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ARTICLE

Optimized infusion rates for N,N-dimethyltryptamine to achieve a target psychedelic intensity based on a modeling and simulation framework

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Abstract

N,N-dimethyltryptamine (DMT) is a psychedelic compound that is being studied as a therapeutic option in various psychiatric disorders. Due to its short half-life, continuous infusion of DMT has been proposed to extend the psychedelic experience and potential therapeutic effects. The primary aim of this work was to design an infusion protocol for DMT based on a desired level of psychedelic intensity using population pharmacokinetic/pharmacodynamic modeling. As a secondary aim, the impact of choosing a continuous variable or a bounded integer pharmacokinetic/pharmacodynamic model to inform such an infusion protocol was investigated. A previously published continuous variable model and two newly developed bounded integer models were used to assess optimal doses for achieving a target response. Simulations were performed to identify an optimal combination of a bolus dose and an infusion rate. Based on the simulations, optimal doses to achieve intensity ratings between 7 and 9 (possible range = 0–10) were a bolus dose of 16 mg DMT fumarate followed by an infusion rate of 1.4 mg/min based on the continuous variable model and 14 mg with 1.2 mg/min for the two bounded integer models. However, the proportion within target was low (<53%) for all models, indicating that individual dose adjustments would be necessary. Furthermore, some differences between the models were observed. The bounded integer models generally predicted lower proportions within a target of 7–9 with higher proportions exceeding target compared with the continuous variable model. However, results varied depending on target response with the major differences observed at the boundaries of the scale.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

N,N-dimethyltryptamine (DMT) is a psychedelic compound, currently being investigated as a treatment option mainly in depression. Due to its short half-life, a continuous infusion has been proposed as a way forward to extend its effects.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aimed to design a dosing protocol for DMT based on a target psychedelic intensity. In addition, the impact of choosing a continuous variable or a bounded integer model to inform such a protocol was investigated.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Dose recommendations for DMT based on a target response is presented for the first time. It is also shown that no single dose is likely to lead to a large proportion of the population within target. Further, differences between the continuous variable model and the bounded integer model that may impact dose selection are demonstrated.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The dose recommendations presented here may impact the clinical development of DMT by providing a starting point for designing infusion studies with DMT.

INTRODUCTION

In recent years, the need for new treatments in psychiatric disorders, such as depression and anxiety, has led to an increase in research with different psychedelic compounds.[1–5] The effects of these compounds naturally include a subjective component related to the psychedelic experience and it has been hypothesized that this component is closely related to therapeutic effects.[6] Consequently, accurate characterization of the relationship between drug exposure and the subjective psychedelic experience may prove important to guide dose decisions in future clinical studies.

The relationship between exposure to the psychedelic compound N,N-dimethyltryptamine (DMT) and its psychedelic effects has previously been investigated using population pharmacokinetic/pharmacodynamic modeling.[7] The psychedelic effects were assessed through a subjective intensity score where individuals were asked to rate the intensity of the experience on a numbered scale from 0 to 10. Higher concentrations of DMT were associated with a higher rating. The concentration needed to achieve a rating of 5, corresponding to 50% of the maximum effect (EC_{50}), was estimated at 92 nM. The model was used to simulate the expected ratings associated with different intravenous bolus doses, demonstrating how this model can be used to guide dose decisions. However, whereas most published studies with DMT so far have used intravenous bolus doses to investigate its effects,[4,8,9] a continuous infusion of DMT rather than bolus doses has been proposed as a suitable way forward to extend the psychedelic experience.[10] Recently, infusions of DMT over varying lengths of time have been evaluated in the clinic.[11,12]

The subjective intensity score used in the aforementioned study[7] is a discrete outcome variable that can only assume integer values within certain boundaries. However, the published model treats the intensity ratings as being continuous which means that predictions of non-integer values can also occur. Another approach to handling this type of data, that was recently suggested by Wellhagen and colleagues,[13] is the bounded integer model. This model respects both the discrete nature of the data and the boundaries of the scale. Previous work has shown that the bounded integer model is able to provide a better fit to the data than corresponding continuous variable models.[13] However, limited information is available on how the two approaches compare in terms of applicability, for example, in a dose-finding context.

The primary aim of this study was to design an infusion protocol for DMT based on a desired level of psychedelic intensity using the previously published continuous variable model as well as a newly developed bounded integer model. As a secondary aim, the impact of choosing one of the two different approaches on dose selection was investigated.

METHODS

Clinical study overview

The data set used in this work was obtained from a previously published, placebo controlled clinical study performed at the Imperial College Clinical Research Facility, Imperial College London.[8] DMT fumarate was administered as an intravenous bolus dose at four different dose levels to 13 healthy subjects. Each subject received placebo on their first visit and DMT on their second visit. Blood samples for quantification of DMT in plasma were collected up to 60 min after administration. The intensity of the subjective effects was assessed by asking subjects to rate the intensity of the experience on a scale from 0

to 10, where 0 is no effect and 10 is the most intense experience imaginable, every minute during the first 20 min after administration.

The study was conducted according to the revised Declaration of Helsinki (2000), the International Committee on Harmonization Good Clinical Practices guidelines, and the UK National Health Service Research Governance Framework, and was approved by the National Research Ethics Committee London – Brent and the Health Research Authority. All subjects provided written informed consent to participate in the study.

Pharmacokinetic/pharmacodynamic modeling approach

A continuous variable model describing the relationship between DMT exposure and subjective psychedelic experience based on these data has already been published.[7] In the present work, a bounded integer model was also developed in order to assess whether the choice of model might impact future dose decisions. The two models are described in more detail below.

Data were analyzed using nonlinear mixed effects modeling in NONMEM version 7.4.3. (ICON Development Solutions).[14] Pirana (version 3.0.0) and Perl-speaks-NONMEM (version 5.2.6)[15] were used for model automation and diagnostics. R (version 4.1.1) was used for model diagnostics and visualization. Models were fitted using the first-order conditional estimation method with interaction or the Laplace estimation method for the continuous variable and bounded integer model, respectively.

A population pharmacokinetic parameter and data approach was used, where the same population pharmacokinetic parameters were used as input in both models whereas individual pharmacokinetic parameters were estimated simultaneously with the pharmacodynamic parameters.[16] Individual pharmacokinetic parameters were assessed to assure that there were no major differences between the models that might impact the interpretation of the results. Effect compartment models were used to describe the slight delay in response as compared to plasma concentrations.[17] The change in concentration in the effect compartment is described according to:

$$\frac{dC_e}{dt} = k_{e0} \times (C_p - C_e)$$

where k_{e0} is the effect compartment equilibrium rate constant, C_p is the plasma concentration of DMT, and C_e represents the theoretical concentration in the effect compartment.

Model discrimination between nested models was based on objective function value (OFV) where a change in OFV of −3.84 was considered a significant model improvement at $p = 0.05$ under the assumption that ΔOFV is approximately χ^2 distributed. The fit of the models to the data was further assessed using visual predictive checks (VPCs). Sampling importance resampling (samples/resamples = 5000/1000) was performed to determine precision of the parameter estimates.[18]

Continuous variable model

The continuous variable model was a previously published model. More details on model development and assessment can be found elsewhere.[7]

In brief, the relationship between DMT exposure and subjective intensity was described by an effect compartment model with a sigmoid maximum effect (E_{max}) response according to:

$$\text{Response} = E_0 + \frac{E_{max} * C_e^{\gamma}}{EC_{50,e}^{\gamma} + C_e^{\gamma}}$$

where E_0 is the baseline response, E_{max} is the maximum response, $EC_{50,e}$ is the concentration of DMT at the effect site required to produce half of the maximum response, and the Hill coefficient γ describes the sigmoidicity of the relationship. For technical reasons, E_0 was fixed to 0.001, a more detailed discussion on this can be found in the original publication. However, for any practical purposes, 0.001 can be considered equal to 0 in this context.

To keep predictions within the boundaries of the scale, a logit transformation was used for every observation j of each individual i as:

$$y = 10 \bullet \frac{e^{\ln\left(\frac{\lambda}{10-\lambda}\right)+\varepsilon_{ij}}}{1 + e^{\ln\left(\frac{\lambda}{10-\lambda}\right)+\varepsilon_{ij}}}$$

where λ is the individual prediction, and ε_{ij} is the residual error, additive on the logit scale, and following a normal distribution.

Development of a bounded integer model

Given a scale with n categories, the area under the standard normal distribution is divided into n equally sized areas in the bounded integer model. This is done using the probit function to define $n-1$ cutoff values ($Z_{1/n}$–$Z_{(n-1)/n}$). Because the subjective intensity rating scale consists of 11 categories, the area under a standard normal distribution was divided into 11 equally sized areas. A function

describing the mean of a normal distribution, using fixed effects (θ), random effects for an individual i (η_i), time, and covariates (X_i), $f(\theta,\eta_{i,f},t,X_{i,f})$, together with a function describing the variance of a normal distribution, using fixed effects (σ), random effects for an individual i (η_i), time, and covariates (X_i), $g(\sigma,\eta_{i,g},t,X_{i,g})$, are used along with the cut-off values to estimate the probability of each score. The probability for the kth score is:

$$P_{i,j}(k) = \Phi\left(\frac{Z_{\frac{k}{n}} - f\left(\theta,\eta_{i,f},t,X_{i,f}\right)}{g\left(\sigma,\eta_{i,f},t,X_{i,f}\right)}\right) - \Phi\left(\frac{Z_{\frac{k-1}{n}} - f\left(\theta,\eta_{i,f},t,X_{i,f}\right)}{g\left(\sigma,\eta_{i,f},t,X_{i,f}\right)}\right)$$

where Φ if the cumulative distribution of the normal distribution function.

For the first category ($k=1$) this collapses into:

$$P_{i,j}(1) = \Phi\left(\frac{Z_{\frac{1}{n}} - f\left(\theta,\eta_{i,f},t,X_{i,f}\right)}{g\left(\sigma,\eta_{i,f},t,X_{i,f}\right)}\right)$$

and for the last category ($k=$n) into:

$$P_{i,j}(n) = 1 - \Phi\left(\frac{Z_{\frac{n-1}{n}} - f\left(\theta,\eta_{i,f},t,X_{i,f}\right)}{g\left(\sigma,\eta_{i,f},t,X_{i,f}\right)}\right)$$

representing the cumulative distribution within the intervals $(-\infty, Z_{1/n})$ and $(Z_{(n-1)/n}, \infty)$, respectively.

Linear and power functions were evaluated to describe the relationship between DMT concentrations and the individual prediction of the mean of the normal distribution. Exemplified here by a linear relationship described as:

$$f\left(\theta,\eta_{i,f},t,X_i\right) = \text{Base} + \text{Slope} * C_e$$

where Base is the mean of the normal distribution before any drug is administrated, Slope is a constant describing the relationship between drug concentration and the individual prediction, and C_e is the drug concentration in the effect compartment.

Between subject variability (BSV) was assessed on drug effect and variance as exponential random effects following a log-normal distribution with mean zero and variance ω.[2]

In addition, a Markov element was implemented to evaluate any serial correlation in the data, as described by Wellhagen and colleagues.[13] This was implemented as:

$$P_{i,j}\left(k|\, Y_{i,j-1} = k\right) = \frac{P_{k,i,j} + \text{PM}}{1 + \text{PM}}$$

where $Y_{i,j-1}$ is the previous observation and $P_{k,i,j}$ is the probability of a score k for individual i at time j. If $Y_{i,j}$ and $Y_{i,j-1}$ are different, the equation simplifies to:

$$P_{i,j}\left(k|\, Y_{i,j-1} \neq k\right) = \frac{P_{k,i,j}}{1 + \text{PM}}$$

A positive value of the Markov parameter PM is associated with a higher probability of an observation having the same value as the previous observation.

A more detailed description of the bounded integer model can be found elsewhere.[13]

Simulations

Simulations including both BSV and residual variability were performed to assess optimal dose levels for achieving different target intensity ratings. Doses were assessed as DMT fumarate doses throughout this work. The overall aim was to identify a combination of a bolus dose and an infusion rate that would keep subjects at steady ratings over a longer period of time (e.g., 60 min). The previously published continuous variable model and two newly developed bounded integer models were used to simulate subjective intensity ratings at 2 min after administration of a bolus dose as well as at steady-state in 1000 virtual subjects across different dose levels. A timepoint of 2 min after bolus administration was chosen, as it is the time where peak effect compartment concentrations would be expected based on the final models. Steady-state was defined as a timepoint where more than five terminal plasma drug half-lives had passed in all simulated subjects. For the purpose of this work, ratings between 7 and 9 were considered desirable. This was to ensure a strong psychedelic experience, as this has been hypothesized to correlate with therapeutic outcome,[6] while also avoiding participants experiencing adverse psychological reactions (i.e., extreme anxiety). Consequently, ratings above 9 were considered undesirable in this context, whereas ratings below 7 were considered a subtherapeutic response. A lower target of ratings between 4 and 6 was also evaluated for the purpose of model comparison. For the continuous variable model, ratings greater than or equal to 6.5 and less than 9.5 would be considered equal to 7–9 and ratings greater than or equal to 3.5 and less than 6.5 would be considered equal to 4–6. For each evaluated dose level, the proportion of the population within, below, or exceeding target was simulated. Once optimal doses had been defined, simulations of ratings over time in a typical subject (i.e., without any variability), following administration of these doses were performed. For the bounded integer models, typical ratings were defined as the rating with the highest probability at each timepoint.

RESULTS

Model comparison

For the bounded integer model, a linear function best described the relationship between drug concentration and effect. BSV was incorporated on drug effect (slope) as well as the variance function (SD). Including variability in the variance function significantly improved the fit of the model to the data. Adding a Markov element provided a better fit to the data (ΔOFV = −83). However, because no element to account for serial correlation is present in the continuous variable model, two final bounded integer models are presented here, with and without a Markov element. Final parameter estimates and VPCs of all models, including the previously published continuous variable model, are presented in Table 1 and Figure 1, respectively. Based on the VPCs, the fit appears similar between models. The number of parameters, parameter precision, and the estimated size of the BSV is also similar between models. Individual pharmacokinetic parameter estimates from the different models were considered similar (data not shown). Residual scatterplots as well as distribution of individual pharmacodynamic parameter estimates are provided in Appendix S1. The model code is provided in Data S1. A simulated dataset is provided in Data S2.

Simulations

The distributions of simulated subjective intensity ratings at 2 min after the administration of different bolus doses as well as at steady-state across different infusion rates with the different models are presented in Figure 2. For the bolus doses, simulated median ratings between 7 and 9 were achieved at dose levels ranging from 12 to 26 mg with the continuous variable model, whereas the corresponding dose ranges were 12–16 and 14–18 mg for the bounded integer model without and with a Markov element, respectively. At steady-state, a predicted median response between 7 and 9 was achieved at infusion rates of 1.2–2.6 mg/min with the continuous variable model and 1.0–1.4 mg/min for the two bounded integer models.

Figures 3 and 4 show the percentage of individuals having an intensity rating within, above, or below target across different dose levels. Tables summarizing the

TABLE 1 Final parameter estimates for the three different pharmacokinetic/pharmacodynamic models describing the relationship between DMT plasma concentrations and subjective intensity ratings.

	Continuous variable model		Bounded integer model		Bounded integer model with Markov element	
Parameter	**Estimate**	**%RSE**	**Estimate**	**%RSE**	**Estimate**	**%RSE**
k_{e0} (min^{-1})	1.38	17.5	1.12	6.5	1.16	5.5
E_{max}	10 FIX	–	–	–	–	–
$EC_{50,e}$ (nM)	94.7	14.9	–	–	–	–
γ	2.87	4.2				
Base	–	–	−1.7	3.8	−1.68	4.0
SD (g())	–	–	0.275	19.7	0.269	15.9
Slope	–	–	0.0163	8.6	0.0159	7.0
PM	–	–	–	–	0.289	22.4
BSV $EC_{50,e}$ (CV%)	38.6	34.1	–	–	–	–
BSV γ (CV%)	77.3	36.6	–	–	–	–
BSV slope (CV%)	–	–	35.8	32.9	31.8	36.9
BSV SD (CV%)	–	–	75.7	35.0	81.9	39.3
Residual error (SD)	0.82	7.8	–	–	–	–

Abbreviations: Base, mean of the normal distribution before any drug is administrated; BSV, between subject variability; CV, coefficient of variation; DMT, N,N-dimethyltryptamine; $EC_{50,e}$, effect compartment concentration required to reach 50% of maximum response; E_{max}, maximum achievable response; k_{e0}, effect compartment equilibrium rate constant; PM, Markov parameter; RSE, relative standard error; SD, standard deviation of bounded integer model as defined by g() function; γ, Hill coefficient describing steepness of relationship.

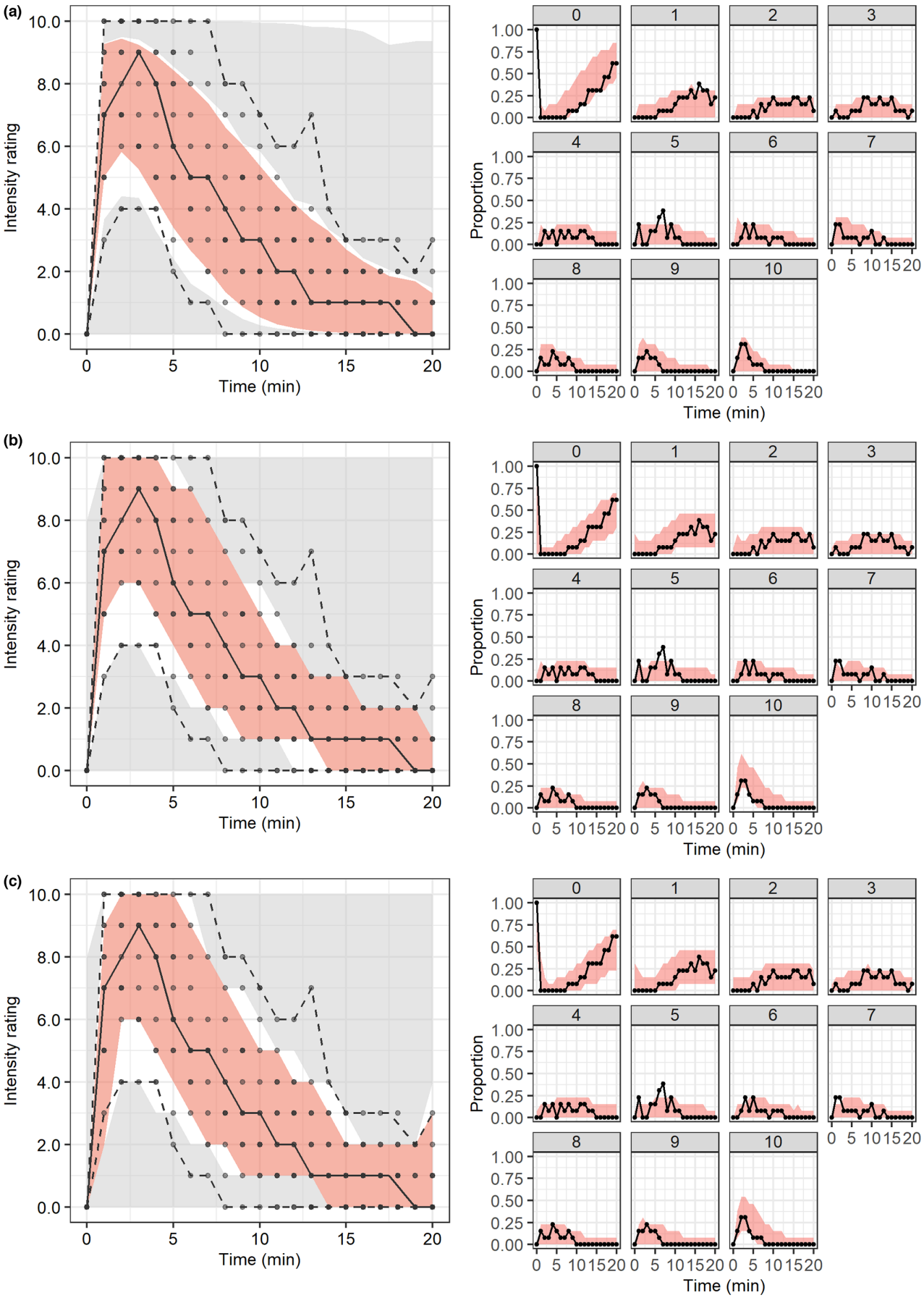
(a)
(b)
(c)
Intensity rating
Time (min)
Proportion
0
1
2
3
4
5
6
7
8
9
10

FIGURE 1 Visual predictive checks ($n = 1000$) of (a) the continuous variable model (b) the bounded integer model without a Markov element and (c) the bounded integer model with Markov element. The left panels demonstrate predicted intensity ratings over time and the right panels demonstrate the proportion of each rating over time. Black circles represent observations, solid lines represent the median observation, and dashed lines represent the 5th and 95th percentiles of the observations. Red areas represent the 90% confidence intervals of the median predictions and gray areas represent the 90% confidence intervals of the predicted 5th and 95th percentiles.

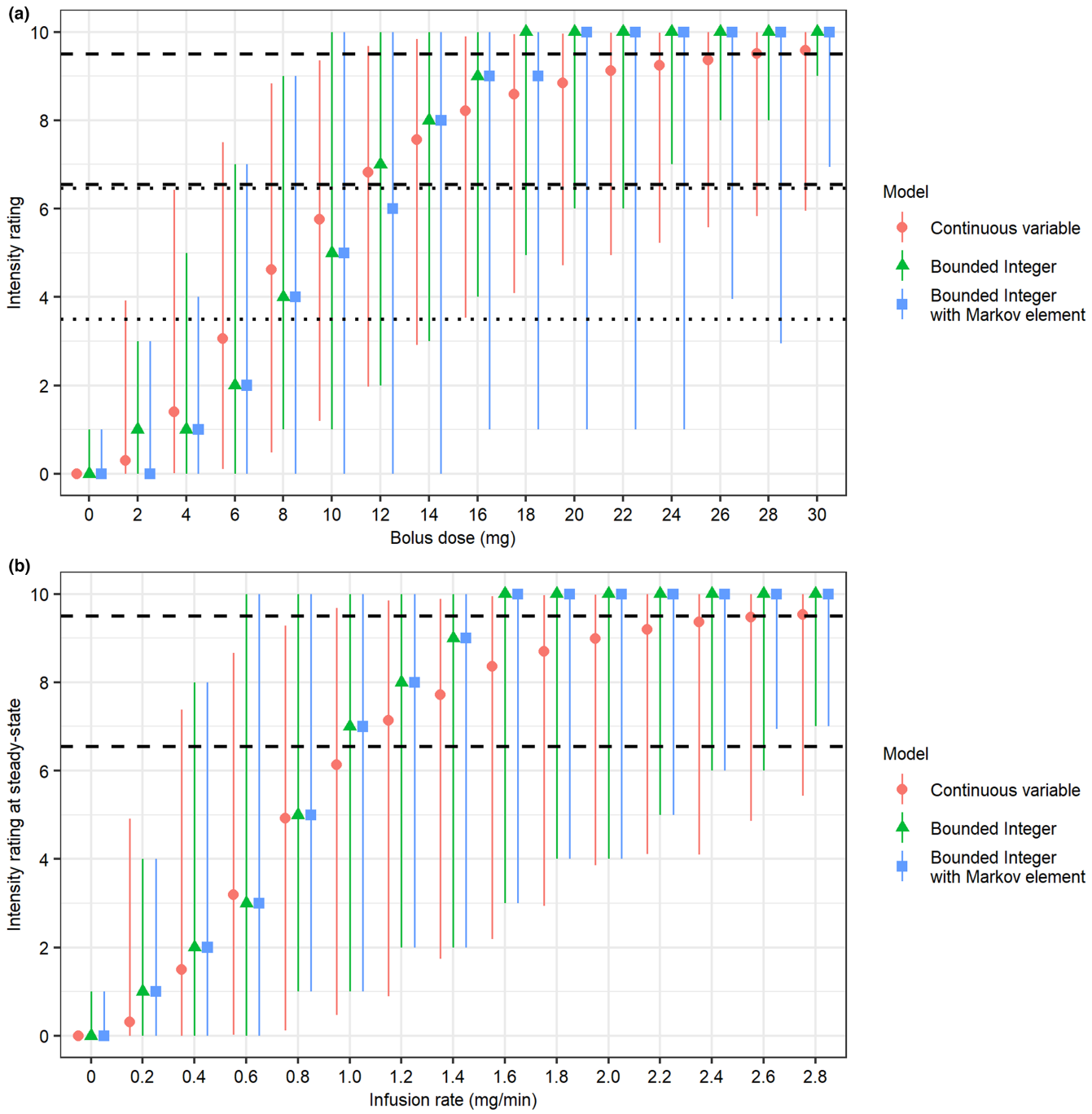

FIGURE 2 Predicted distribution of intensity ratings at (a) 2 min after a DMT bolus dose across different dose levels and (b) at steady-state across different infusion rates. Solid lines represent the 90% prediction interval at each dose level with filled shapes representing the median prediction. Dashed lines demonstrate a target response interval of 7–9 and the dotted line represent a target response interval of 4–6. Simulations were performed in 1000 subjects. Doses are expressed as mg DMT fumarate. DMT, N,N-dimethyltryptamine.

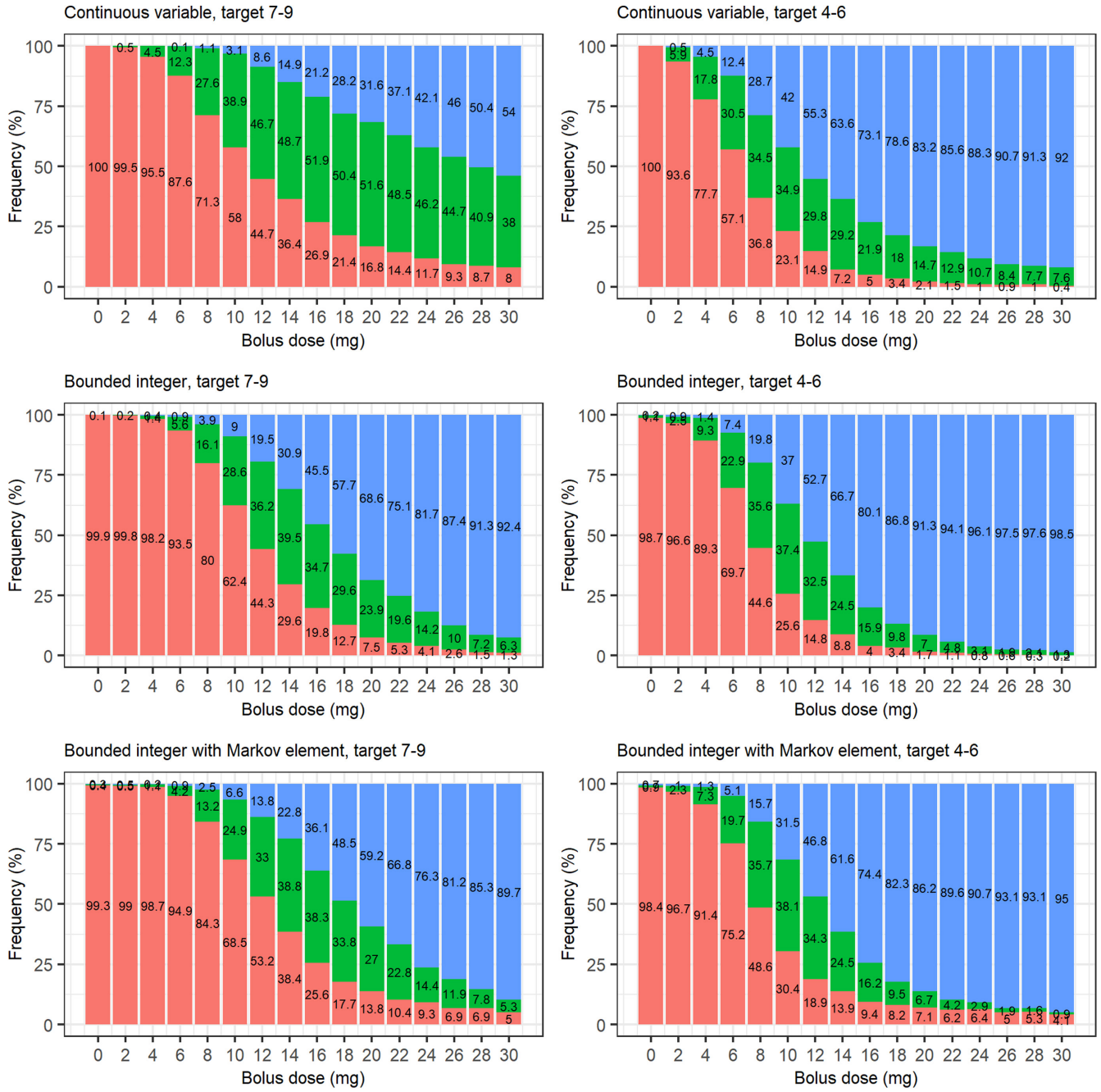

FIGURE 3 Predicted proportions of the population having an intensity rating within target (green), below target (red), and above target (blue) 2 min after the administration of a bolus dose across different DMT dose levels. Simulations were performed in 1000 subjects. Doses are expressed as mg DMT fumarate. DMT, N,N-dimethyltryptamine.

predicted percentages can be found in Appendix S1. The doses that are predicted to achieve the highest proportion of the population within target with the different models are summarized in Table 2. At a target of 7–9, the proportions within target at the optimal dose levels varied substantially between the different models whereas they are more similar at a target of 4–6. Figure 5 demonstrates the simulated typical ratings after administration of the optimal doses to achieve ratings between 7 and 9 presented in Table 2.

DISCUSSION

The primary aim of this work was to design a dosing protocol for achieving a target psychedelic intensity level over an extended period of time (e.g., 60 min) using a previously published continuous variable model as well as a newly developed bounded integer model describing the relationship between DMT plasma concentrations and ratings of the subjective intensity of the psychedelic experience. The data used in this work come from a previously

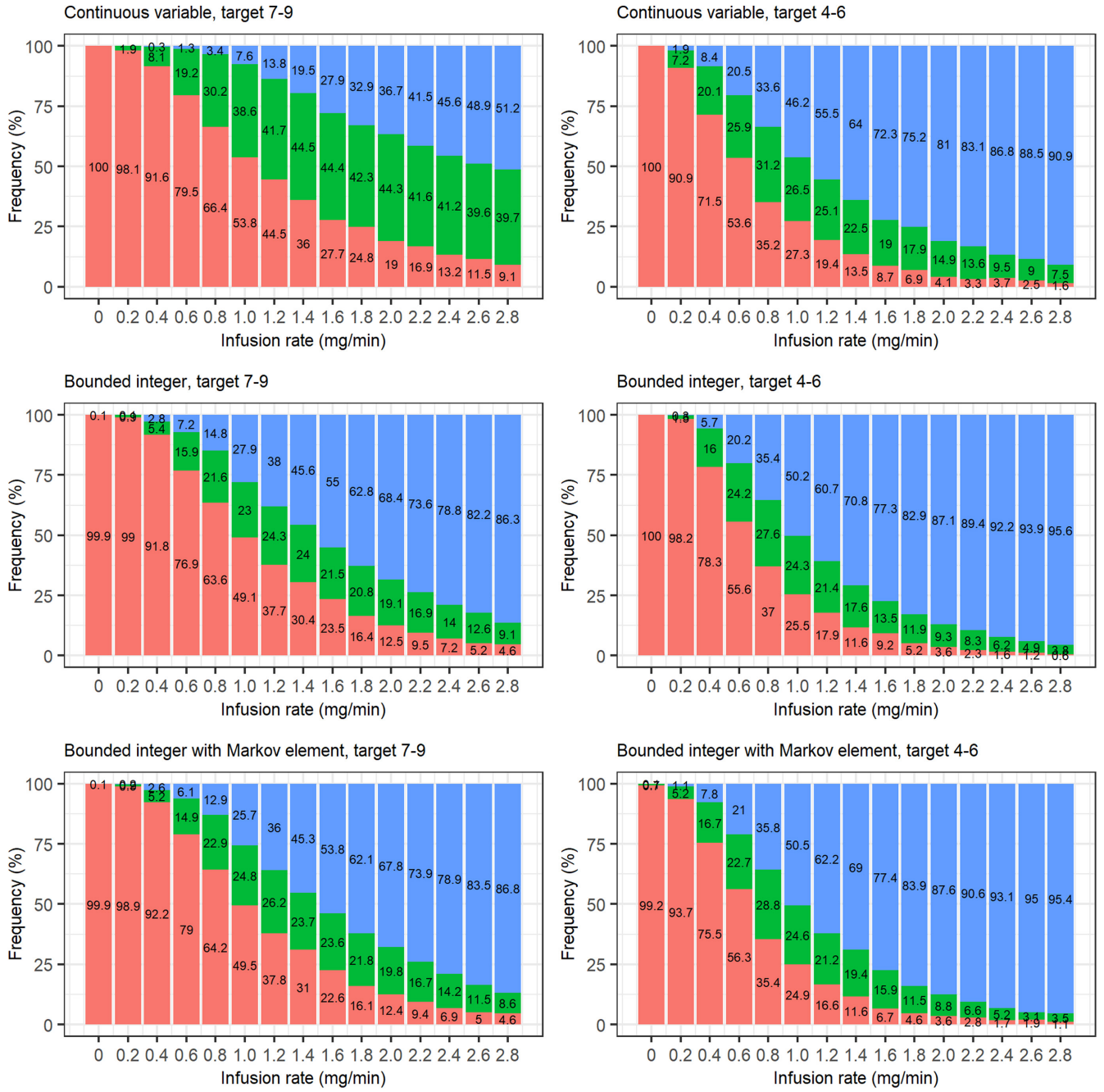

FIGURE 4 Predicted proportions of the population having an intensity rating within target (green), below target (red), and above target (blue) at steady-state across different DMT infusion rates. Simulations were performed in 1000 subjects. Doses are expressed as mg DMT fumarate. DMT, N,N-dimethyltryptamine.

published study where the psychedelic experience was assessed through a subjective rating score on a scale from 0 to 10.[8] Two bounded integer models are presented here, with and without a Markov element accounting for serial correlation in the data. However, no clear impact of the Markov element on the simulations presented here was observed. Although the addition of a Markov element led to a slightly larger proportion below target at each bolus dose as compared to the bounded integer model without a Markov element, the influence on dose decisions has to be considered minor.

Based on the results of the simulations, optimal dose levels to achieve target ratings between 7 and 9 or 4 and 6 were explored. Using the continuous variable model, we predict that the highest proportion within a target of 7–9 would be achieved with a bolus dose of 16 mg followed by an infusion of 1.4 mg/min. The corresponding combination for the bounded integer models was 14 mg combined

TABLE 2 Suggested optimal doses based on predicted proportions within the target response. Response is measured as a subjective intensity rating on a scale from 0 to 10.

Model	Target 7–9		Target 4–6	
	Bolus dose [mg] (% within target)	Infusion rate [mg/min] (% within target)	Bolus dose [mg] (% within target)	Infusion rate [mg/min] (% within target)
Continuous variable	16 (52%)	1.4 (45%)	10 (35%)	0.8 (31%)
Bounded integer	14 (40%)	1.2 (24%)	10 (37%)	0.8 (28%)
Bounded integer with Markov element	14 (39%)	1.2 (26%)	10 (38%)	0.8 (29%)

Note: Doses are expressed as mg DMT fumarate.

Abbreviation: DMT, N,N-dimethyltryptamine.

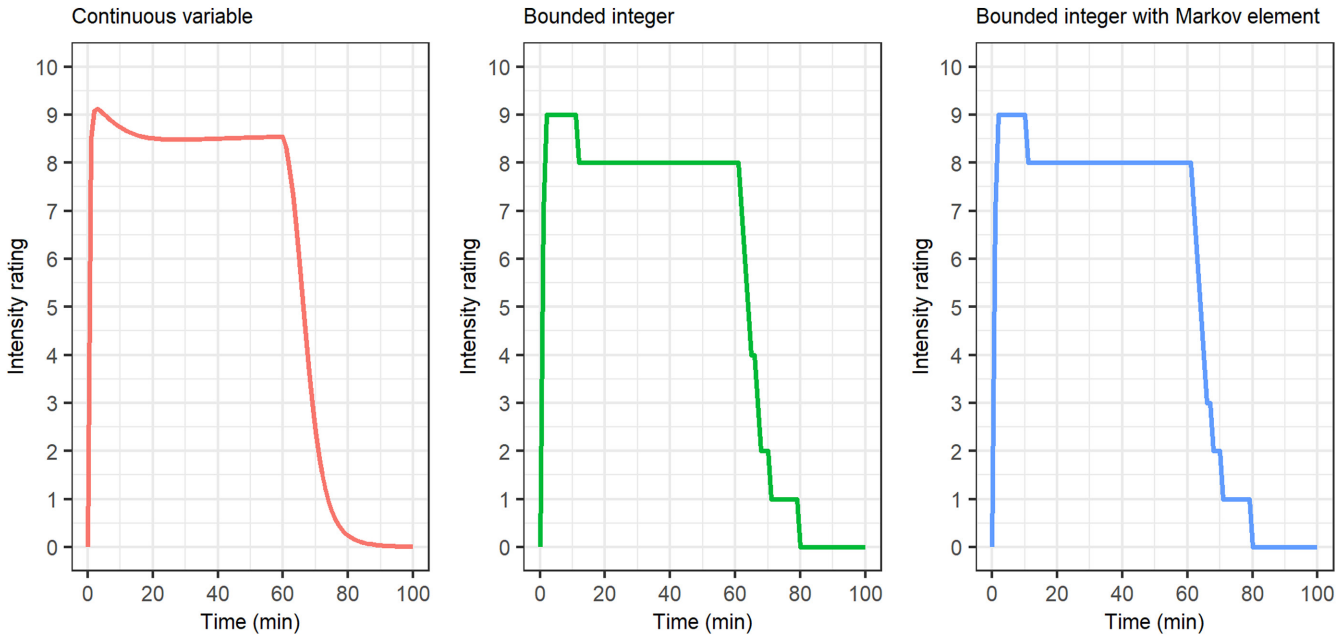

FIGURE 5 Simulated typical rating over time after administration of a 16 mg DMT bolus dose followed by an infusion of 1.4 mg/min over 60 min for the continuous variable model and a 14 mg bolus dose followed by an infusion of 1.2 mg/min over 60 min for the bounded integer models. For the bounded integer models, the plotted typical rating corresponds to the rating with the highest simulated probability at each timepoint. DMT, N,N-dimethyltryptamine.

with 1.2 mg/min. These doses can be expected to provide ratings within target over an extended period of time in a typical subject. However, taking variability into account, the predicted proportions within target are generally low (<53%), indicating that individually adjusted doses are necessary to achieve a large proportion of the population within target. At a target response of 4–6, the highest proportion within target was achieved with a bolus dose of 10 mg combined with an infusion rate of 0.8 mg/min for all models. In addition, for this target, the proportions within target were low (<40%) and individually tailored doses are recommended. Nevertheless, whereas ratings above 9 were considered undesirable here, DMT is generally considered safe[19] and there are no established adverse levels. Although ratings of 10 might imply intolerance, one cannot make that inference directly from these ratings alone. Further questions regarding, for example, anxiety would have to be asked to infer negative valence or intolerance with a rating of 10. Furthermore, bolus doses higher than the ones proposed here have been tested in the clinic without resulting in any safety concerns.[4,8,9] Consequently, we believe that the proposed doses could serve as a good starting point. Potentially, one could then adjust the infusion rate gradually based on the reported ratings of each individual subject. There may also be underlying covariates, such as weight, polymorphisms in metabolizing enzymes, or baseline neuropsychological factors, driving the large variability observed here. Unfortunately, due to the low number of subjects in this study, no covariate analysis could be performed here. Future studies should

focus on characterizing potential covariates to allow for individualized dosing based on such variables.

A secondary aim of this work was to further investigate the impact of the model structure, that is, either a continuous variable model or a bounded integer model, on dose decision making. Interestingly, although the simulated optimal doses were similar between the different models, some key differences were identified. One major difference lies in the frequency of the predicted population falling within target as well as below or above target at the predicted optimal dose levels (Figures 3 and 4). At the predicted optimal infusion rates to achieve ratings between 7 and 9 of 1.4 and 1.2 mg/min for the continuous variable and the bounded integer models, respectively, the corresponding proportions within target are 45% for the continuous variable model and 24%–26% for the two bounded integer models. This difference is mainly due to a higher proportion of ratings exceeding the target of 9 based on the bounded integer models rather than any difference in the proportion of people at subtherapeutic levels. The bounded integer model thus indicates that a larger proportion of the population would need dose adjustments to reach therapeutic levels as compared to the continuous variable model. Furthermore, with a target level of ratings between 7 and 9, the continuous variable model predicts a larger proportion within target even at higher doses as compared to the bounded integer model. This can again mainly be attributed to a smaller proportion of the population above target with the continuous variable model. With the bounded integer model, we predict up to 94% of people having a rating of 10 at the highest simulated dose level as compared to 52% with the continuous variable model. Similarly, there is a difference in the predicted dose intervals leading to median ratings between 7 and 9. For the continuous variable model bolus doses between 12 and 26 mg as well as infusion rates between 1.2 and 2.6 mg/min are predicted to lead to median ratings within target. The corresponding dose intervals for the bounded integer models are 12–16 mg (or 14–18 mg when a Markov element is included) and 1.0–1.4 mg/min. In other words, the bounded integer model predicts a higher risk of people reporting ratings of 10, which could potentially mean an increased risk for adverse psychological reactions, at dose levels where only a small proportion of the population would be expected to report ratings of 10 based on the continuous variable model. This difference could have a major impact on decision making and consequently study outcomes in a clinical development setting.

It should be noted that it is clear from the results of the simulations that the impact of choosing different modeling approaches depends on the target response and that the major difference between the two models is the behavior at the boundaries of the scale. Because the continuous variable model does not truly respect the boundaries or the discrete nature of the data this naturally affects the predictions. However, the impact is most prominent at the higher dose levels where the predicted score gradually gets closer to 10 without being able to reach an actual value of 10. If on the other hand, one is aiming for a medium intensity rating of between 4 and 6, the results from the two different models are very similar. The predicted optimal doses are identical between the models. However, the dose intervals leading to a median response within target varies slightly at bolus doses of 8–10 mg for the continuous variable model and bounded integer model without a Markov element compared to 8–12 mg when a Markov element is added. For the two bounded integer models, only an infusion rate of 0.8 mg/min is predicted to lead to a median response within target, whereas the corresponding range for the continuous variable model is 0.8–1.0 mg/min. Additionally, Figures 3 and 4 demonstrate that the predicted proportions of the population falling within a target of 4–6 are similar between the models, further demonstrating that the main difference lies at the boundaries of the scale.

Whereas we believe that the dose recommendations provided here may serve as a good starting point when designing an infusion study, some limitations should be highlighted. First, this work focuses on a single dataset, based on only 13 subjects, and the models and hence dose recommendations may change with more data available. It should also be pointed out that the data which the models are built on are derived from subjects with previous experience of psychedelics. Consequently, there could be an underestimation of the intensity ratings if applied to the general population. Second, because the recommended doses have not yet been tested in the clinic, no conclusions can be made at this point regarding their clinical suitability. However, although a recent study, using doses similar to what has been reported here, observe slightly lower mean intensity ratings than what would be predicted based on the models presented here, the large variability observed also in that study further demonstrates that individualized dosing will likely be necessary.[11] Further, this work was not focused on making the models fully comparable as such and that may have impacted the results. For example, the included BSV term in the variance function of the bounded integer models allows the consistency in ratings to vary between individuals, something that could be considered equivalent to including BSV in the residual error for the continuous model.[13] However, to make sure that this had no major impact on the comparison between the models, simulations were also performed using a bounded integer model without BSV in

the variance function. These simulations showed that, whereas this BSV term improved the fit of the model to the data, it had no major impact on the behavior of the model in the context of designing a dose protocol based on the simulations presented here (data not shown). Moreover, based on the VPCs presented in Figure 1, all models seem to fit the data well. More importantly, the fit appears similar between them. Nevertheless, there are some expected differences in the behavior of the models that may impact predictions. For example, for the continuous model, the baseline intensity score was fixed at 0. Whereas with the bounded integer model, based on the estimated base parameter and variability, scores above 0 are sometimes predicted even before any drug has been administered. This can also be observed in the simulations where the 90% prediction interval includes ratings of 1 when the administered dose is zero (Figure 2). Furthermore, because individual pharmacokinetic parameters were estimated for each model, this could cause differences in simulated outcomes. However, the aim was not to perform an extensive investigation on the behavior or appropriateness of the different models but rather to give dose recommendations for DMT specifically as well as to provide an example of how the choice of model might impact dose selection when planning a clinical study.

To conclude, this study presents, for the first time, dose recommendations for DMT based on a target response level. Overall, it appears that the choice of optimal dose levels based on the target intensity would be similar regardless of model choice. However, it is clear that individual dose adjustments will be needed and that no single dose will lead to a high proportion of the population within the target range. Furthermore, the bounded integer and the continuous variable models do behave differently in terms of describing the variability. Hence, there are larger differences at target response levels approaching the boundaries of the rating scale. Dose decisions based on a continuous variable model may lead to a higher risk of observing maximum ratings of 10, whereas predictions based on the bounded integer model favor a more conservative approach in this context.

AUTHOR CONTRIBUTIONS

E.E., J.K., C.T., R.C.-H., D.R., and M.A. wrote the manuscript. E.E., J.K., C.T., R.C.-H., D.R., and M.A. designed the research. E.E., J.K., C.T., R.C.-H., D.R., and M.A. performed the research. E.E. and J.K. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

E.E. and M.A. are employees of Sahlgrenska Academy at the University of Gothenburg. C.T. is an employee of the Centre for Psychedelic Research, Imperial College London. All other authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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