Translational PKPD modeling in schizophrenia
Pilla Reddy, Venkatesh

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Pharmacokinetic-Pharmacodynamic modelling of antipsychotic drugs in patients with schizophrenia: Part I: the use of PANSS total score and clinical utility

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Submitted

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**ABSTRACT**

**Background and Objectives:** To develop a pharmacokinetic-pharmacodynamic (PKPD) model using individual-level data of Positive and Negative Syndrome Scale (PANSS) total score to characterize the antipsychotic drug effect taking into account the placebo effect and dropout rate. In addition, a clinical utility (CU) criterion that describes the usefulness of a drug therapy was calculated using the efficacy of the drug and dropout rates.

**Methods:** Data from 12 clinical trials in schizophrenia patients was used to quantify the effects of the antipsychotic drugs (APs), namely, haloperidol, risperidone, olanzapine, ziprasidone and paliperidone. Compartmental PK models were used to describe the time course of plasma drug concentrations. The combination of an $E_{\text{max}}$ and the Weibull model was used to describe the drug and placebo effects. The steady-state drug concentrations were assumed to be the drivers of the exposure-response relationship. An exponential model was utilized to identify the predictors of probability of dropout. Simulations were performed to check the predictability of the model, and to calculate the CU of the drugs based on PANSS scores and dropout rates.

**Results:** The maximal drug effect ($E_{\text{max}}$) was highest for olanzapine whilst it was lowest for ziprasidone. Higher observed PANSS scores resulted in a greater likelihood of dropout. Taking into account the efficacy and the drop-out rate, all APs possessed a comparable CU at the therapeutic doses. The resulting PKPD model parameters were used to compute the effective concentration and dose required to produce a clinically meaningful 30% drop in PANSS score from the baseline.

**Conclusions:** The developed PKPD model and the associated CU score allow the evaluation of the time course of the PANSS scores of the different APs and a proper comparison of their clinically relevant treatments effects.
INTRODUCTION
The discovery and development of new antipsychotic drugs (APs) is complicated by the subjectivity in the diagnosis of schizophrenia and in the evaluation of the clinical effect of the drugs, the lack of truly predictive preclinical animal models, the significant placebo effects (PE) and the high dropout rates in clinical trials.\[1\] A better understanding of the link between drug exposure and clinical effect is one of the ways whereby the efficiency of developing new antipsychotics can be improved. Model-based approaches which have become indispensible tools in drug development offer an opportunity to achieve this purpose.\[1,2\] Recently, Kemp and co-authors\[3\] discussed the role of advanced methods such as pharmacokinetic-pharmacodynamic (PKPD) modelling and simulation that could eventually help in discriminating the overlapping drug and placebo effects as commonly seen in antipsychotic clinical trials.

The traditional linear regression methods applied to most exposure or dose-response curves in psychiatric research rely on observed variables and assume a linear relationship between the exposure and these variables. In real life, the trajectory of treatment effects or dropout events often exhibits non-linear trends limiting the value of linear regression models. In contrast, PKPD models that typically utilize a non-linear mixed-effects modelling approach, usually allow discrimination between system and drug-specific properties, both of which can be defined as model parameters. This conceptual difference in data analysis has major implications in the interpretation of results.

In our earlier papers,\[4,5\] the trends in the placebo effect (PE) in schizophrenia trials using the Positive and Negative Syndrome Scale (PANSS) total score were explored by pooling data from different trials conducted between 1989-2009. A model was developed describing this PE which identified predictors of the PE (normalized PE) and dropouts.

In addition to a significant PE, high dropout rates are very common in psychiatric clinical trials.\[6\] Therefore, while developing models to evaluate the drug effect, data from patients who drop out of a trial should be taken into account to allow an accurate interpretation of the results. More details on the concepts of dropout modelling and its consequences during the model building process are discussed elsewhere.\[6-9\] Recently, using a pooled dataset from five antipsychotic drug trials, Rabinowitz and Davidov\[6\], demonstrated that dropouts in these trials are related to the observed PANSS scores and suggested there is a need for a methodology that jointly describes the longitudinal scores and the hazard of dropout related to the clinical response variables.

Thus, it is very important that dropout rates will be taken into account when studying the effectiveness of a new pharmacotherapeutic treatment in patients care during AP drug development. The clinical utility (CU) criterion is a tool that quantifies the proportion of patients completing the trial while maintaining a predetermined efficacy level which eventually helps in optimizing
proof-of-concept trials. In other words, the CU of a treatment is defined as the average trial time during which a patient, while continuously receiving that treatment and not dropping out, maintains a clinically relevant efficacy level. This criterion helps in true risk–benefit assessment as compared to the traditional approach based on comparing the % change from baseline in the efficacy score during the trial period accounting for placebo response and dropouts.

Therefore, to quantify the true drug effect in the presence of a heterogeneous placebo response and high dropout rates, one would require normalization of the PE by accounting for different predictors of the PE and the likelihood of dropout should be linked to the change in PANSS score or exposure following antipsychotic drug administration.

The objective of this study (part I) was to develop a PKPD model to describe the longitudinal changes in total PANSS score using individual-level data across a range of compounds accounting for a (normalized) placebo effect. In addition, a clinical utility criterion was constructed using the efficacy of the drug and dropout rates. The developed PKPD model was subsequently utilized to quantify the efficacy of APs based on the PANSS subscales with the aim of investigating the hypothesis that atypical antipsychotics result in a better negative symptom control than conventional antipsychotics. These results are presented in a separate publication (part II) including also the relationship between the clinical efficacy, in vitro receptor pharmacology profiles, and the dopamine or serotonin receptor occupancy (D$_2$RO or 5-HT$_{2A}$RO levels).

**METHODS**

**Patients and Study Design**

The individual-level pharmacokinetic (plasma concentrations) and pharmacodynamic (PANSS) data from 4999 schizophrenic patients was used to develop and to evaluate the PKPD models. The APs included in this analysis were haloperidol (a typical antipsychotic), and four atypical antipsychotics (ATAPs), namely, risperidone, olanzapine, ziprasidone, and paliperidone extended release. The PK and PANSS data (n=387) of paliperidone palmitate (intramuscular formulation), which was not available at the time of model development, were used for the purpose of external validation of the developed PKPD model. Exposure-response results of haloperidol obtained from a PK and PKPD model developed earlier were used along with that of ATAPs for defining the CU. The overview of trial designs, summary statistics of the PANSS scores and dropout rates across the studies used in the development of exposure-response models is shown in Table 1.

**Overall Model Development Approach**

An overview of the PKPD model is shown in Figure 1. In PKPD modelling of AP drugs in schizophrenia, it is essential to first develop a disease progression and
PKPD MODELLING AND CLINICAL UTILITY OF ANTIPSYCHOTIC DRUGS USING PANSS TOTAL

A placebo model, before adding a model for the drug effect. At any given point of time, the status of the patient is a reflection of the status of the disease. The disease status changes with time, therefore modelling of the disease status in the absence of treatment describes the expected changes in patient’s disease progression. The disease progression model can be extended by including the treatment effects (placebo or drug) that refer to all the underlying PK and PD processes involved in producing a treatment effect on the time course of disease progression as shown below.\[12\]

\[
PANSS(t) = PANSS(t_0) + \text{disease progression}(t) + \text{placebo effect}(t) + \text{drug effect}(t)
\]

(Eq. 1)

A model for the natural disease progression and the placebo effect can be developed separately for diseases such as Alzheimer’s and Parkinson’s disease.\[13,14\] However, in other cases, it is difficult to separate the disease progression from the placebo effect due to the episodic nature of the disease (e.g. schizophrenia). In such cases disease progression and PE need to be considered as a single entity and Equation 1 reduces to

\[
PANSS(t) = PANSS(t_0) + \text{placebo effect}(t) + \text{drug effect}(t)
\]

(Eq. 2)

To describe the time course of the PE, several placebo models were tested as described earlier by Pilla Reddy et al.\[6\] In order to estimate the drug effect, a patient-specific steady state concentration ($C_{ss}$) was calculated using the dosing...
<table>
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<th>Study Year</th>
<th>Trial Phase</th>
<th>Study Duration</th>
<th>ROA</th>
<th>Population</th>
<th>Drug/Dose</th>
<th>#Subjects</th>
<th>Baseline PANSS (SE)</th>
<th>PANSS Change*</th>
<th>Dropout (%)</th>
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<td>III</td>
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<td>143</td>
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#Subjects, baseline and change results are for all treatment groups from that study excluding the placebo arm. **ROA**: Route of Administration, **QD**: Once Daily; **BID**: Twice Daily, **IM**: Intramuscular; **SE**: Standard Error; *Mean change in PANSS from baseline using last observation carried forward (LOCF). Data of haloperidol are also shown in this table 1.
regimen and the empirical Bayesian estimate of clearance obtained by fitting a PK model to the measured plasma concentrations. The calculated individual $C_{ss}$ was then linked to the time-course of PANSS score via an $E_{max}$ model. Estimation of the inter-individual variability (IIV) accounts for differences in variability between individuals among the population. IIV for structural model parameters was evaluated using a log-normally or a normally distributed model. The intra-individual or residual unexplained variability (RUV) describes the difference between observed and model predicted values that remain unexplained by IIV. Residual variability in the plasma concentration was modelled using a proportional error model, while, an additive error model was used to account for the unexplained variability in the PANSS scores.

The non-linear mixed-effects modelling approach to describe the time course of PK and PANSS scores was implemented using the NONMEM VII software. Perl-speaks-NONMEM (PsN, v 3.2.4) was used to communicate with NONMEM. R (version 2.11; www.r-project.org) and Pirana were used for graphical inspection of the results.

**Pharmacokinetic Model**

The plasma concentration-time profiles of each antipsychotic drug were modelled using a compartmental model. During model building, differences in NONMEM objective function value (OFV; difference denoted as $\Delta$OFV) between the models together with % RSE (< 30%) of the parameters and goodness-of-fit plots were used to guide the selection of the best base PK models. The PK dataset consisted of sparse PK samples collected on different days under steady-state condition for olanzapine and paliperidone (6 samples/patient), and for ziprasidone (3-6 samples/patient). Independent PK models were developed for olanzapine, paliperidone, and ziprasidone. On the other hand, the PK model parameters of risperidone were estimated by combining the sparse dataset (where only single PK sample per patient was available) with rich PK datasets, that were earlier used by Vermeulen et al. The CYP2D6 polymorphism of risperidone conversion to 9-hydroxy-risperidone, both during first-pass as well as during systemic circulation, was also accounted for in the risperidone PK model. Moreover, the active moiety (risperidone + 9-hydroxy-risperidone) was assumed responsible for the efficacy, and therefore the calculated individual $C_{ss}$ of active moiety (for equations see Appendix 1) was used in the PD model.

**Pharmacokinetic and Pharmacodynamic Model**

As a first step in building the exposure-effect relationship, a placebo model developed and validated previously was incorporated into the PKPD model such that the pharmacological effectiveness of the drug was estimated on top of the PE. The treatment effect was modelled as a relative change from the baseline PANSS score as shown in Equation 3.
PANSS Score = Baseline PANSS × (1 - placebo effect) × (1 - drug effect) \hspace{1cm} (Eq. 3)

**Placebo Model**

Among the various placebo models tested, the Weibull and the Indirect Response Models were shown to be the best models to describe the change in PANSS from the baseline score for placebo treated patients.[4] In this paper, we used the Weibull placebo model for the reason of simplicity and the fact that parameters are easier to interpret in clinical practice.

\[
\text{Placebo Effect} = \text{Baseline PANSS} \times \left[ 1 - P_{\text{max}} \times \left(1 - \exp\left(\frac{\text{time}}{\text{TD}^{\text{POW}}}ight)\right) \right] \tag{Eq. 4}
\]

The Weibull model (Equation 4) describes the decrease of the PANSS score from baseline, which eventually reaches a plateau. \(P_{\text{max}}\) is the maximum PE, \(\text{TD}\) is the time to reach 63.2% of the maximum change from baseline, and \(\text{POW}\) is the shape parameter. In this model, the IIV for the BASL and \(P_{\text{max}}\) parameters were assumed to follow a log-normal and normal distribution, respectively. The normal distribution of the IIV for the \(P_{\text{max}}\) parameter allows the PE to be worsening (negative \(P_{\text{max}}\)) or improving (positive \(P_{\text{max}}\)).

**Drug Effect Model**

In the drug effect model, the PK model-predicted steady-state concentrations (\(C_{ss}\)) of APs were related to the PANSS score using an \(E_{\text{max}}\) model as shown in Equation 5.

\[
\text{Drug Effect} = \left( \frac{E_{\text{max}} \times C_{ss}}{E_{50} + C_{ss}} \right) \times \left(1 - e^{-KT \times \text{time}}\right) \tag{Eq. 5}
\]

where \(E_{\text{max}}\) is the maximum effect reached, \(E_{50}\) is the steady-state concentration required to achieve half \(E_{\text{max}}\), \(KT\) is a rate constant associated with the time required to obtain the maximum drug effect. The IIV for \(E_{50}\) and \(E_{\text{max}}\) parameters were assumed to follow a log-normal and normal distribution, respectively. The normal distribution of the IIV for the \(E_{\text{max}}\) parameter allows the drug effect to be worsening (negative \(E_{\text{max}}\)) or improving (positive \(E_{\text{max}}\)). An additive error model was used to describe the RUV in PANSS score. The pharmacokinetics and efficacy of haloperidol (a typical antipsychotic) obtained from a PK and PKPD model developed earlier were discussed elsewhere.[11] A common PKPD model for four ATAPs was developed by estimating separate PD parameters (\(E_{\text{max}}\) and \(E_{50}\)) for each drug (PKPD model NONMEM code is shown in the Appendix file 2). A common value for the parameter \(KT\) was assumed for the ATAPs.
**Covariate Model**

The covariates of the PE were identified and their clinical relevance was discussed recently. In addition to the predictors of the PE, the influence of various covariates on the PK and PKPD model parameters were also investigated. To test the covariate-parameter relationship, the covariates were added to the structural parameters using the step-wise covariate modelling approach (SCM), as implemented in the software package PsN. This technique tests different covariate-parameter relationships in a forward fashion (p<0.05 and ΔOFV:3.84, df=1) to build up the full model, which in turn are evaluated in the backward elimination step (p<0.01 and ΔOFV:6.63, df=1). The resulting final PKPD model contains only covariates that meet the pre-defined statistical criteria, in addition to an acceptable precision of parameter estimates.

**Study-Specific vs. Normalized Placebo Effect for Quantifying the Drug Effect**

To quantify the true drug effect in the presence of a heterogeneous placebo response and high dropout rates, normalization of the PE is required by accounting for different predictors and the likelihood of dropout. We used an earlier reported placebo model, to quantify the antipsychotic drug effect sequentially under two circumstances i) by using the normalized PE, ii) by considering the study-specific PE.

**Dropout Model**

Based on the data exploration and earlier reported results, an exponential model was employed to account for dropouts. The exponential time-to-event (TTE) dropout model (Equation 6) assumes that the baseline hazard (BHAZ) is independent of time and estimates the BHAZ and BETA as dropout model parameters.

\[
 h(t) = BHAZ \times \exp(- \text{predictor} \times BETA) \quad \text{(Eq. 6)}
\]

BHAZ is the baseline hazard without influence of predictors, while BETA is a parameter that describes the probability of a patient dropping out based on the predictors such as the observed PANSS score, unobserved or predicted PANSS scores, and change in the PANSS score from baseline or drug exposure. Several predictors can be included within the TTE model structure with parameterizing different BETAs for each of the predictors, but only the significant predictors, based on ΔOFV and Kaplan-Meier-based VPC plots were included in the dropout model.

The probability of a patient dropping out can be modelled by describing the hazard for the event. Hazard is the instantaneous rate or probability of the event: \( h(t) \). Cumulative hazard (CHZ) predicts the risk of a patient dropping out from the study over a time interval, which is obtained by integrating the hazard with respect to time: \( \int h(t) \). The probability of not dropping out can be predicted from
the cumulative hazard: \( S(t) = \exp(-CHZ) \). Finally, the probability of dropping out at any given time is described as \( D(t) = S(t) \times h(t) \). The BHAZ parameter describing the baseline hazard of a patient dropping out at baseline levels of covariates or predictors may be different for different treatments, hence we estimated separate BHAZ for different drugs. A BETA parameter that describes the hazard of a patient dropping out from a trial based on the observed PANSS irrespective of treatment was estimated.

**Model Evaluation**

The bootstrap re-sampling technique and the Monte-Carlo simulations were used as model evaluation tools to check the stability and predictability of the model, respectively. Parameter estimates for each of the re-sampled bootstrap datasets (stratified based on the study) were obtained by fitting the final PK, and PKPD models to each of the newly generated datasets. Finally, 95% confidence intervals (95% CIs) of all model parameters were calculated, and the medians of the bootstrap estimates were compared with parameter values obtained from the original dataset.[20,21] Monte-Carlo simulations were performed for the PKPD model by simulating 1000 datasets identical in structure and covariate values to the original dataset. Visual Predictive Check plots (VPC) were plotted after calculating the 2.5th, 50th and 97.5th percentiles of PANSS scores for the simulated datasets.[22]

**External Validation**

The Monte-Carlo simulations (n=1000) were performed to evaluate the predictive performance of the PKPD model to a new dataset that was not available during the time of model development and evaluation. The dataset for external validation was obtained from a randomized, double-blind, placebo-controlled, dose-response study evaluating the efficacy and safety of paliperidone palmitate at doses of 50, 100 and 150 mg equivalent. A previously reported paliperidone palmitate PK model[22] was utilized to fit the observed PK profiles. A patient-specific \( C_{ss} \) was then calculated using the dosing regimen and the empirical Bayesian estimate of clearance values. One thousand simulations were performed based on the available covariates in the external dataset to obtain model-based individual predicted PANSS scores. These predicted PANSS scores were then plotted versus the PANSS scores that were actually observed in this external dataset. Adequacy of the model was tested by calculating the % bias and % RMSE (Root Mean Squared Error) as described by Beal et al.[23]

**Clinical Utility of Antipsychotics Based on the PKPD model**

Joint modelling of a PKPD model with a dropout model is considered be helpful to assess the CU of an AP drug at an individual patient level. CU calculations based on the simulations (n=200), using the joint model (PKPD model with a dropout model), at the antipsychotic therapeutic doses as reported in the literature[24,25] and FDA documents, were performed. For CU calculations, we used only datasets
of 6-week efficacy trials, identical in structure and covariate values to the original dataset. Model predicted \( C_{ss} \) values at their respective therapeutic doses were used during the simulations.

For each of the simulated datasets the proportion of subjects completing the trial (1-number of dropouts/total number of patients) and the proportion of trial duration for which a subject maintains a pre-defined efficacy level (number of the PANSS observations lower than pre-defined PANSS score/total number of the PANSS observations) on a particular drug treatment were computed. The desired pre-defined efficacy level or desired % change in PANSS score from the baseline can be calculated using following equation

\[
\text{% Change in PANSS} = \frac{\text{PANSS} - \text{Baseline PANSS}}{\text{Baseline PANSS} - 30} \times 100
\]  
(Eq. 7)

where baseline PANSS was estimated by the PKPD model. The corresponding PANSS value was obtained using the desired percentage change. For 30% decrease in PANSS from baseline\(^{[20]}\): \( \text{PANSS} = -30/100 \times (\text{Baseline PANSS} - 30) + \text{Baseline PANSS} \). For baseline PANSS of 90, the pre-defined efficacy level will be 72. As the PANSS individual items are scored on an interval scale (range 1-7), resulting in the lowest level of PANSS total score of 30 points for a patient with no symptoms, the scale level was changed into a ratio scale by subtracting 30 points while calculating percentage change from baseline score.\(^{[27,28]}\) CU in this paper is the product of the proportion of patients that remained in the study and percentage of trial time the patients spent with a pre-defined efficacy level.

**RESULTS**

**Pharmacokinetic Model**

The describe the disposition of risperidone (active-moiety) was adequately described using a two-compartment PK model with a consecutive zero-and first-order absorption process and a lag-time.\(^{[17]}\) The PK of paliperidone ER was adequately modelled according to a one-compartment model with a sequential zero-order (with a lag time) and first-order absorption, while a classical one-compartment model with first-order absorption described the olanzapine and ziprasidone PK profiles adequately. The typical PK parameters listed along with 95% CIs obtained from bootstrap analysis are depicted in Table 2. Due to the long run times we did not perform a bootstrap analysis for the risperidone PK model, however we reported parametric 95% CIs obtained from the NONMEM model estimation step. The significant covariate-PK parameter relationships are shown in Table 2. The estimated typical CL/F values for each drug were comparable with reported values in the literature.\(^{[11,17,29,30,31]}\)
**Pharmacokinetic and Pharmacodynamic Model**

The PKPD model parameter estimates for different antipsychotics using the normalized PE model are depicted in Table 2. The uncertainties in the parameters estimates were less than 30%, except for the EC\(_{50}\) parameter of risperidone, olanzapine, and paliperidone, which ranged from 33 to 46%. The maximum drug effect (E\(_{\text{max}}\)) was found to be highest for olanzapine, followed by haloperidol, risperidone, paliperidone, and ziprasidone. Estimation of a KT for each of the ATAPs separately resulted in a similar value for each of them, hence we estimated a single KT parameter. The time required to achieve half of the E\(_{\text{max}}\) was about 18 days for ATAPs while, it was 5 days for haloperidol. Covariate analysis failed to identify any clinically relevant potential relationship between the PD model parameters (E\(_{\text{max}}\) and EC\(_{50}\)) at a p value of 0.01.

Various predictors of dropouts such as the observed PANSS, the predicted PANSS, the change in PANSS from the baseline, baseline PANSS, antipsychotic drug’s exposure (C\(_{ss}\)) and combination of observed PANSS and C\(_{ss}\) resulted in a significant drop in OFV. However, hazard relating to observed PANSS had the lowest OFV. Thus, based on the ΔOFV and Kaplan-Meier-based VPC plots (data not shown), the probability of a patient dropping out from a trial was best described by the observed PANSS score. We used an earlier published methodology\[11\] based on parameter estimates of the PKPD model to calculate the antipsychotic drug’s therapeutic dose and respective exposure to produce a 30% decrease in PANSS score from baseline at the same time accounting for the PE. The calculated effective mean concentrations and doses (Table 2) were comparable to values reported in the literature.[32-34]

**Model Evaluation and External Validation of the Final PKPD Model**

In the bootstrap analysis of the population PK, PKPD, and dropout model, the median parameter estimates obtained from the successful bootstrap replicates were in agreement with the original model parameter estimates obtained from an original data set. The narrow range of bootstrap 95% CIs for most of the PK and PKPD model parameters (Table 2) indicate that they were estimated with good precision. VPC plots for the base PKPD model and the PKPD model accounting for the dropouts and predictors of the PE are shown in Figure 2. In the first scenario, simulations were performed only with the base PKPD model without predictors of the PE and the dropout model (Figure 2a; top panel). For the second scenario, simulations were performed with the combined PKPD model, including PE with its predictors and dropout model, in which the observed PANSS scores were replaced with the simulated PANSS scores from the PKPD model accounting for dropouts via the dropout model (Figure 2a; bottom panel). When dropout was ignored, the simulations showed wide prediction intervals at the end of the study, while the actual observed percentile intervals were much narrower. When the dropout model was included in the simulations, the simulated prediction intervals were in close agreement with that of the observed percentile intervals, indicating that
patients who had higher PANSS (worsening of disease condition), had a higher chance to drop out from a trial before the end of the study.

The final PKPD model was utilized to determine the model’s adequacy to describe the PANSS scores data obtained from paliperidone palmitate as an external validation. The final PKPD model describe the PANSS time course reasonably well (Figure 2b). The accuracy (% bias) and precision (% RMSE) of the model predictions were 2.8 and 4.4%, respectively.

Study-Specific vs. Normalized Placebo Effect for Quantifying the Drug Effect

In order to understand the influence of the strongly increasing PE as observed in clinical trials over the years\cite{3} on the drug effect, we used a drug-specific PE (placebo data from a specific drug trial; e.g. placebo arm of several paliperidone trials) and normalized PE (pooled placebo data with predictors of PE). We tested the influences of these two placebo effects on ziprasidone and paliperidone drug effects, as for these drugs rich data with a wide dose range were available. Moreover, these studies were conducted in the mid-1990s and mid-2000s, respectively, allowing to evaluate the effect of the study year. Table 1 of the supplementary file shows that the use of a study-specific PE leads to a higher drug effect for ziprasidone than the use of a normalized PE. On other hand, no difference in drug effect was observed for paliperidone ER. However, utilization of the normalized placebo model with a drug effect model resulted in more precise parameter estimates.

Clinical Utility of Antipsychotics Based on the PKPD model

The CU for the different APs based on 200 simulations is depicted in figure 3. The left panel of Figure 3a shows the proportion of patients remaining in the study against the percentage of trial time with PANSS score below the pre-defined value of 72. Each of the individual open circles corresponds to predictions from a single simulated trial. Placebo treatment had the lowest % time spent with the PANSS score of at least 72 and high dropout rates due to lack of efficacy. Figure 3a exhibits different characteristics for different APs in terms of efficacy and dropout rates. The box plot (Figure 3b; right panel) displays the CU for the different antipsychotics. Results indicated that all antipsychotic drugs showed quite similar CU scores.

DISCUSSION

In the present analysis, a potential interaction of placebo effects with AP drug effects on the efficacy and CU was investigated by using a PKPD model and adding the drug effect sequentially to the placebo effect. To our knowledge, there is no literature available comparing the efficacy and the CU of APs using a PKPD modelling approach.
Table 2. Model Parameter Estimates (with bootstrap 95% CI) obtained from the PK and PKPD models using total antipsychotic drug concentrations

<table>
<thead>
<tr>
<th>PK Model</th>
<th>Haloperidol</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Ziprasidone</th>
<th>Paliperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-Compartment</td>
<td>2-Compartment</td>
<td>1-Compartment</td>
<td>1-Compartment</td>
<td>1-Compartment</td>
</tr>
<tr>
<td>ALAG1 (h)</td>
<td>-</td>
<td>0.16 (0.13-0.18)</td>
<td>-</td>
<td>-</td>
<td>0.67*</td>
</tr>
<tr>
<td>DUR (h)</td>
<td>-</td>
<td>0.47 (0.40-0.54)</td>
<td>-</td>
<td>-</td>
<td>23.6*</td>
</tr>
<tr>
<td>Ka (1/h)</td>
<td>0.23 (0.056-0.39)</td>
<td>2.37 (1.65-3.08)</td>
<td>0.30 (11)</td>
<td>0.07 (0.05-0.08)</td>
<td>0.57*</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>88 (77-101)</td>
<td>2.57 (0.99-4.41)</td>
<td>21.8 (20.5-23.1)</td>
<td>54 (51.56)</td>
<td>14.1 (13.2-14.9)</td>
</tr>
<tr>
<td>CL (gender) (L/h)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.82 (0.44-1.25)</td>
</tr>
<tr>
<td>CL: Poor Metabolizers</td>
<td>-</td>
<td>0.44 (0-0.9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CL: Medium Metabolizers</td>
<td>-</td>
<td>2.81 (1.44-4.18)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CL: Fast Metabolizers</td>
<td>-</td>
<td>18.4 (15.6-21.2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Q (L/h)</td>
<td>233 (56-391)</td>
<td>3.8 (2.9-4.6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>V (L)</td>
<td>669 (91-1143)</td>
<td>144 (122-165)</td>
<td>700 (560-814)</td>
<td>87.5 (67-115)</td>
<td>475 (325-678)</td>
</tr>
<tr>
<td>V (L)</td>
<td>2500 (573-3565)</td>
<td>101 (71-130)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IIV CL (CV%)</td>
<td>44 (31-55)</td>
<td>169 (137-196)</td>
<td>-</td>
<td>33 (28-36)</td>
<td>51 (46-55)</td>
</tr>
<tr>
<td>IIV V (CV%)</td>
<td>116 (95-180)</td>
<td>54 (9-116)</td>
<td>39 (35-41)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IIV Ka (CV%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>52 (41-60)</td>
</tr>
<tr>
<td>RUV Proportional</td>
<td>0.44 (0.38-0.50)</td>
<td>0.301 (0.25-0.35)</td>
<td>0.28 (0.26-0.31)</td>
<td>0.23 (0.20-0.25)</td>
<td>0.38 (0.35-0.40)</td>
</tr>
</tbody>
</table>

PKPD Model

<table>
<thead>
<tr>
<th></th>
<th>Haloperidol</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Ziprasidone</th>
<th>Paliperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline PANSS</td>
<td>91.6 (90.8-92.3)</td>
<td>91.1 (90.7-91.7)</td>
<td>91.1 (90.7-91.7)</td>
<td>91.1 (90.7-91.7)</td>
<td>91.1 (90.7-91.7)</td>
</tr>
<tr>
<td>Pmax</td>
<td>0.081 (0.064-0.096)</td>
<td>0.073 (0.058-0.089)</td>
<td>0.073 (0.058-0.089)</td>
<td>0.073 (0.058-0.089)</td>
<td>0.073 (0.058-0.089)</td>
</tr>
<tr>
<td>Emax</td>
<td>0.31 (0.19-0.66)</td>
<td>0.23 (0.20-0.25)</td>
<td>0.39 (0.23-0.70)</td>
<td>0.22 (0.15-0.32)</td>
<td>0.23 (0.16-0.29)</td>
</tr>
<tr>
<td>EC50 (ng/ml)</td>
<td>3.58 (1.89-10.78)</td>
<td>3.72 (0.55-8.92)</td>
<td>24.8 (4.81-69.1)</td>
<td>39.7 (11.9-114)</td>
<td>6.89 (0.5-19.3)</td>
</tr>
</tbody>
</table>

continued next page
<table>
<thead>
<tr>
<th></th>
<th>KT (1/day)</th>
<th>BHAZ (1/day)</th>
<th>BETA</th>
<th>IIV P_max (SD)</th>
<th>IIV BL (CV %)</th>
<th>IIV E_max (SD)</th>
<th>RUV as SD (Additive)</th>
<th>#Effective Conc. (ng/ml)</th>
<th>#Effective Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.116 (0.062-0.167)</td>
<td>0.039 (0.029-0.057)</td>
<td>0.039 (0.029-0.057)</td>
<td>0.039 (0.029-0.057)</td>
<td>0.039 (0.029-0.057)</td>
<td>0.039 (0.029-0.057)</td>
<td>0.039 (0.029-0.057)</td>
<td>0.039 (0.029-0.057)</td>
<td>0.039 (0.029-0.057)</td>
</tr>
<tr>
<td></td>
<td>0.0009 (0.00066-0.00111)</td>
<td>0.00032 (0.00024-0.00042)</td>
<td>0.00047 (0.00035-0.00062)</td>
<td>0.00022 (0.00017-0.00029)</td>
<td>0.00059 (0.00045-0.00077)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>-0.0295 (-0.0317- -0.0271)</td>
<td>-0.035 (-0.038- -0.032)</td>
<td>-0.035 (-0.038- -0.032)</td>
<td>-0.035 (-0.038- -0.032)</td>
<td>-0.035 (-0.038- -0.032)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.20 (0.19-0.22)</td>
<td>0.20 (0.19-0.21)</td>
<td>0.20 (0.19-0.21)</td>
<td>0.20 (0.19-0.21)</td>
<td>0.20 (0.19-0.21)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>16 (15-17)</td>
<td>16.1 (15.7-16.4)</td>
<td>16.1 (15.7-16.4)</td>
<td>16.1 (15.7-16.4)</td>
<td>16.1 (15.7-16.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.50 (0.41-0.67)</td>
<td>0.22 (0.07-0.30)</td>
<td>0.22 (0.07-0.30)</td>
<td>0.22 (0.07-0.30)</td>
<td>0.22 (0.07-0.30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.7 (8.3-9.1)</td>
<td>8.3 (8.1-8.5)</td>
<td>8.3 (8.1-8.5)</td>
<td>8.3 (8.1-8.5)</td>
<td>8.3 (8.1-8.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>2.7</td>
<td>5.2</td>
<td>13.8</td>
<td>63</td>
<td>9.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.6</td>
<td>0.8</td>
<td>7.3</td>
<td>82</td>
<td>3.3</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

For risperidone, total clearance was calculated as a sum of parent, conversion to its metabolite and metabolite elimination. Inter-individual variability is expressed as percent coefficient of variation (% CV) which is the square root of ω²*100 or as standard deviation (square root of ω²).¹ for parent;² for metabolite. # Effective dose and its respective exposure required to have a 30 % decrease in the PANSS score from Baseline. 

CL = apparent total clearance; CV = coefficient of variation; DUR = duration of input for the zero order process; Q = inter-compartmental clearance; IIV = interindividual variability; ka = absorption rate constant; ALAG1 = lag time; VC = central volume of distribution; VP = peripheral volume of distribution; BASL = Baseline; E_max = maximum drug effect; EC50: steady-state concentration required to achieve half of E_max; RUV = residual unexplained variability; IIV = inter-individual variability; KT = rate constant associated with the time required to obtain the maximum drug effect; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; BHAZ: baseline hazard without influence of predictors; BETA: indicates that probability of a patient dropping out from a trial increased exponentially with increasing PANSS score.
In our earlier placebo data analysis, a clear trend of increase in the PE (P\text{max}) with study year was observed. It should be noted that this PE is the sum of disease progression, changes in patient characteristics, and the true PE. It is not completely understood how the study year could affect the PE, thus it is a covariate with an as yet unknown mechanistic background. Therefore, in our placebo model, the effect of study year was included to take the increase in P\text{max} with study year into account. The trend in PE over study year is included as a fixed factor while estimating the antipsychotic drug effect parameters. We investigated both the sequential (with fixed placebo parameters), and the simultaneous (estimating both the placebo and the drug parameters) approach with respect to placebo and drug effect parameters. However, when analyzed simultaneously, we could not estimate the parameter that relates the study year as a covariate to the PE precisely (153 % RSE) and EC\text{50} estimates of risperidone and paliperidone were less precise (>50 % RSE). Hence, the sequential estimation method was utilized to estimate the drug effect parameters.

To quantify the exposure-response relationship, we linked a patient specific steady-state concentration obtained from a PK model to the PANSS score. Reasonably rich PK profiles including peak plasma concentrations were available for paliperidone, ziprasidone, and olanzapine; however, at least one steady-state concentration was measured for all the drugs. Hence, we decided to use the C\text{ss} rather than the peak plasma concentrations. The plasma C\text{ss} exposure also seemed to be more physiologically plausible than peak levels assuming that clinical improvement in schizophrenia may be related to the average D\text{2} dopamine receptor occupancy, which in turn is dependent on the average steady-state plasma exposure.

Ignoring missing data due to dropouts may bias the model-simulated trial outcome (thus biasing the prediction of future trial results). Joint modelling of the PANSS scores with dropout events using only the placebo data showed the relationship between the chance of a patient dropping out of a trial and the high preceding observed PANSS scores. The dropout model combined with the drug effect, where drug treatment showed a lower dropout rate compared to placebo, also indicated that the dropout rate is related to the observed PANSS score. Moreover, our dataset allows using the dropout hazard relating to the observed PANSS scores as it is a reasonable choice for the primary analysis in the highly controlled situation of confirmatory clinical trials. Relating the dropout hazard jointly to the observed and unobserved (predicted) PANSS may result in better dropout predictions than relating to only the observed PANSS scores under certain assumptions [35,36] but these assumptions are difficult to test and model misspecification could be more severe with the former approach.

Clinical utility is a novel concept that describes the usefulness of a therapeutic intervention and may help in making a decision to proceed to Phase III after a Phase II proof-of-concept trial. Moreover, comparison of CU of a test drug with existing drugs may help in ascertaining its market penetration value. The clinical
Fig. 2a. Visual predictive check (VPC) plots of the PKPD model for different antipsychotics. Top panel: base PKPD model; bottom panel: final PKPD model with dropout model and placebo effect with its predictors. The grey shaded areas represent the 95% confidence intervals of the corresponding 2.5th, 50th and 97.5th percentiles of the simulated data, the black dashed represents the 2.5th, 97.5th percentiles of the observed data and black solid line represents median of the observed data.
efficacy and the proportion of patients remaining in the trial are important clinical endpoints for CU criterion that enable quantitative decision-making for critical questions that arise in drug development. Additionally, the CU criterion can be extended by incorporating other endpoints such as adverse events, tolerability, and patient compliance information (in progress). An integrated approach for comparing relative treatment effect of marketed antipsychotics on top of normalized PE helps in detecting the true drug effect. Recently, Goyal and Gomeni[37] demonstrated the use of a model-based joint approach to define the CU of a treatment. We applied the same metric to a more number of compounds at their respective therapeutic doses. Our data shows that with this approach new drugs can be compared to existing ones and an effective dose at which the patient gets maximum benefit out of the drug can be identified.

In conclusion, using a combined PKPD, PE and drop-out model it was shown that the effect size ($E_{\text{max}}$) of the different ATAPs is in the same range as that for the typical antipsychotic drug haloperidol. Based on exposure-response analysis, the effect size was highest for olanzapine. All APs exhibited similar CU scores with the highest for risperidone. This integrated modelling approach and associated CU score allow the evaluation of the time course of the PANSS scores of the different APs and a proper comparison of their clinically relevant treatments effects.

Fig. 2b. Visual predictive check plots for external validation dataset using the final PKPD model (including covariates of placebo effect and dropout model). The grey shaded areas represents the 95% confidence intervals of the corresponding 2.5th, 50th and 97.5th percentiles of the simulated data, the black dashed represents the 2.5th, 97.5th percentiles of the observed data and black solid line represents median of the observed data.
Fig. 3. Clinical Utility of antipsychotics based on joint PKPD and dropout model for different antipsychotics at their therapeutic doses. Haloperidol (5-7.5 mg/day), risperidone (4-8 mg/day), olanzapine (10-15 mg/day), ziprasidone (40-100mg/day) and paliperidone (6-12 mg/day).

Left Panel- Figure 3a: shows the proportion of patients remaining in the study against the percentage of trial time with PANSS score less than predefined value of 72; Right Panel- Figure 3b: Displays the clinical utility for the different antipsychotics.
ACKNOWLEDGEMENTS

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APPENDIX 1

Calculations of $C_{ss}$ for Risperidone Active Moiety

Steady-state concentration of risperidone (parent) and 9-hydroxy-risperidone (metabolite) after repeated oral administration

**Definitions:**
- **Dose:** dose per dosing interval
- **tau:** dosing interval
- **F1:** total fraction of drug absorbed as risperidone + 9-hydroxy-risperidone
- **FP:** fraction of drug converted to paliperidone during absorption
- **CLP:** clearance of parent (excluding conversion to metabolite)
- **CLPM:** conversion clearance of parent compound to metabolite
- **CLM:** clearance of metabolite
- **RATE:** average rate of administration of risperidone + 9-hydroxy-risperidone
- **CSSP:** steady-state concentration of parent at rate of administration
- **CSSM:** steady-state concentration of metabolite at rate of administration

**Equations:**

\[
\text{RATE} = F1 \times \frac{\text{Dose}}{\tau}
\]

\[
CSSP = \frac{\text{RATE} \times (1 - FP)}{CLP + CLPM}
\]

\[
CSSM = \frac{\text{RATE} \times FP + CLPM \times CSSP}{CLM}
\]

\[
CSS = CSSP + CSSM
\]

Calculations of Effective dose for Risperidone using the CL/F:

\[
\text{RATE} = F1 \times \frac{\text{Dose}}{\tau}
\]

\[
C_{ss} = CSSP + CSSM
\]

\[
C_{ss} = \text{RATE} \times (1 - FP) / (CLP + CLPM) + \text{RATE} \times ((FP \times CLP + CLPM) / (CLP + CLPM)) / CLM
\]

\[
C_{ss} = \text{RATE} \times \frac{1}{(CLP + CLPM)} \times [1 - FP + FP \times CLP + CLPM/CLM]
\]

\[
\text{RATE} = \frac{CSS}{X}
\]

Effective Dose = RATE $\times$ $\frac{\tau}{F1}$
APPENDIX 2

NONMEM code for PKPD model for simulation of PANSS and Dropout

$PROBLEM Model code for simulation of PANSS and Dropout of Placebo effect
$INPUT
  ID ; Patient number
  TIID ; Study number
  DAY ; Scheduled Day of PANSS measurement
  TIME ; Actual Day of PANSS or dropout event
  DV ; PANSS or dropout Event
  FLG ; FLG=0 PANSS; FLG=3 dropout; FLG=4 completer;
  DOSE ; Dose
  AMT ; Dose administered
  BASE ; Baseline PANSS
  CMT ; CMT=1 Dosing; CMT=2 PANSS; CMT=3 Dropout
  DIS ; Disease type
  ADM ; Route of Administration
  US ; Study Centre (US vs. NON USA)
  YEAR ; Study Year
  DUR ; Study Duration (short-term vs. long-term)
  PHAS ; Trial Phase

$DATA Data.csv IGNORE=@

$PK
$SUBROUTINE ADVAN=6 TOL=9
$MODEL NCOMP=1 COMP (HAZ)

PK;

############################ Parameter-Covariate Relationship#############################
IF(US.EQ.1) WUS = 1 ; Most common
IF(US.EQ.0) WUS = ( 1 + THETA(12))

IF(DIS.EQ.0) WDIS = 1 ; Most common
IF(DIS.EQ.1) WDIS = ( 1 + THETA(11))

IF(ADM.EQ.0) WADM = 1 ; Most common
IF(ADM.EQ.3) WADM = ( 1 + THETA(9))
IF(ADM.EQ.2) WADM = ( 1 + THETA(10))

WCOV=WADM*WDIS*WUS

IF(US.EQ.1) TDUS = 1 ; Most common
IF(US.EQ.0) TDUS = ( 1 + THETA(8))

TDCOV=TDUS

IF(DUR.EQ.0) PXDUR = 1 ; Most common
IF(DUR.EQ.1) PXDUR = (1 + THETA(7))
PXYEA = (1 + THETA(13) * (YEAR - 2000.5))
PXCOV = PXDUR * PXYEA

IF(DIS.EQ.0) BLDIS = 1 ; Most common
IF(DIS.EQ.1) BLDIS = (1 + THETA(6))
BLCOV = BLDIS

; ################################ Placebo Effect Parameters ################################
TVBL = BLCOV * (THETA(1))
BL = TVBL * EXP(ETA(2)) ; BASLINE PANSS
TVTD = TDCOV * (THETA(2))
TD = TVTD
   TVPX = PXCOV * (THETA(3))
   PMAX = TVPX + ETA(1) ; P_MAX
POW = THETA(4)
TVW = WCOV * (THETA(5)) ; Residual Variability as Standard deviation
W = TVW

; ################################ Drug Effect Parameters ################################
KT = THETA(14) ; Delay in drug effect (Common Parameter)
TVEXR = THETA(15) ; Emax for Risperidone
EXR = TVEXR
TVEXO = THETA(16)
EXO = TVEXO + ETA(3) ; Emax for Olanzapine
TVEXPL = THETA(17)
EXPL = TVEXPL + ETA(3) ; Emax for Paliperidone
TVEXZ = THETA(18)
EXZ = TVEXZ + ETA(3) ; Emax for Ziprasidone

; ################################ EC50 ################################
TVD50R = THETA(19)
C50R = TVD50R * EXP(ETA(4)) ; EC50 for Risperidone
TVD50O = THETA(20)
C50O = TVD50O * EXP(ETA(4)) ; EC50 for Olanzapine
TVD50P = THETA(21)
C50P = TVD50P * EXP(ETA(4)) ; EC50 for Paliperidone
TVD50Z = THETA(22)
C50Z = TVD50Z * EXP(ETA(4)) ; EC50 for Ziprasidone
PKPD MODELLING AND CLINICAL UTILITY OF ANTIPSYCHOTIC DRUGS USING PANSS TOTAL

-------------Dropout Model-----------------------------------------------

BH=(THETA(23))
IF(TRT.EQ.1)BH=THETA(24) ; Risperidone
IF(TRT.EQ.2)BH=THETA(25) ; Olanzapine
IF(TRT.EQ.4)BH=THETA(26) ; Paliperidone
IF(TRT.EQ.5)BH=THETA(27) ; Ziprasidone

BE=(THETA(28))

$DES
IF(DAY.LE.7) PTIM=0
IF(DAY.LE.7) LOCF=BL

PLAC=PMAX*(1-EXP(-((T/TD)**POW)))
RIS=EXR*CSS/(C50R+CSS)*(1-EXP(-KT*TIME))
OLA=EXO*CSS/(C50O+CSS)*(1-EXP(-KT*TIME))
PALI=EXPL*CSS/(C50P+CSS)*(1-EXP(-KT*TIME))
ZIPRA=EXZ*CSS/(C50Z+CSS)*(1-EXP(-KT*TIME))

MOD=0
IF(TRT.EQ.1)MOD= RIS
IF(TRT.EQ.2)MOD= OLA
IF(TRT.EQ.4)MOD= PALI
IF(TRT.EQ.5)MOD= ZIPRA

PANT=BL*(1-PLAC)*(1-MOD) ; Predicted PANSS

IF(T.LE.TIME.AND.TRTEQ.1)
LOCF=BL*(1-PMAX*(1-EXP(-(PTIM/TD)**POW)))*(1-EXR*CSS/(C50R+CSS))*(1-EXP(-KT*PTIM))
IF(T.LE.TIME.AND.TRTEQ.2)
LOCF=BL*(1-PMAX*(1-EXP(-(PTIM/TD)**POW)))*(1-EXO*CSS/(C50O+CSS))*(1-EXP(-KT*PTIM))
IF(T.LE.TIME.AND.TRTEQ.4)
LOCF=BL*(1-PMAX*(1-EXP(-(PTIM/TD)**POW)))*(1-EXPL*CSS/(C50P+CSS))*(1-EXP(-KT*PTIM))
IF(T.LE.TIME.AND.TRTEQ.5)
LOCF=BL*(1-PMAX*(1-EXP(-(PTIM/TD)**POW)))*(1-EXZ*CSS/(C50Z+CSS))*(1-EXP(-KT*PTIM))

DADT(1)=BH*EXP(-BE*LOCF) ; Baseline hazard +BETA relating to observed PANSS score
IF(ISFINL.EQ.1) PTIM=TIME

$ERROR

;#########################################PANSS PREDICTION #######################################
P=PMAX*(1-EXP(-(TIME/TD)**POW))
P=EXR*CSS/(C50R+CSS)*(1-EXP(-KT*TIME))
IOLA = ((EXO*CSS)/(C50O+CSS))*(1-EXP(-KT*TIME))
IPALI = ((EXPL*CSS)/(C50P+CSS))*(1-EXP(-KT*TIME))
IZIPRA = ((EXZ*CSS)/(C50Z+CSS))*(1-EXP(-KT*TIME))
EMOD = 0
IF(TRT.EQ.1) EMOD = IRIS
IF(TRT.EQ.2) EMOD = IOLA
IF(TRT.EQ.4) EMOD = IPALI
IF(TRT.EQ.5) EMOD = IZIPRA
IEFF = BL*(1-IPLA)*(1-EMOD)

; IF (FLG.LT.2) THEN
; F_FLAG = 0
; IPRED = IEFF + ERR(1)*W
; Y = IPRED
; IRES = DV-IPRED
; IWRES = IRES/W
; OPAN = Y
; ENDIF;

------------------ HAZARD PREDICTION ---------------------------------------------
IF (NEWIND.NE.2) LOC = 0 ; Set LOCF value to 0 for new ID at time 0
IF (NEWIND.NE.2) TIM1 = 0 ; Set time value to 0 for new ID at time 0
IF (NEWIND.NE.2) CHZ1 = 0 ; Set CHZ value to 0 for new ID at time 0

CHZ2 = BH*EXP(-BE*LOC) ; Calculate cumulative hazard for each time
TOCH = CHZ1 + CHZ2*(TIME-TIM1) ; Total cumulative hazard over time
CHZ1 = TOCH ; Redefine previous CHZ to current
TIM1 = TIME
LOC = OPAN ; Redefine previous PANSS to the currently simulated
SUR = EXP(-TOCH) ; Survival
IF (FLG.EQ.3) IPRED = SUR*BH*EXP(-BE*LOC) ; Hazard of Dropout from a trial
IF (FLG.EQ.4) IPRED = SUR ; No dropout event Completers
IF (FLG.GT.2) THEN
F_FLAG = 1 ; For categorical data (dropout event)
Y = IPRED ; Y is probability for TTE data
ENDIF

; for different study designs different conditions, one such example is given here
IF (TIID.EQ.384.AND.TMP.GT.SUR.AND.TIME.LT.52.AND.FLAG1.EQ.0) THEN
  DV=1
  FLG=3 ; Dropout event
ENDIF

; Once patient drops out no more event happens in this patient
IF (FLG.EQ.3) FLAG1=1
IF (TIID.EQ.384.AND.FLAG1.EQ.1.AND.TIME.GT.52.AND.FLG.EQ.-1)THEN
  DV=0
  FLG=5 ; Once patient drops out no more event happens in this patient
ENDIF

; If ID had no event until time 52 then censor last observation and FLG to 4
IF (TIID.EQ.384.AND.FLAG1.EQ.0.AND.TIME.GT.52.AND.FLG.EQ.-1)THEN
  DV=0
  FLG=4 ; Completed the study
ENDIF
ENDIF

;-----------------------------------------------------------------------------------------------------
$THETA

........

$OMEGA

........

$SIGMA

$SIMULATION (578988566) (1234 UNIFORM) ONLYSIM SUB=1000
Supplementary Figure 1: Algorithm used for population-based analysis of exposure-response relationship of antipsychotic drugs

Supplementary Table 1: Comparison of drug effect using study-specific vs. normalized placebo effect

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ziprasidone</th>
<th></th>
<th>Paliperidone</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study-specific placebo effect</td>
<td>Normalized placebo effect</td>
<td>Study-specific placebo effect</td>
<td>Normalized placebo effect</td>
</tr>
<tr>
<td>Basline PANSS (units)</td>
<td>89.2 (1)</td>
<td>91.1 (1)</td>
<td>91.5 (1)</td>
<td>91.1 (1)</td>
</tr>
<tr>
<td>$P_{\text{max}}$</td>
<td>0.035 (45)</td>
<td>0.073 (7)</td>
<td>0.067 (25)</td>
<td>0.073 (7)</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>0.28 (33)</td>
<td>0.22 (12)</td>
<td>0.26 (10)</td>
<td>0.23 (10)</td>
</tr>
<tr>
<td>$EC_{50}$ (ng/ml)</td>
<td>87.4 (58)</td>
<td>39.7 (28)</td>
<td>6.63 (53)</td>
<td>6.89 (46)</td>
</tr>
<tr>
<td>IIV BASL (CV %)</td>
<td>19 (3)</td>
<td>16 (2)</td>
<td>12 (3)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>IIV $P_{\text{max}}$ (SD)</td>
<td>0.19 (4)</td>
<td>0.20 (2)</td>
<td>0.22 (5)</td>
<td>0.20 (2)</td>
</tr>
<tr>
<td>IIV $E_{\text{max}}$ (SD)</td>
<td>0.39 (12)</td>
<td>0.22 (9)</td>
<td>0.16 (7)</td>
<td>0.22 (9)</td>
</tr>
<tr>
<td>RUV: $\sigma$</td>
<td>8.2 (1)</td>
<td>8.3 (1)</td>
<td>6.9 (1)</td>
<td>8.3 (1)</td>
</tr>
</tbody>
</table>

*only relevant parameters are shown here*
REFERENCES


