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# Effect Compartment Model for the Evaluation of Tolerance to Psychological Highness Following Smoking Marijuana

**Sumeet Singla, PhD[1,2] and Robert Block, PhD[3]**

**Abstract**

The purpose of this study is to evaluate the development of tolerance, using a population modeling approach, in recreational marijuana users after acute pulmonary administration of tetrahydrocannabinol (THC), a primary ingredient in marijuana. A total of 85 subjects in 3 separate studies smoked marijuana cigarettes (dose = 13–49 mg) under controlled conditions. Each study was designed as a randomized, crossover, double-blind, and placebo-controlled study. Up to 5 THC plasma samples and corresponding user-reported psychological highness were pooled for population modeling analyses. Age, sex, user status, and body mass index were evaluated as covariates. Population pharmacokinetic (PK) parameters were estimated in the 2-compartment PK model. PK parameters were fixed in the effect compartment model to describe the relationship between THC plasma concentration–psychological highness. The distribution rate constant in the effect compartment was estimated to be 0.988 (95%CI 0.964–1.010)/h. The population mean half-maximal effective concentration ($EC_{50}$) was 23.8 (95%CI 22.7–24.9) ng/mL. Covariate analysis revealed that user status was a significant covariate, and that chronic users appear to need higher plasma concentrations compared with occasional users to achieve a similar degree of highness. The modeling results conclude that chronic users develop tolerance to euphoria, which is the primary central nervous system effect of smoking marijuana.

**Keywords**

effect compartment, marijuana, population modeling, psychological highness, tetrahydrocannabinol, tolerance

Tetrahydrocannabinol (THC) is the primary active ingredient in marijuana. It is well recognized that a time delay exists between the maximal plasma concentrations of THC after intravenous (IV) administration or smoking of marijuana and the manifestation of psychological highness, a primary central nervous system (CNS) effect. Hollister et al intravenously administered 5 mg of THC over 2 minutes, and although the peak THC plasma concentration was reached within 3 minutes, the peak "highness" reported by the subjects was delayed for 20–30 minutes, resulting in an inadequately predicted relationship between the plasma concentration and the degree of highness.[1] Chiang et al observed an anticlockwise hysteresis between reported highness scores and plasma THC concentrations, suggesting that after THC enters the bloodstream, a delay in peak CNS effect is experienced by the subjects.[2] Strougo et al employed an effect compartment to model the CNS effects of THC and found that the equilibration half-life for psychological highness was approximately 47 minutes, suggesting that the euphoric effect was slow to develop and reach its peak.[3] Awasthi et al used a similar approach to relate THC concentrations in the effect compartment to the observed highness. Hysteresis was observed when psychological highness was plotted against THC plasma concentration. However, this was resolved, and a direct relationship was established between the effect-site concentrations predicted by the effect compartment model and the observed effect.[4] A similar approach was also used to establish a direct relationship between effect compartment concentrations of the hydroxy metabolite of THC (THC-OH) and observed highness. The metabolite was assumed to be either twice as potent or equipotent as THC-OH. For both potency assumptions, the effect-site equilibration rate constant was 3- to 4-fold higher for THC-OH as compared with

[1]Department of Pharmaceutical Sciences, College of Pharmacy, University of Iowa, Iowa City, Iowa, USA
[2]Regeneron Pharmaceuticals, Tarrytown, New York, USA
[3]Department of Anesthesia, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, Iowa, USA



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**Corresponding Author**:
Sumeet Singla, PhD, Department of Pharmaceutical Sciences, College of Pharmacy, University of Iowa, Iowa City, IA 52246
Email: sumeetsingla651@gmail.com

**Table 1.** Demographics, Dose, and Data Utilized in Population Analyses

| Dataset Name | 2001 | 2007 | 2008 | Summary |
|---|---|---|---|---|
| Subjects (N) | 36 | 21 | 28 | 85 |
| User status | O = 24, C = 12 | O = 12, C = 9 | O = 15, C = 13 | O = 51, C = 34 |
| Sex | M = 17, F = 19 | M = 10, F = 11 | M = 12, F = 16 | M = 39, F = 46 |
| Age range (years) | 21–36 | 19–23 | 19–24 | 19–59 |
| Dose | 20 mg | O = 21 mg<br>C = 42 mg | Low = 13.2 mg<br>Medium = 24.9 mg<br>High = 45 mg | Variable |
| THC | √ | √ | √ | √ |
| PD end point | Psychological Highness | | | |

C, chronic users; F, female; M, male; O, occasional users; PD, pharmacodynamic; THC, tetrahydrocannabinol.

THC, suggesting a shorter equilibration time for the metabolite to contribute to psychoactive effects.[5]

The purpose of this research is to attempt to evaluate the development of tolerance to psychological highness in recreational subjects using a previously developed effect-compartment model derived for IV administration of THC in a different study population,[5] thus cross-validating that model in the process. The effects of covariates including sex, body mass index (BMI), age, and user status (chronic and occasional) on interindividual variability of pharmacodynamic parameters were evaluated using the effect compartment model.

## Methods

### Source of Data

The research described in this article was approved by the Institutional Review Board of the University of Iowa and conformed to recognized standards of US federal policy for the protection of human subjects. All subjects provided written informed consent in compliance with guidelines of the University of Iowa Institutional Review Board. All studies were conducted at the University of Iowa. The THC concentrations used for the model building process were obtained from individual subject data provided by Dr Daniel O'Leary at the University of Iowa.[6–8] Pharmacokinetics data were pooled from 3 studies conducted in 2001, 2007, and 2008. Composite demographic information regarding the subjects in the studies is presented in Table 1. The population consisted of 85 subjects who were either occasional (n = 51) or chronic (n = 34) users, including male (n = 39) and female (n = 46) participants. Subjects ranged from 19 to 59 years of age, with the majority being <30 years of age. Occasional users were those who had a marijuana smoking history of fewer than 10 times per month (with a mean of approximately once per week) and chronic users were those who reported smoking 7 or more times weekly (on average, 1.8 times/day) for at least the past 2 years. All studies were placebo controlled except for the 2008 study, where occasional users smoked low-dose (approx. 13 mg) and medium-dose (approx. 25 mg) marijuana cigarettes and chronic users smoked medium-dose (approx. 25 mg) and high-dose (approx. 45 mg) marijuana cigarettes to evaluate the dose–response relationship differences between occasional and chronic users. The administered protocol employed a timed, paced smoking routine in a ventilated space, where subjects inhaled for 5 seconds, held the smoke in their lungs for 5 seconds, and then exhaled. Subjects rested for 25 seconds and again inhaled, held, and exhaled. This procedure was repeated until the whole cigarette was smoked. Marijuana cigarettes were obtained from the National Institute on Drug Abuse.[8,9]

Blood samples were collected before and immediately after smoking, and at approximately 15-minute intervals thereafter. Four or 5 blood samples were collected over 1.0–1.5 hours post-smoking, that is, when the subject finished the whole cigarette. Subjects were asked how high they were feeling after smoking on a scale of 0–10 (10 = maximum highness and 0 = no highness). For population pharmacodynamic modeling, absolute values of psychological highness were used for modeling. Individual plots for the time course of THC plasma concentration, the time course of psychological highness, and highness versus THC plasma concentration plots for all 3 datasets have been provided in the supporting information (Figures S1–S9). THC samples were assayed by established radioimmunoassay techniques at the Research Triangle Institute (Research Triangle Park, North Carolina).[10,11] The gas–liquid chromatography (GLC) method was linear in the range 0.1–100 ng/mL, with a limit of quantification (LOQ) of 0.1 ng/mL.

### External Validation

When 2 datasets are available, one upon which a model was developed (reference model or reference dataset) and another (external dataset) that can be used to validate the findings from the reference dataset, external

validation can be conducted by applying the previously developed model to the new dataset (validation dataset). When a model is validated externally, it provides the strongest evidence of model transportability.[12] Model parameters obtained from the external dataset are then compared with model parameters obtained from the reference dataset for external validation of the model. Conclusions drawn from this approach are based on the degree of similarity, that is, whether or not parameter estimates are similar between the 2 datasets and inferences are drawn from the degree of similarity between the parameter estimates obtained from the 2 datasets.[13] In this investigation the data from the O'Leary studies, that is, the datasets used in this article, acted as an external dataset to validate the previously developed effect compartment model and associated parameters reported by Awasthi et al, based on data obtained following IV administration of THC.[5]

### Software and Model-Building Criteria

All modeling analyses were conducted using NONMEM 7.4 (ICON Development Solutions, Ellicott City, Maryland) with a GFortran compiler. Pirana 2.9.8 (Certara, Gaithersburg, Maryland) was used as an interface to perform analyses using NONMEM. The model diagnostic plots were generated using RStudio 1.1.456 (RStudio, Inc., Boston, Massachusetts) and the packages Xpose 4.6.1 (https://uupharmacometrics.github.io/xpose4/) and ggplot2 3.3.5 (https://ggplot2.tidyverse.org). A first-order conditional estimation (FOCE) method was used for estimation and a user-defined subroutine (ADVAN6) was used to estimate the conditional population predictions (CPREDs) and individual subject predictions (IPREDs).

For covariate models, that is, nested models, the addition of each covariate added to the model was tested by examining the change in the objective function value (OFV = –2 times the log-likelihood) using the likelihood ratio test (LRT).[14] Age, sex, marijuana user status (chronic/occasional smokers), and body mass index (BMI) were evaluated as covariates to explain the interindividual variability in the dataset.[5] Evaluation of the covariates involved a forward inclusion step and a backward elimination step. In the forward step, parameter–covariate relationships were added to the model in a stepwise manner until no further relationship was statistically significant ($P < .05$). This was determined from the difference in OFV for 2 models differing by just one parameter when the OFV exceeds 3.84. In the subsequent backward step, the parameter–covariate relationships identified earlier were excluded from the model, in a similar stepwise manner. If the covariate fails to achieve statistical significance at the $P < .001$ level, when the difference in OFV for 2 models differing by just one parameter exceeds 10.83, the covariate was determined to be insignificant and eliminated from the model. The differences in OFV values follow a chi-squared distribution with degrees of freedom (*df*) equal to the difference in the number of parameters.[14,15]

Model development was supported by successful convergence, successful estimation of covariance, goodness-of-fit plots, and OFV. For further guidance on model development, goodness-of-fit plots, including scatter plots of observed versus CPRED concentrations and observed versus IPRED concentrations, and diagnostic plots, such as conditional weighted residual (CWRES) versus CPRED and CWRES versus time, were evaluated. In addition, bootstrap analysis with resampling was performed where 1000 datasets were replicated and summary statistics (mean and bootstrap 95%CI) for each final parameter estimate was compared with the corresponding population pharmacodynamic parameter estimated from the effect compartment model. The residual variability was estimated in the form of additive error for psychological highness.

### Relating the Plasma Tetrahydrocannabinol Concentrations to the Observed Psychological Highness: Population Modeling Approach

The structural model is a 2-compartment pharmacokinetic (PK) model, with the central compartment connected to the effect compartment, where euphoria is experienced by subjects after smoking marijuana (Figure 1). First, population PK parameters were estimated using a 2-compartment PK model to describe the time course of THC concentrations measured over 2 hours. Then, population PK estimates were fixed in the effect compartment model and THC concentrations were correlated with PD effect, that is, psychological highness, while the simultaneous estimation of pharmacodynamic parameters related to the effect compartment and the effect-site concentrations were performed (Figures S10 and S11; Table S1). $E_{max}$ was fixed to 10 (maximal highness rating). The effect compartment model is a variant of the sigmoidal $E_{max}$ model where the pharmacodynamic effect is related to effect-site concentrations, instead of plasma concentrations, as shown in Equation 1:

$$E = E_{max,THC} * C_{e,THC} / (EC_{50} + C_{e,THC}) \quad (1)$$

where $E_{max,THC}$ is the maximum effect from THC, E is the observed psychological effect after smoking marijuana, $EC_{50}$ is the effect-site concentration of THC resulting in 50% of the maximum effect, and $C_{e,THC}$ is the concentration of THC at the "hypothetical" effect site. As the baseline highness values were zero, the baseline effect was not included in the equation. Pharmacodynamic parameters and effect-site

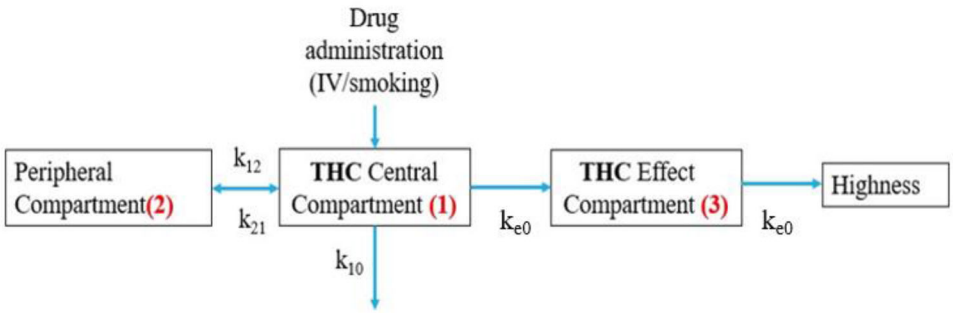


**Figure 1.** Schematic representation of the effect compartment model relating effect compartment concentrations of tetrahydrocannabinol derived from plasma tetrahydrocannabinol concentrations to the central nervous system effect, that is, psychological highness. IV, intravenous; $k_{12}$, distribution rate constant from central to peripheral compartment; $k_{21}$, distribution rate constant from peripheral to central compartment; $k_{10}$, elimination rate constant from the central compartment; $k_{e0}$, rate of input as well as rate of removal of parent drug from the effect compartment; THC, tetrahydrocannabinol.

**Table 2.** Pharmacodynamic Parameter Estimates Obtained from Fitting the Tetrahydrocannabinol Effect Compartment Concentrations, Derived from Plasma Concentrations, for the Parent Drug (THC) to the Observed Psychological Highness in the Studies Conducted by O'Leary and by Awasthi

| | Effect Compartment Model (Smoking, O'Leary Study) | | | Effect Compartment Model (IV, Awasthi Study) | | |
|---|---|---|---|---|---|---|
| | Estimate (%RSE) | IIV (%RSE) | Shrinkage (%) | Estimate | IIV (%RSE) | Shrinkage (%) |
| $E_{max}$ | 10 (fixed) | – | – | 10 (fixed) | – | – |
| $K_{e0}$ ($h^{-1}$) | 0.91 (11) | 87.0 (10) | 23 | 1.57 (6.88) | – | – |
| $EC_{50}$ (ng/mL) | 32.4 (8) | 109 (8) | 8 | 17.2 (4.03) | – | – |
| Hill | 1 (fixed) | – | – | 1.28 (7.63) | – | – |
| Additive Error ($\sigma^2$) | 0.667 (7) | – | 15 | 0.060 (38.7) | – | – |

$EC_{50}$, potency; $E_{max}$, peak highness effect; IIV, interindividual variability; IV, intravenous; $K_{e0}$, distribution rate constant for effect compartment; RSE, relative standard error.

concentrations were estimated using FOCE in NONMEM with a user-defined subroutine in ADVAN 6.

The effect compartment (biophase) concentration–time profile for the parent drug can be described by the following differential equation:

$$dC_{e,THC}/dt = k_{e0}\left(\left(A_{plasma,THC}/V_{central,THC}\right) - C_{e,THC}\right) \quad (2)$$

where $C_e$, $A_{plasma}$, and $V_{central}$ stand for the concentration in the effect compartment, quantity in the central compartment (plasma), and the volume of the central compartment, respectively. The first-order rate constant ($k_{e0}$) denotes the transfer of the parent drug to the effect compartment from the central compartment and is also set as the rate of removal of the drug from the effect-site compartment.

## Results

### Effect Compartment Model: Relating Effect Compartment Tetrahydrocannabinol Concentrations to Observed Highness

The THC concentrations were related to the observed highness and the pharmacodynamic parameters, as well as the effect-site concentrations, were predicted. Pharmacodynamic parameters obtained from the O'Leary datasets after applying the Awasthi's effect compartment model were compared with the parameters described by Awasthi et al.[5] The estimation of pharmacodynamic parameters and associated interindividual variability along with the percent relative standard error are summarized in Table 2.

### Covariate Analysis

Age, sex, BMI, and user status were evaluated using linear and power models on $EC_{50}$. The Hill factor was fixed at 1 to improve model stability. $E_{max}$ had a maximal rating of 10 and it was treated as a fixed effect. Therefore, variability around $E_{max}$ was not estimated and consequently covariates on $E_{max}$ were not evaluated. Statistically, user status on $EC_{50}$ (Equation 3) was considered to be a significant covariate during the forward and backward covariate selection process. After covariate inclusion, $EC_{50}$ in Equation 1 was replaced by the following equation for occasional and chronic users:

$$EC_{50i} = TVEC_{50} * (1 + \text{“covariate effect”} * \text{“user status”}) \quad (3)$$

**Table 3.** Covariate–Effect Compartment Model: Pharmacodynamic Parameter Estimates Obtained from Fitting the Tetrahydrocannabinol Effect Compartment Concentrations, Derived from Plasma Concentrations, for the Parent Drug (THC) to the Observed Psychological Highness

| Covariate–Sigmoidal $E_{max}$ Model | | | | |
|---|---|---|---|---|
| | Estimate (%RSE) | IIV (%RSE) | Shrinkage (%) | Bootstrap Mean (95%CI) |
| $E_{max}$ | 10 (fixed) | – | – | – |
| $K_{e0}$ ($h^{-1}$) | 0.988 (12) | 90.6 (10) | 21 | 1.01 (0.77–1.2) |
| $EC_{50}$ (ng/mL) | 23.8 (22) | 100.5 (7) | 9 | 24.2 (16.8–30.8) |
| Hill | 1 (fixed) | – | – | – |
| User $EC_{50}$ (covariate effect) | 1.78 (46) | – | – | 1.81 (0.63–2.9) |
| Additive error ($\sigma^2$) | 0.656 (7) | – | 14 | 0.658 (0.49–0.82) |
| Covariate equation for $EC_{50}$ | $EC_{50i} = TVEC_{50}$*(1 + "covariate effect" * "user status"), where user status is 1 for chronic user and 0 for occasional user | | | |

95%CI, 95% confidence interval; $EC_{50}$, potency; $E_{max}$, peak highness effect; IIV, interindividual variability; IV, intravenous; $K_{e0}$, distribution rate constant for effect compartment; RSE, relative standard error.

where $EC_{50i}$ and $TVEC_{50}$ are individual and population values of $EC_{50}$ and "covariate effect" (estimated to be 1.78; also referred to as USER-$EC_{50}$; Table 3) was derived from stepwise covariate methodology,[16] which accounts for the variability in $EC_{50}$ based on user status (occasional user = 0; chronic user = 1). For occasional users, $EC_{50}$ was 23.8 ng/mL, whereas for chronic users $EC_{50}$ is calculated to be 66.2 ng/mL using Equation 3. Therefore, covariate analysis using the O'Leary dataset revealed that chronic users appear to need higher plasma concentrations, compared with occasional users, to achieve a similar degree of highness.

Figure 2 shows the goodness-of-fit and diagnostic plots. The scatter plot of IPRED versus observed highness shows that the model can capture the highness response for all subjects, thus supporting the use of the effect compartment model to characterize the THC plasma concentration–highness relationship. The CWRES versus CPRED plot and the CWRES versus time plot showed that most values are evenly centered around zero, with most values within 2 standard deviations around zero, suggesting no major bias in the model. The final effect compartment model had good precision, as indicated by relative standard errors (%RSE) around the parameter point estimates. Mean and 95% confidence intervals generated by bootstrapping indicated that bootstrapping parameters were in agreement with the model (Table 3).

Individual spaghetti plots of THC concentrations and psychological highness as well as population PK parameters have been provided in the supporting information (Figures S1-S11, Table S1).

## Discussion

THC, the primary psychoactive ingredient in marijuana (or cannabis), exerts CNS effects in the form of psychological highness primarily via interactions with CB1 receptors.[5] Psychological highness is the primary motivation behind the recreational consumption of cannabis via various routes, including IV, pulmonary, and oral administration. Several studies have shown the lack of a direct relationship between the plasma concentration of THC and the observed psychoactive effects, that is, peak plasma concentrations do not overlap with the peak occurrence of highness, which suggests that the plasma concentration is not a good surrogate for predicting THC pharmacodynamics in the brain.[2,17] A lack of correspondence between THC concentrations and highness is often characterized by the presence of hysteresis in the plasma concentration–highness plots, and hysteresis has been observed after both IV and intrapulmonary administration.[3,17]

As a result of the inability to directly measure the drug concentration at the site of action, that is, in the brain, it is critical to understand the relationship between plasma concentrations of THC and observed psychological highness. Awasthi et al previously demonstrated that an effect compartment, serving as a link between THC plasma concentrations and degree of highness, was able to predict effect-site concentrations that were in direct correspondence with the reported degree of highness.[5] To characterize the measured THC plasma concentrations and psychological highness for the O'Leary datasets, the effect compartment model developed by Awasthi et al was validated by comparing parameter estimates from the reference dataset (the dataset used by Awasthi) with the parameter estimates obtained when the O'Leary datasets were evaluated.[5]

Physiologically relevant parameter estimates were comparable with the pharmacodynamic estimates reported by Awasthi et al (Table 2). In the current study, $K_{e0}$ and $EC_{50}$ were 0.910/h and 32.4 ng/mL, respectively, and the $K_{e0}$ reported by Awasthi et al was very similar, 1.57/h, and $EC_{50}$ was 17.2 ng/mL. It

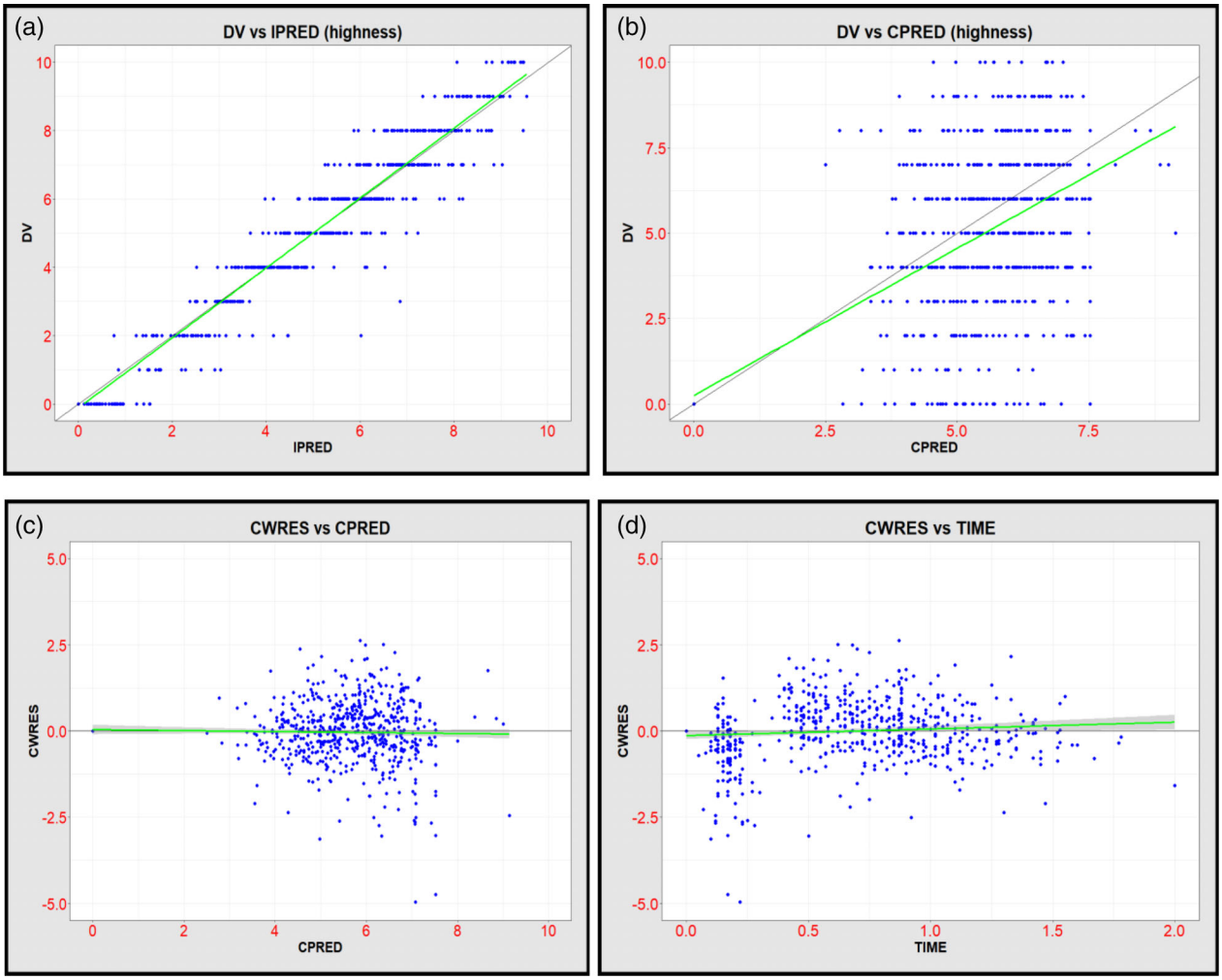


**Figure 2.** Goodness-of-fit plots for the effect compartment pharmacodynamic model relating plasma effect compartment concentrations to the observed psychological highness (DV). Observed versus individual predicted (IPRED) concentrations (a) and observed versus conditional population predicted (CPRED) concentrations (b) were obtained from fitting the individual tetrahydrocannabinol concentration–highness profiles. The solid line is the line of identity. Plots of weighted residuals (CWRES) versus CPRED concentrations (c) and CWRES versus time (d) show a symmetrical distribution around the line of zero, with most weighted residuals within 2 standard deviations. The green line indicates the line of regression. Time is in hours.

should be noted that the data used by Awasthi et al were derived from just 11 male subjects, with the mean highness ratings reported over a 4-hour time interval only; no individual data were available. The O'Leary dataset provided individual highness ratings reported for up to 1.5–2.0 hours by 85 subjects. These differences in study design contributed to differences in $EC_{50}$. In Awasthi's effect compartment model, the estimation of interindividual variability around the pharmacodynamic parameters was not feasible as individual data were not reported, and thus only mean results were used for modeling. In the current study, covariates were investigated to explain the interindividual variability in the O'Leary dataset and pharmacodynamic parameters were estimated from the effect compartment model. Chronic users displayed higher $EC_{50}$ values than occasional users. This suggests that to achieve the same degree of highness, chronic users need to have higher plasma concentrations, thus suggesting the development of tolerance to psychological highness with the frequent use of marijuana. With respect to tolerance, the extent and rate of its development also need to be taken into consideration. However, the O'Leary studies only measured single-day effects and the occurrence of tolerance can further be inferred from differences in results between chronic and occasional users after the administration of multiple doses of marijuana in users stratified by frequency of smoking.

Cannabis administration has been shown to produce less pronounced and shorter periods of intoxication in chronic users compared with occasional users.[18] The development of tolerance has been observed following repeated THC administration by previous investigators. For example, Babor et al administered

THC during a 21-day study to subjects with reported moderate and heavy cannabis use. Heavy users reported a decrease in psychological highness upon continued THC exposure.[19] In a placebo-controlled study conducted by Jones et al, repeated oral administration of THC every 4 hours in 42 subjects with a history of heavy cannabis use, who smoked at least twice weekly, showed significant decreases in self-reported intoxication.[20] Mechanistically, the development of tolerance has been attributed to the downregulation of CB1 receptors in the brain and the subsequent reduced interaction between the ligand and receptor.[21] THC is metabolized to THC-OH, which subsequently converts to THC-COOH (the carboxy metabolite). It is unlikely that the competitive binding of THC-OH to CB1 receptors is responsible for tolerance as THC-OH is also pharmacologically active and at least equipotent to THC and the binding of THC-OH to CB1 receptors still induces psychological highness. Whether the competitive binding of THC-COOH to CB1 receptors contributes to tolerance is not yet clear.

THC acts on CB1 receptors in both the brain and the heart. However, it is not yet clear whether tolerance develops at a similar rate and to the same extent in both organs. An increasing number of reports are revealing adverse cardiovascular effects after cannabis intake by various administration routes. There is increasing evidence that THC is linked to adverse cardiovascular events, including acute coronary syndrome,[22–26] ventricular/atrial fibrillation,[27–30] and myocardial infarction,[24,26,31–34] in individuals who are young, old, healthy, or with pre-existing cardiovascular disease, suggesting a causal mechanism between cannabis use and cardiovascular dysfunctionality; however, the exact pathophysiology behind this relationship is not yet fully understood.[35] These adverse cardiovascular events might be attributed to the fact that marijuana users are developing a tolerance to euphoria, the primary psychological effect they are seeking, which might be a driving force for these users in seeking strains with higher potency or higher exposure, to experience the same degree of euphoria that they were experiencing before developing this tolerance. This might be motivating chronic users to inhale THC more efficiently to get higher exposure to the drug. In fact, in a study by Alvarez et al, a population modeling approach was used to detect significant differences in the bioavailability of inhaled THC between chronic and occasional users. Exposure in chronic users was approximately 2.5-fold higher than in occasional users.[36]

The percentage of THC in illicit drugs has indeed increased from 4% in 1995 to 12% in 2014.[37] Thus, the consumption of higher potency marijuana products to overcome tolerance might be a factor behind the unwanted cardiovascular effects. In a study by Chait, 10 regular marijuana smokers self-administered cigarettes with low (0.5% w/w), medium (1.7% w/w), or high (2.7% w/w) THC content on 5 separate occasions within 2 weeks to investigate the potency of THC after smoking on prior occasions. Psychological highness and heart rate increased with increases in potency among the 3 dose groups. The authors argued that a broader range of potencies needs to be investigated to confirm the results. Interestingly, at every potency level, tolerance to the development of increased heart rate and highness was observed.[38]

## Conclusion

The goal of this modeling effort was to evaluate the development of tolerance in marijuana users while also externally validating a previously derived effect compartment model based on IV administration of THC, where data from the O'Leary datasets using pulmonary delivery served as the external validation datasets. Parameter estimates were similar for the effect compartment model describing the reference and external dataset. BMI, age, and sex were not significant covariates to explain the interindividual variability around $EC_{50}$ for the external dataset. However, in the current study, only 8 out of 85 subjects had a BMI higher than 30 $kg/m^2$, considered to be obese according to the Centers for Disease Control and Prevention. Well-controlled clinical trials with a larger sample size of people who are obese must be conducted for further evaluation of the pharmacokinetic–pharmacodynamic relationship of THC with regards to psychological highness in obese populations. In terms of sex as a covariate, the current results indicate that there is no difference in the plasma concentrations of THC and the resulting psychological highness between males and females. Chronic users developed tolerance to marijuana, which might be driving them to seek high-potency marijuana strains and higher THC exposure.

## Conflicts of Interest

The authors declare that they have no conflicts of interest associated with this work.

## Data Sharing

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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## Author Contributions

Dr Robert Block (Co-Principal Investigator) made substantial contributions to the conception and design and acquisition of data, whereas Dr Sumeet Singla was solely responsible for model building, model analysis, and interpretation of the data. Both have been involved in drafting the article and revising it critically for publication.

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## Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.