A Time-to-Event Model Relating Integrated Craving to Risk of Smoking Relapse Across Different Nicotine Replacement Therapy Formulations

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Smoking increases the risk of cancer and other diseases, causing an estimated 7 million deaths per year. Nicotine replacement therapy (NRT) reduces craving for smoking, therefore, increasing an individual’s probability to remain abstinent. In this work, we for the first time quantitatively described the relationship between craving and smoking abstinence, using retrospectively collected data from 19 studies, including 3 NRT formulations (inhaler, mouth spray, and patch) and a combination of inhaler and patch. Smokers motivated to quit were included in the NRT or placebo arms. Integrated craving (i.e., craving over a period of time) was assessed with 4-category, 5-category, or 100-mm visual analogue scale. The bounded integer model was used to assess latent craving from all scales. A time-to-event model linked predicted integrated craving to the hazard of smoking relapse. Available data included 9,323 adult subjects, observed for 3 weeks up to 2 years. At the study end, 9% (11% for NRT and 5% for placebo), on average, remained abstinent according to the protocol definition. A Gompertz–Makeham hazard best described the data, with a hazard of smoking relapse decreasing over time. Latent integrated craving was positively related to the hazard of smoking relapse, through a sigmoidal maximum effect function. For the same craving, being on NRT was found to reduce the hazard of relapse by an additional 30% compared with placebo. This work confirmed that low craving is associated with a high probability of remaining smoking abstinent and that NRT, in addition to reducing craving, increases the probability of remaining smoking abstinent.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Tobacco use is responsible for over 7 million avoidable deaths per year, posing a major global health problem. A challenge with smoking cessation is the nicotine craving, reducing the chances of a successful quit attempt. Craving changes over time and may be a sensitive and consistent predictor of relapse.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ We quantitatively characterized the relationship between relapse to smoking and integrated craving assessed by three different scales, with and without nicotine replacement therapy.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ A time-to-event model was developed, which for the first time ever quantitatively confirms that integrated craving is a key driver of smoking relapse. Additionally, no/low craving was shown to increase the probability of remaining abstinent.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Our modeling showed that it is important to keep craving at a minimum for a successful quit attempt. Additionally, the developed model may be useful for clinical trial simulations, evaluating the effect of different craving scores from different craving scales on smoking abstinence.

Several of these compounds can cause cancer, and many are otherwise harmful. Besides increasing the risk of cancer, cigarette smoke can also increase the risk of and/or accelerate other diseases (e.g., chronic obstructive pulmonary disease, cardiac and peripheral vascular disease, and diabetes through insulin resistance).
Nicotine is the substance in tobacco that is mainly responsible for smoking addiction. When nicotine distributes into the brain, it binds to the nicotinic acetylcholine receptors, causing release of neurotransmitters (e.g., dopamine and serotonin). The release of dopamine causes a reward effect, thus is one of the key reasons that smokers crave nicotine. However, habitual tobacco use may reduce the positive reward of smoking via nicotine tolerance development, therefore, long-term smokers mainly smoke to relieve the withdrawal symptoms. These symptoms include: a) dysphoria or depressed mood, b) insomnia, c) irritability, frustration, or anger, d) anxiety, e) difficulty concentrating, f) restlessness or impatience, and g) increased appetite or weight gain.

The aim of nicotine replacement therapy (NRT) is to reduce the motivation to smoke by reducing nicotine craving and withdrawal symptoms, thereby increasing chances of a successful quit-attempt. A recent Cochrane review of 136 studies (including in total around 64,000 subjects) corroborated that NRT formulations increase the relative rate of long-term quitting compared with placebo (by 50–60%), regardless of the clinical setting. The overall risk ratio of abstinence for any form of NRT relative to control was 1.55 and the effects of NRT were mainly independent of the intensity of additional support provided.

The US Food and Drug Administration (FDA) recently published a document discussing the need for more work in the smoking cessation area in relation to NRT. Several factors that might influence smoking cessation have been identified, for example, sex, age, mental health, socioeconomic status, being overweight, college education, and Hispanic or Asian race. Craving has also been identified as an important risk factor for an individual to relapse to smoking. Unlike other risk factors, craving changes over time, similar to the risk of smoking relapse, and might thus hypothetically be the most sensitive and consistent predictor of relapse.

Craving is subjective and, as such, measured using rating scales. There is a lack of consistency in how craving is assessed, both in terms of the scales used and the question asked to the individuals assessing their craving. In smoking cessation studies, subjects are asked to assess their overall craving over a period of time, commonly 24 hours. This craving is hereafter referred to as “integrated craving.” In short-term studies (e.g., investigations of nicotine pharmacokinetics of nicotine), subjects are instead asked to assess their current or “momentary craving.” Both types of craving can be assessed using 4-category or 5-category scales, or visual analogue scale (VAS). Despite using the same/similar scales to assess craving, integrated and momentary craving are very different, as integrated craving is an assessment of craving over a time-interval, whereas momentary craving is a snapshot at a certain time point. The main focus of the work presented here will be on the integrated craving.

Surprisingly perhaps, the hypothesis that changes in longitudinal measurements of integrated craving are highly predictive of the risk of smoking relapse has previously not been quantitatively confirmed. Several examples are available in which Kaplan–Meier time-to-event (TTE) models are used to analyze smoking cessation data with the event being relapse to smoking after continuous smoking abstinence. However, none of these connect longitudinal craving measurements to the risk of relapse. In recent work by Courvoisier et al., mixed-effects TTE models were used to investigate longitudinal smoking cessation data. However, in their work, the event was not relapse to smoking after continuous smoking abstinence, but instead time-to-first morning cigarette, not linked to craving and subjects were only followed for 1 week.

One reason for the lack of work linking integrated craving to the relapse of smoking might be the lack of consistency in how craving is assessed, as mentioned above. However, recently, we published a methodology that enables simultaneous analysis of craving, assessed with different scales. The methodology was applied to momentary craving for the purpose of describing the relationship between nicotine pharmacokinetics and momentary craving, however, the methodology can be adapted for integrated craving, enabling usage of data from studies where craving is heterogeneously assessed.

Thus, the objective of this work was to verify, characterize, and quantify the relationship between integrated craving (assessed with different scales) and smoking cessation following administration of three different NRT formulations, a combination thereof, and placebo. This was done using a model-based approach assessing the time until first relapse.

**METHODS**

**Data**

Data were retrospectively collected from prospective studies performed in smokers who were motivated to quit smoking. Studies were designed to assess quit rates. Subjects in 19 separate studies were included in either a placebo arm or an active treatment arm, where they received one of the 3 NRT formulations (i.e., inhaler, mouth spray, or patch), or a combination of inhaler and patch. Selection of formulations was limited by availability of long-term craving measurements.

Smoking abstinence until first relapse was defined per protocols as a subject that had reported “no smoking” since the last study visit, and had a carbon monoxide (CO) concentration in exhaled air below 10 ppm, given that the subject at any earlier visit also fulfilled these 2 criteria. Each study included an initial phase, typically 1 to 2 weeks, during which subjects received treatment but relapse was not assessed. A subject was thus assumed to have quit smoking in this initial phase and information about how many subjects actually quit during this phase was unavailable. If self-reported smoking and/or CO measurements were missing (when for example a subject did not show up on a scheduled study visit), this was per definition relapse to smoking. This definition of relapse to smoking is based on FDA guidance and recommendations to sponsors, now codified in the draft FDA Guidance for Industry from February 2019. The FDA definition of relapse to smoking combines “verified” relapse to smoking with dropout, assuming that all subjects who drop out are smokers. Consequently, subjects who did not show up for a visit were excluded from the rest of the study. In general, the intervals between study visits were short early in the studies and increased with study duration, from 1 week early on to 6–9 months later in the studies.

Integrated craving in the studies was self-assessed by subjects using 1 of the 3 scales: a 4-category scale, a 5-category scale, or a 100-mm VAS. In most cases, the integrated craving was defined as craving in the last 24 hours. In the 4-category scale, the craving score corresponded to 0 = none, 1 = mild, 2 = moderate, and 3 = severe; in the 5-category scale, the craving score corresponded to 0 = not at all, 1 = somewhat, 2 = moderate, 3 = very much, and 4 = extreme; using VAS, a craving score = 0 corresponded to “no craving at all,” whereas a score = 100 corresponded to “worst craving imaginable.”

**Time-to-first-relapse model development**

The time-to-first-relapse model was developed in a stepwise fashion. First, a hazard function was determined, and then relationships between predictors and the hazard (i.e., momentary risk of relapsing
to smoking) were investigated. Each step was followed by a model assessment. To fit the model to the data, we used NONMEM 7.4 (ICON plc, Gaithersburg, MD). The exact likelihood was used as the model is probabilistic. To examine the output of NONMEM, and to produce plots and summary statistics, we used Perl-speaks-NONMEM 4.8.10 (PsN, https://uupharmaometrics.github.io/PsN/), R 3.5.0, and R packages, for example, Xpose4 4.6.1, ggplot2 3.0.0, and vpc.

Relapse to smoking was only assessed at study visits; therefore, the exact time of a relapse was unknown, and this interval-censoring was accounted for in the model. To determine the hazard function that best describes the data, we explored time-constant and time-varying (bi-exponential, the Gompertz, and the Weibull distributions) hazards, as well as combinations.

Connecting craving scales with a different number of scores
As integrated craving was measured with three different scales, a bounded integer, mixed-effects model was developed for integrated craving, similar to our previous work with momentary craving. This model translated the observed score (dependent on scale) to a latent variable, called ‘Latent Integrated Craving’, which is independent of scale. The model described the changes of latent integrated craving (LIC) over time. Linear and exponential time relationships were investigated, as well as treatment effect (placebo/active) on the baseline LIC. Random effects, describing between-subject variability, were explored on the baseline LIC and these were assumed to arise from a normal distribution.

Including predictors on the hazard
Once the structural model components were determined, the relationship between the integrated craving and smoking cessation was investigated. Linear, maximum effect (E max)-type and sigmoidal E max-type relationships between latent integrated craving and relapse to smoking were considered. The inclusion of latent integrated craving at the current study visit (i.e., the visit when relapse was recorded) was explored. In addition to testing craving, the effect of the treatment (i.e., placebo vs. NRT), was also investigated as a predictor of the hazard.

Model discrimination and evaluation
To discriminate between the models, we examined how well each model fit the data through the difference in objective function value, uncertainty in the model parameter estimates, and visual diagnostics, such as visual predictive checks (VPCs), using Kaplan–Meier plots. For a more complex model to be selected, a significant (P < 0.01) improvement over the compared less-complex model was required.

Simulations
The final model estimates were used to visualize outcomes of interest in the clinical trials, such as how craving (for different craving scales) impacts the probability of remaining smoking abstinent over time. Simulations were performed with constant LIC to illustrate the changes in risk of relapse independent of changes in craving as well as to visualize the difference in score between scales.

RESULTS
Available data
The data was retrospectively collected from 19 studies (described in more detail in Table S1), and included 9,323 adult subjects. Subjects in the studies had median (95% central range) two (0–10) previous attempts to quit smoking (Table 1). The largest proportion of subjects (33%) smoked their first cigarette 6–30 minutes after waking up and 22% < 5 minutes after waking up (Table 1). Overall, 9% of subjects (5% on placebo and 11% on NRT) remained abstinent from smoking until the end of the studies, with study durations ranging from 3 weeks to 2 years. On study visits when the relapse was determined or the study ended (i.e., right censored time point) integrated craving was missing in 37% of cases. For the craving model, data from nonstudy visits were also available (when e.g., the subjects only filled in the questionnaire) and included 17,867 integrated craving observations on the 4-category scale, 43,784 observations on the 5-category scale, and 5,779 observations recorded with the VAS.

Table 1. Baseline characteristics of the studied subjects

| Characteristic                          | Median (95% central range) or count (%) |
|----------------------------------------|----------------------------------------|
| Total number of subjects               | 9,323                                  |
| Number of subjects who remained abstinent | 825 (9%)                             |
| Female                                 | 4,805 (52%)                            |
| Age, years                             | 42 (23–66)                             |
| BMI, kg/m²                              | 25 (19–38)                             |
| Cigarettes per day                     | 21 (10–50)                             |
| Years smoking                          | 25 (7–49)                              |
| Number of previous attempts to quit    | 2 (0–10)                               |
| Time to first daily cigarette (%)      | < 5 minutes (21.7%), 6–30 minutes (33.3%), 5–15 minutes (0.6%), < 30 minutes (12.2%), 31–60 minutes (11.4%), > 30 minutes (2.5%), > 60 minutes (6.3%) |

BMI, body mass index.

Results of the time-to-first-relapse modeling
A combination of a time-constant hazard and the Gompertz hazard, also called the Gompertz-Makeham hazard, provided the best fit to the data. The instantaneous hazard of first relapse to smoking for subjects who stayed abstinent throughout the study was found to decrease with duration of time in the study, which is in line with results of previous cessation studies. Thus, the highest risk of relapse is immediately after stopping smoking, and this risk decreases the longer a subject stays abstinent.

The latent integrated craving was found to decrease nonlinearly with time, with different slope parameter estimates per craving scale (Table S2). Treatment effect (i.e., the placebo or the active treatment arm) was included on the baseline latent integrated craving, according to the following equation:

\[ \text{LIC} = \text{LIC}_{\text{baseline}} + \delta \cdot \text{NRT} + \text{NRT}_{\text{NRT}} \cdot I_{\text{NRT}} \] (1)

where LIC_{baseline} is the latent integrated craving for a subject without NRT when time approaches infinity, \( \delta \) is the slope of time-changing latent integrated craving, which was estimated based on scale, and NRT_{LIC} is the constant effect of NRT on...
LIC. Allowing δ to be different for the three scales improved the fit significantly as illustrated in Supplementary Material Figure S1.

A relationship between the LIC and the instantaneous hazard of relapse to smoking was then investigated. In addition to LIC, we found a significant effect of NRT on the hazard (difference in objective function value = −211), which also improved the predictive performance of the model as assessed by VPC. The equation below describes the final model for the hazard, and shows the relationship between the predictors and the hazard.

\[
b(t) = \left( \lambda + \alpha \cdot e^{\beta t} \right) \cdot \left( 1 + \frac{E_{\max} \cdot \left( e^{LIC} \right)^{\text{Hill}}}{\left( e^{LIC} \right)^{\text{Hill}} + \left( e^{LIC_{50}} \right)^{\text{Hill}}} \right) \cdot e^{NRT \cdot I_{\text{NRT}}} \tag{2}
\]

where the hazard of relapse to smoking \( b(t) \) was described by an intercept parameter, \( \lambda \), a scale parameter, \( \alpha \), and a shape parameter, \( \beta \), in the Gompertz–Makeham model. The effect of LIC was described by a sigmoidal \( E_{\max} \) relationship, where \( E_{\max} \) is the maximal effect of latent integrated craving on the hazard, \( LIC_{50} \) is the LIC giving 50% of maximal hazard, and Hill is the sigmoidicity parameter. The LIC is normally distributed, ranging from \(-\infty\) to \(\infty\) and the variable was exponentiated to constrain it to positive values. The treatment effect was described by a constant addition to the hazard, \( NRT \cdot I_{\text{NRT}} \) for active arms (i.e., \( I_{\text{NRT}} \) is 1 for NRT arm and 0 for the placebo arm). Thus, both the hazard itself and the predictor LIC are time-dependent.

Final parameter estimates with uncertainty are presented in Table 2, and Kaplan–Meier VPCs in Figure 1. The VPCs indicated some model misspecification, also after accounting for integrated craving and NRT; for some formulations (e.g., patch), the relapse risk was overpredicted at early time points, whereas for other formulations (e.g., mouth spray), the relapse rate was underpredicted at late time points. Figure 2 shows how integrated craving scores from the three different craving scales are related to the probability of remaining smoking abstinent, and how this relationship changes over time. According to Figure 2, integrated craving score = 0 predicts similar abstinence probability, independent of the scale. Additionally, score = 2 and 50 on the 5-category scale and VAS, respectively, gives similar abstinence probability as score = 1 on the 4-category scale. Most importantly, the abstinence probability is much higher when having score = 0, compared with the higher score.

**Table 2 Parameter estimates, with uncertainty, of the hazard model**

| Parameter description | Parameter | Estimate^b |
|-----------------------|-----------|------------|
| Time-constant hazard [day^{-1}] | \( \lambda \) | 0.000542 (7%) |
| Shape hazard parameter [day^{-1}] | \( \beta \) | −0.127 (4%) |
| Scale hazard parameter [day^{-1}] | \( \alpha \) | 0.0085 (2%) |
| Maximum effect of latent integrated craving [-] | \( E_{\max} \) | 10.5 (2%) |
| Latent integrated craving giving 50% of \( E_{\max} \) [-] | \( LIC_{50} \) | −0.405 (6%) |
| Sigmoidicity factor [-] | Hill | 3.37 (4%) |
| Hazard for NRT treatment [-] | \( \theta_{\text{NRT}} \) | −0.361 (7%) |

\( E_{\max} \), maximum effect; \( LIC_{50} \), latent integrated craving giving 50% of maximal hazard; NRT, nicotine replacement therapy.

\^b Typical estimate (relative standard error).

\(^c\)Expressed as a Z-score from a normal distribution.

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**Figure 1.** Kaplan–Meier visual predictive checks for different formulations, stratified by treatment arm and formulation. Black lines represent the observed probability of staying abstinent and the light blue areas are the corresponding 95% confidence intervals from 100 simulations. There were no placebo data for the combination therapy with inhaler and patch. Time is shown on log scale. [Colour figure can be viewed at wileyonlinelibrary.com]
DISCUSSION

This work, to the best of our knowledge, is the first to quantitatively confirm that integrated craving, through a latent variable, is predictive of the risk of smoking relapse; replacing partly time as a predictor of staying smoking abstinent. This work also characterizes the relationship between hazard of smoking relapse and integrated craving. Data from almost 10,000 subjects and 3 NRT formulations and 1 combination were used to develop the time-to-smoking-relapse model; making this analysis the largest attempt to quantify and characterize the relationship to date.

The time-to-first-relapse model showed that a lower or complete absence of integrated craving was related to a much higher probability of remaining smoking abstinent, compared with higher craving (Figure 2). This might indicate that for individual smokers with a motivation to stop smoking, successfully managing their craving is of major importance for the success of their attempt to quit smoking. NRT reduces craving through nicotine concentrations, which has previously been shown and thus NRT reduced the risk of relapse mediated by craving. Although no covariate analysis was performed in this current work, craving has been shown to be higher for men and subjects with a short “time until first cigarette”, thus implicitly these covariates also affects the risk of relapse.

The only other predictor in the TTE model in addition to integrated craving was the treatment arm. Hazard of smoking relapse was shown to be lower for subjects in the NRT arm at all time points, even after accounting for the overall lower craving scores for subjects on NRT. For example, at 1 year (after the study initiation), the hazard of a relapse was 0.012/month and 0.018/month for NRT and placebo arms, respectively, for 0 craving (i.e., a score of 0 on the VAS). For maximal craving (i.e., a score of 100 on the VAS), the hazard of a relapse was 0.048/month and 0.056/month for NRT and placebo arms, respectively. These findings imply that NRT reduces the risk of relapse mediated by craving, and that the effect of NRT is greater for subjects with higher craving.

Figure 2 The model-predicted probability of staying abstinent over time (top panels: up to 3 months; bottom panels: up to 1 year) for the three modeled scales (left panel: 4-category scale; middle panel: 5-category scale; right panel: visual analogue scale (VAS)). The graphs illustrate the difference between the scores for predicting abstinence probability as well as the relative difference between the scores of difference scales. The color indicates the score, where the lightest color represents the lowest score (e.g., score = 0 on all scales) and the darkest color represents the highest score (e.g., score = 100 for VAS). The left panel includes scores 0, 1, 2, and 3, the middle panel includes scores 0, 1, 2, 3, and 4, and the right panel includes scores = 0, 50, and 100, which corresponds to the lowest, middle, and highest scores for VAS. [Colour figure can be viewed at wileyonlinelibrary.com]
VAS), hazard of smoking relapse at 1 year was 0.14/month and 0.20/month for NRT and the placebo arms, respectively (i.e., 43% higher hazard for subjects on placebo to relapse than subjects on NRT). Apart from NRT reducing the craving, 15 NRT relieves additional symptoms of withdrawal that the integrated craving does not account for, such as depressed mood, insomnia, irritability, and weight gain. It may thus be possible to replace the NRT effect in the model with measurements of such symptoms, however, such information was not available in the current work and could not be investigated. After LIC and NRT were included in the model, the predictive performance of the model improved considerably and further attempts to improve the model were unsuccessful, showing that although there were differences in smoking abstinence probability between different formulations, this was mostly already captured by the integrated craving.

In the current analysis, the regulatory definition or relapse to smoking was used, including both “verified relapse” and dropout into overall relapse. This is a reasonable, although conservative approach, because subjects not showing up for scheduled visits are more likely to have relapsed, than those that show up to visits. Additionally, a model using the regulatory definition of relapse is more useful for clinical trial simulations. The assumption, however, comes with a risk if there are different predictors of “verified relapse” and dropout or if predictors influence “verified relapse” and dropout differently. An alternative approach would be to model “verified relapse” and dropout separately, allowing different predictors/predictor relationships and thereafter combine to the regulatory definition. This approach, however, requires access to dropout separated from relapse, which was not available in this work.

Another limitation of the work, related to data, is the assumption that all subjects quit smoking during the initial phase where relapse was not assessed. Study subjects were recruited based on their willingness to quit, however, a subject unable to quit during the initial phase was thus assessed as relapsed only at the first assessment of relapse, assuming that the subject had been able to quit. The implication of this would be an overestimation of the momentary relapse rate at the first visit, and potentially an underestimation of the moment of relapse, assuming that the subject had been able to quit. This approach, however, requires access to dropout separated from relapse, which was not available in this work.

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Li et al. 28 presented a method to quantitatively assess the proportion of observed effect attributed to a treatment or biomarker. This methodology was developed for linear relationships and thus is not directly applicable to the current work, where a sigmoidal E_max model was the preferred relationship between the latent integrated craving and risk of smoking relapse. However, if a linear relationship between craving and relapse to smoking was implemented, the craving was shown to explain ~40% of the smoking cessation. This means that the integrated craving alone did not explain the overall NRT effect (as discussed above) and thus did not fulfill the criteria for surrogate end point. Integrated craving did, however, explain a considerable portion of the smoking cessation. 29

There are several advantages of using TTE models; a commonly used methodology for analysis of this type of data. For example, in a TTE model, the data from the entire time course of a study (up to the event) are used, utilizing all available data for the analysis, thus extracting more information from the data (such as, how the hazard of having an event changes over time), compared to, for example, a t-test or a risk-ratio analysis, where the time component is ignored. Furthermore, including studies of different duration is not a problem with TTE models, unlike, for example, a binary response model, as the hazard of subjects not having an event at the end of study (i.e., subjects that are right censored, are appropriately handled). Additionally, interval censoring can be implemented in a TTE model, as was done in this work, and thus accounts for the fact that it is only known that an event has occurred between two visits, and not the exact time when the event occurred.

Although the model described the data adequately for the purpose “to verify, characterize, and quantify the relationship between craving and smoking cessation,” there were some misspecifications (Figure 1). Notable though, with the size of the dataset, the 95% confidence intervals around the Kaplan–Meier curves are narrow and misspecification is emphasized, although being quite small in absolute terms. We assumed that the underlying hazard of relapse to smoking is the same for all studies. Considerable effort was made to find a suitable shape of the hazard, resulting in the Gompertz–Makeham function. The most pronounced misspecification was observed between days 30 and 150 of the mouth spray studies, where, according to the model, fewer subjects relapsed to smoking, compared with the observed data (Figure 1). The studies with the mouth spray formulation were the most recently performed (i.e., after the year 2000), and the smoking populations have changed over time. In addition, in the more recent studies, the inclusion criteria did not specify a maximal number of allowed smoked cigarettes per day in contrast to older studies. It appears as if the assumption that the underlying hazard is the same, is erroneous. The year of performing the studies and the formulation overlap, thus the apparent misspecification between formulations, may in fact be differences in underlying hazard. More recent studies, with similar study design and several formulations are required to tease out if there is a difference between formulations. Generally, the integrated craving model was able to describe the data quite well (Figure S2, Figure S3, Figure S4 and Figure S5), but some overpredictions and underpredictions of proportions of scores could be observed for a few VPCs, stratified by formulation and treatment arm, which would also affect the predictions of abstinence probability.

Data were collected retrospectively from studies, although they were not designed for this purpose, the primary end point in all but one of the studies was smoking cessation, therefore, the studies were deemed appropriate for our analysis. In the model, we used LIC instead of observed craving, partly because on 37% of the events the right censored time points craving was missing. Having a model to describe craving over time was, therefore, considered an appropriate approach to handle missing craving observations. Additionally, this allowed us to only use one set of parameters in the sigmoidal E_max model relating the risk of smoking relapse to the LIC, and not three separate sets of parameters—one set for each craving scale as otherwise would have been needed. The LIC also allowed us to characterize and quantify the relationship between craving and risk of smoking relapse using all data simultaneously.
The model may be useful for performing simulations of different craving scores, and for exploring how this translates to smoking abstinence, with due caution when extrapolating beyond investigated conditions. Worth mentioning, in relation to simulations, is the overprediction of relapse for early time points, where predictions thus are most likely conservative. Because we also developed a model for integrated craving, which connects all three scales, this expands the use of the model further, as all craving scores regardless of the scale can be predicted. A limitation of the work, with regard to the translation between the scales, is the lack of measured scores on more than one scale in the same subject, which would enable assessment of the Cohen’s kappa coefficient. Although our work shows an alternative approach, it would benefit from such validation. Further work could include investigating the effects of other (demographic) predictors, such as markers of smoking addiction, on the hazard of smoking relapse.

CONCLUSION
A TTE model was developed, quantitatively confirming that integrated craving is a key driver of the hazard of smoking relapse in a sigmoidal $F_{\text{max}}$ fashion, and that no/low craving leads to a considerably higher probability of remaining abstinent from smoking. The hazard of smoking relapse was shown to decrease over time, and was higher in the placebo treatment arm: at 1 year after study initiation for 0 craving the instantaneous hazard of a relapse to smoking was predicted as 0.012/month for NRT and 0.018/month for the placebo arm.

SUPPLEMENTARY INFORMATION
Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).

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CONFLICT OF INTEREST
A.H., Ä.W., P.A.S., and A.V. are (former) employees of affiliated companies of Johnson & Johnson. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
E.G., A.H., M.O.K., P.A.S., A.V., and M.C.K. wrote the manuscript. E.G., A.H., M.O.K., P.A.S., A.V., and M.C.K. designed the research. E.G., A.H., A.V., and M.C.K. performed the research. E.G. and Ä.W. analyzed the data.

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