only a weak and non-

significant association with FTCD remained. Regarding tobacco exposure, no associations were observed between CO level and NRT consumption in any of the models. As expected, strong associations with NRT consumed were observed with the prescribed patch and supplemental oral NRT doses being low or high (*Table 1*).

Testing mediation of the effect of FTCD-assessed dependence on mean daily NRT consumption

For total consumption of NRT (i.e., patch and supplemental oral NRT), we first ran a simple mediation model for the effect of FTCD on consumption, with MPSS as the mediator, while controlling for CO level. This model revealed that MPSS partially mediated the effect of FTCD on consumption: Indirect effect *B* = .10 (Beta = .03), *p*=.022; Direct effect *B* = .58 (Beta = .17), *p* = .038; Total effect *B* = .68 (Beta = .19); *p* = .013. The direct paths from FTCD to MPSS (*B*=.74 (Beta=.21), *p* = .001), and MPSS to consumption (*B*=.13 (Beta=.14), *p*=.040) were both significant (the latter naturally corresponding with the regression models). We then ran a second mediation model that added the same potentially confounding factors that were included in regression Model 3 as predictors of consumption, namely trial arm, participant genotype, baseline heaviness of smoking (cigarettes per day), high/low patch dose, and high/low supplemental oral NRT dose. This model similarly found a significant indirect effect of FTCD on consumption, mediated by MPSS, but a weak direct effect accounting for the strong associations of consumption with NRT dosage variables: Indirect effect *B* = .09 (Beta = .03), *p*=.022; Direct effect *B* = .05 (Beta = .01), *p* = .829; Total effect *B* = .14 (Beta = .04); *p* = .587. The direct paths from FTCD to MPSS (*B*=.74 (Beta=.21), *p* = .001), and MPSS to consumption (*B*=.12 (Beta=.13), *p*=.040) were both significant.

In a post-hoc exploratory analysis, we added smoking cessation to this final model as an outcome assessed subsequent to NRT use (it being measured at four weeks), finding that increased consumption of NRT directly predicted subsequent smoking cessation: *B* = .010 (Beta = .157), *p*=.008. Higher baseline FTCD was associated with lower validated cessation at four weeks: Indirect effect *B* = -.008 (Beta = -.035), *p*=.061; Direct effect *B* = -.024 (Beta = -.102), *p* = .084; Total effect *B* = -.032 (Beta = -.137); *p* = .022. Greater

withdrawal in the first week of the quit attempt (MPSS) was in total associated with lower cessation (Direct effect *B* = -.013 (Beta = -.211), *p* = .001; Total effect *B* = -.012 (Beta = -.191); *p* = .002) but had an indirect effect of increasing cessation via increasing NRT consumption (Indirect effect: *B* = .001 (Beta = .020), *p*=.022).

For supplemental oral NRT only, the models produced similar results. A simple mediation model for the effect of FTCD found that MPSS mediated the direct effect of FTCD on consumption: Indirect effect *B* = .08 (Beta = .04), *p* = .001; Direct effect *B* = .28 (Beta = .14), *p* = .061; Total effect *B* = .37 (Beta = .17); *p* = .012. Direct paths from FTCD to MPSS (*B* = .74 (Beta = .21), *p* = .001), and MPSS to consumption (*B* = .11 (Beta = .19), *p* = .002) were both significant. The second model including additional controlling variables, similarly found an indirect effect of FTCD on consumption, mediated by MPSS: Indirect effect *B* = .09 (Beta = .04), *p* = .001; Direct effect *B* = .11 (Beta = .05), *p* = .489; Total effect *B* = .20 (Beta = .09); *p* = .212. Direct paths from FTCD to MPSS (*B* =.74 (Beta=.20), *p* = .001), and MPSS to consumption (*B* = .12 (Beta = .20), *p* = .001) were both significant. The models for supplemental oral NRT and for total NRT consumption showed indirect effects of similar magnitudes - suggesting that effects on total NRT may be largely accounted for by those on supplemental oral NRT - although beta coefficients for the specific association between withdrawal and consumption were notably greater for supplemental oral NRT only.

Discussion

Participants showing higher levels of tobacco dependence with the FTCD consumed more NRT when they tried to stop smoking, and there was evidence that this effect was explained by experiencing stronger withdrawal. In line with prior findings (Hollands et al., 2013), the magnitude of prescribed NRT dose was the strongest predictor of NRT consumption, thus reinforcing that high (yet feasible) doses should typically be prescribed. Notably, withdrawal symptom severity was found to be strongly linked to dependence, that is, people with higher dependence experienced worse withdrawal. Withdrawal was also associated with consumption of total NRT and supplemental oral NRT, suggesting that an improved understanding of these

relationships could help to better optimize NRT use. In highlighting the value of the FTCD in explaining withdrawal and NRT use, these data concord with previous studies finding that smokers scoring more highly on this measure consume more NRT (Hollands et al., 2013; Hood et al., 2013). It is not clear why baseline CO level was not found to be associated with NRT use, although prior evidence of such an association is limited and has relied on participant self-reports (Okuyemi et al., 2010). This finding therefore requires further examination, but could possibly be explained by the short half-life of CO meaning that exhaled CO concentration varies throughout the day. As we did not standardize appointments by time of day, this would reduce the likelihood of this measure being associated with consumption. Finally, as expected, we found that increased consumption of NRT predicted subsequent smoking cessation. As higher dependence is associated with lower abstinence rates, increased withdrawal appearing to drive greater use of NRT may partly offset such effects.

From a therapeutic perspective, these results may appear encouraging. We advised patients to consume as much NRT as necessary to stave off withdrawal, and those who experienced greater withdrawal consumed more NRT. However, although the precise temporal relationships are not discernible, these data also suggest that despite consuming more NRT, more dependent patients experienced greater withdrawal symptoms over the week-long period. It therefore appears that adhering to this instruction is not in itself able to eliminate the association between higher dependence and a worse experience while quitting smoking. This would imply that there is still more to be done to ensure that more dependent patients use medication appropriately. One measure of dependence used to tailor treatment is heaviness of consumption, measured by cigarettes per day, and there is evidence that giving higher doses to heavier smokers is more effective than using standard doses for all (Lindson et al., 2019). Because cigarettes per day is a poor index of nicotine intake, the possibility of tailoring treatment to heaviness of smoking assessed by salivary cotinine while smoking has also been examined, but has revealed no substantial benefit from tailoring treatment dose in this way (Berlin et al., 2011, 2014), albeit with confidence intervals not excluding such benefit (RR=1.15 (0.80, 1.63)). An alternative strategy may be to tailor treatment to match withdrawal intensity. It is not clear how best this might be accomplished, and it may require faster-acting products to titrate the dose. One possibility is to

base initial dosing on the occurrence of urges to smoke which smokers experience prior to becoming abstinent, given evidence that this may predict the outcome of cessation attempts more accurately than other measures of dependence (Fidler et al., 2011). Further work to understand this and its application to giving patients advice on dosing is required. Beyond tailoring pharmacological characteristics of the treatment, supplementary behavioral support interventions focused on increasing adherence to smoking cessation medications can modestly improve consumption of NRT and thus could also contribute to more optimal medication use (Hollands et al., 2019).

A principal strength of this study was the close attention to measuring NRT consumption using high quality measures, and validated measures of withdrawal, dependence, and abstinence; all features that will maximize precision of the estimates of the associations. Historically, NRT use has often been determined as a result of retrospective and infrequent self-report assessments, and studies often present data concerning adherence to a prescribed dose, whereas actual consumption of NRT is what is of central importance in determining key clinical outcomes (Hollands et al., 2013). Second, we assessed NRT use in only those participants who were abstinent, or who continued trying to quit, for the period that measure applied to. Other studies often present NRT use across the entire study population, thereby including those people who abandon a quit attempt and therefore stop using (or are not prescribed) further NRT. While this may give some indication of general patterns of use, it means we are unable to elucidate the determinants of use among those who are prescribed and use NRT. Relatedly, such studies may misrepresent the relationship of dependence with consumption because more dependent smokers may be more likely to abandon a quit attempt prematurely and so are observed to use less NRT (Vaz et al., 2016). Third, the study was conducted in a general population sample attending standard smoking cessation services. Whilst not a limitation per se, many past studies have been carried out among specialist treatment groups or in clinical contexts (Fish et al., 2009; Stein et al., 2006; Wiggers et al., 2006) that can limit the generalisability of the findings.

The study also has some important limitations. The data are observational, with neither the independent variable nor the hypothesized mediator subject to randomization, and it remains possible that factors

associated with dependence explain the relationship between dependence and consumption. For example, in both trial arms, cigarettes per day, a component of FTCD, was used to determine a high or low dose for the prescribed NRT patch, although we controlled for this (and for the prescribed dosages) and it did not eliminate the association. Another limitation was that withdrawal and consumption were measured retrospectively at the end of one week; it is plausible that a study with daily measurement of withdrawal and consumption may have shown stronger associations.

In conclusion, this study shows that more dependent smokers appear to experience greater withdrawal, which appears to drive greater consumption of NRT. Relating dosing instructions to urges to smoke or withdrawal intensity by advising the use of sufficient NRT to suppress withdrawal, may improve NRT consumption and increase abstinence rates.

Table

Table 1: Regression analysis of predictors of mean daily NRT consumption

	Model 1 (n=526)[a]		Model 2 (n=279[b])		Model 3 (n=277[b])	
Included	*B* (Beta)	SE	*B* (Beta)	SE	*B* (Beta)	SE
FTCD	*.83 (.22)	.18	**.64 (.18)	.24	.05 (.01)	.27
CO level	-.03 (-.04)	.04	.06 (.07)	.06	-.01 (-.01)	.06
MPSS			*.13 (.14)	.06	*.12 (.13)	.06
Patch dose (high)					***7.79 (.41)	1.23
Supplemental dose (high)					**4.23 (.22)	1.46
Intervention arm					1.21 (.08)	.87
Genotype					-.82 (-.04)	1.33
Cigs per day					-.09 (-.11)	.06
Adjusted R^2	.04		.07		.19	
F for model	***11.78		***8.00		***9.03	

**= p<.05, **= p<.01, ***= p<.001; [a]FTCD or CO level data were missing for 13 participants; [b]As MPSS was only assessed in those who reported current abstinence from smoking, Models 2 and 3 were applied to smaller samples than was Model 1 (for Model 3, genotype data were missing for a further two participants included in Model 2).*

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Declaration of Interests

None of the authors declare any competing interests.

Author contributions

GJH and PA conceived the study and designed the procedures. GJH performed the data analyses. GJH and PA drafted the manuscript, with SS providing critical revisions. All authors read and approved the final manuscript.

CRediT authorship contribution statement

GJH: Conceptualization, Methodology, Formal analysis, Writing – Original Draft, Writing - Review & Editing. SS: Writing – Review & Editing. PA: Conceptualization, Methodology, Supervision, Writing – Original Draft, Writing - Review & Editing.

References

Alterman, A. I., Gariti, P., Cook, T. G., & Cnaan, A. (1999). Nicodermal patch adherence and its correlates. *Drug and Alcohol Dependence*, *53*(2), 159–165. https://doi.org/10.1016/S0376-8716(98)00124-0

Berlin, I., Grangé, G., Jacob, N., & Tanguy, M.-L. (2014). Nicotine patches in pregnant smokers: Randomised, placebo controlled, multicentre trial of efficacy. *BMJ*, *348*. https://doi.org/10.1136/bmj.g1622

Berlin, I., Jacob, N., Coudert, M., Perriot, J., Schultz, L., & Rodon, N. (2011). Adjustment of nicotine replacement therapies according to saliva cotinine concentration: The ADONIS* trial—a randomized study in smokers with medical comorbidities. *Addiction*, *106*(4), 833–843. https://doi.org/10.1111/j.1360-0443.2010.03306.x

Carpenter, M. J., Hughes, J. R., Solomon, L. J., & Callas, P. W. (2004). Both Smoking Reduction With Nicotine Replacement Therapy and Motivational Advice Increase Future Cessation Among Smokers Unmotivated to Quit. *Journal of Consulting and Clinical Psychology*, *72*(3), 371–381. https://doi.org/10.1037/0022-006X.72.3.371

Fagerström, K. (2012). Determinants of Tobacco Use and Renaming the FTND to the Fagerström Test for Cigarette Dependence. *Nicotine & Tobacco Research*, *14*(1), 75–78. https://doi.org/10.1093/ntr/ntr137

Fagerström, K. O., & Hughes, J. R. (2002). Nicotine concentrations with concurrent use of cigarettes and nicotine replacement: A review. *Nicotine & Tobacco Research*, *4*(Suppl 2), S73–S79. https://doi.org/10.1080/1462220021000032753

Fidler, J. A., Shahab, L., & West, R. (2011). Strength of urges to smoke as a measure of severity of cigarette dependence: Comparison with the Fagerström Test for Nicotine Dependence and its components. *Addiction*, *106*(3), 631–638. https://doi.org/10.1111/j.1360-0443.2010.03226.x

Fish, L. J., Peterson, B. L., Namenek Brouwer, R. J., Lyna, P., Oncken, C. A., Swamy, G. K., Myers, E. R., Pletsch, P. K., & Pollak, K. I. (2009). Adherence to nicotine replacement therapy among pregnant smokers. *Nicotine & Tobacco Research*, *11*, 514–518. https://doi.org/10.1093/ntr/ntp032

Hartmann-Boyce, J., Chepkin, S., Ye, W., Bullen, C., & Lancaster, T. (2018). Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database of Systematic Reviews*, *5*. https://doi.org/10.1002/14651858.CD000146.pub5

Heatherton, T., Kozlowski, L., Frecker, R., & Fagerstrom, K. (1991). The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction*, *86*, 119–127. https://doi.org/10.1111/j.1360-0443.1991.tb01879.x

Hollands, G. J., Naughton, F., Farley, A., Lindson, N., & Aveyard, P. (2019). Interventions to increase adherence to medications for tobacco dependence. *Cochrane Database of Systematic Reviews*, *8*. https://doi.org/10.1002/14651858.CD009164.pub3

Hollands, G. J., Sutton, S., McDermott, M. S., Marteau, T. M., & Aveyard, P. (2013). Adherence to and consumption of nicotine replacement therapy and the relationship with abstinence within a smoking cessation trial in primary care. *Nicotine & Tobacco Research*, *15*(9), 1537–1544. https://doi.org/10.1093/ntr/ntt010

Hood, N. E., Ferketich, A. K., Paskett, E. D., & Wewers, M. E. (2013). Treatment adherence in a lay health adviser intervention to treat tobacco dependence. *Health Education Research*, *28*(1), 72–82. https://doi.org/10.1093/her/cys081

Hughes, J. R., Lesmes, G. R., Hatsukami, D. K., Richmond, R. L., Lichtenstein, E., Jorenby, D. E., Broughton, J. O., Fortmann, S. P., Leischow, S. J., McKenna, J. P., Rennard, S. I., Wadland, W. C., & Heatley, S.

A. (1999). Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine & Tobacco Research*, *1*(2), 169–174. https://doi.org/10.1080/14622299050011281

Hurt, R. D., Ebbert, J. O., Hays, J. T., & McFadden, D. D. (2009). Treating Tobacco Dependence in a Medical Setting. *CA: A Cancer Journal for Clinicians*, *59*(5), 314–326. https://doi.org/10.3322/caac.20031

Jorenby, D. E., Smith, S. S., Fiore, M. C., Hurt, R. D., Offord, K. P., Croghan, I. T., Hays, J. T., Lewis, S. F., & Baker, T. B. (1995). Varying Nicotine Patch Dose and Type of Smoking Cessation Counseling. *JAMA*, *274*(17), 1347–1352. https://doi.org/10.1001/jama.1995.03530170027027

Lindson, N., Chepkin, S., Ye, W., Fanshawe, T., Bullen, C., & Hartmann-Boyce, J. (2019). Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews*, *4*. https://doi.org/10.1002/14651858.CD013308

Marteau, T. M., Aveyard, P., Munafò, M. R., Prevost, A. T., Hollands, G. J., Armstrong, D., Sutton, S., Hill, C., Johnstone, E., & Kinmonth, A. L. (2012). Effect on adherence to nicotine replacement therapy of informing smokers their dose is determined by their genotype: A randomised controlled trial. *PLoS ONE*, *7*(4), e35249. https://doi.org/10.1371/journal.pone.0035249

Marteau, T. M., Munafo, M. R., Aveyard, P., Hill, C., Whitwell, S., Willis, T. A., Crockett, R. A., Hollands, G. J., Johnstone, E. C., Wright, A. J., Prevost, A. T., Armstrong, D., Sutton, S., & Kinmonth, A. L. (2010). Trial Protocol: Using genotype to tailor prescribing of nicotine replacement therapy: A randomised controlled trial assessing impact of communication upon adherence. *BMC Public Health*, *10*(1), 680.

Okuyemi, K., Zheng, H., Guo, H., & Ahluwalia, J. (2010). Predictors of Adherence to Nicotine Gum and Counseling among African-American Light Smokers. *Journal of General Internal Medicine*, *25*(9), 969–976. https://doi.org/10.1007/s11606-010-1386-x

Pacek, L. R., McClernon, F. J., & Bosworth, H. B. (2018). Adherence to Pharmacological Smoking Cessation Interventions: A Literature Review and Synthesis of Correlates and Barriers. *Nicotine & Tobacco Research*, *20*(10), 1163–1172. https://doi.org/10.1093/ntr/ntx210

Pomerleau, C. S., Marks, J. L., & Pomerleau, O. F. (2000). Who gets what symptom? Effects of psychiatric cofactors and nicotine dependence on patterns of smoking withdrawal symptomatology. *Nicotine & Tobacco Research*, *2*(3), 275–280. https://doi.org/10.1080/14622200050147547

Raupach, T., Brown, J., Herbec, A., Brose, L., & West, R. (2014). A systematic review of studies assessing the association between adherence to smoking cessation medication and treatment success. *Addiction*, *109*(1), 35–43. https://doi.org/10.1111/add.12319

Rohsenow, D. J., Monti, P. M., Hutchison, K. E., Swift, R. M., MacKinnon, S. V., Sirota, A. D., & Kaplan, G. B. (2007). High-dose transdermal nicotine and naltrexone: Effects on nicotine withdrawal, urges, smoking, and effects of smoking. *Experimental and Clinical Psychopharmacology*, *15*(1), 81–92. https://doi.org/10.1037/1064-1297.15.1.81

Shiffman, S. (2008). Effect of nicotine lozenges on affective smoking withdrawal symptoms: Secondary analysis of a randomized, double-blind, placebo-controlled clinical trial. *Clinical Therapeutics*, *30*(8), 1461–1475. https://doi.org/10.1016/j.clinthera.2008.07.019

Shiffman, S., Ferguson, S., Gwaltney, C., Balabanis, M., & Shadel, W. (2006). Reduction of abstinence-induced withdrawal and craving using high-dose nicotine replacement therapy. *Psychopharmacology*, *184*(3), 637–644. https://doi.org/10.1007/s00213-005-0184-3

Shiffman, S., West, R. J., & Gilbert, D. G. (2004). Recommendation for the assessment of tobacco craving and withdrawal in smoking cessation trials. *Nicotine & Tobacco Research*, *6*(4), 599–614. https://doi.org/10.1080/14622200410001734067

Stein, M. D., Anderson, B. J., & Niaura, R. (2006). Nicotine Replacement Therapy: Patterns Of Use After A Quit Attempt Among Methadone-Maintained Smokers. *Journal of General Internal Medicine*, *21*(7), 753–757. https://doi.org/10.1111/j.1525-1497.2006.00504.x

Vaz, L. R., Aveyard, P., Cooper, S., Leonardi-Bee, J., & Coleman, T. (2016). The Association Between Treatment Adherence to Nicotine Patches and Smoking Cessation in Pregnancy: A Secondary Analysis of a Randomized Controlled Trial. *Nicotine & Tobacco Research*, *18*(10), 1952–1959. https://doi.org/10.1093/ntr/ntw080

West, R., Hajek, P., Stead, L., & Stapleton, J. (2005). Outcome criteria in smoking cessation trials: Proposal for a common standard. *Addiction*, *100*(3), 299–303. https://doi.org/10.1111/j.1360-0443.2005.00995.x

West, R. J., Jarvis, M. J., Russell, M. A. H., Carruthers, M. E., & Feyerabend, C. (1984). Effect of Nicotine Replacement on the Cigarette Withdrawal Syndrome. *British Journal of Addiction*, *79*(4), 215–219. https://doi.org/10.1111/j.1360-0443.1984.tb03858.x

West, R., & Hajek, P. (2004). Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. *Psychopharmacology*, *177*(1), 195–199. https://doi.org/10.1007/s00213-004-1923-6

West, R., Ussher, M., Evans, M., & Rashid, M. (2006). Assessing DSM-IV nicotine withdrawal symptoms: A comparison and evaluation of five different scales. *Psychopharmacology*, *184*(3), 619–627. https://doi.org/10.1007/s00213-005-0216-z

Wiggers, L., Smets, E., Oort, F., de Haes, H., Storm-Versloot, M., Vermeulen, H., Legemate, D., van Loenen, L., & Peters, R. (2006). Adherence to nicotine replacement patch therapy in cardiovascular patients. *International Journal of Behavioral Medicine*, *13*(1), 79–88. https://doi.org/10.1207/s15327558ijbm1301_10