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Pharmacokinetic–pharmacodynamic modelling of antipsychotic drugs in patients with schizophrenia: Part II: The use of subscales of the PANSS score

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ABSTRACT

Background and objectives: The superiority of atypical antipsychotics (also known as second-generation antipsychotics (SGAs)) over typical antipsychotics (first generation antipsychotics (FGAs)) for negative symptom control in schizophrenic patients is widely debated. The objective of this study was to characterize the time course of the scores of the 3 subscales (positive, negative, general) of the Positive and Negative Syndrome Scale (PANSS) after treatment of patients with antipsychotics, and to compare the control of negative symptom by SGAs *versus* a FGA (haloperidol) using pharmacokinetic and pharmacodynamic (PKPD) modelling. In addition, to obtain insight in the relationship between the clinical efficacy and the *in vitro* and *in vivo* receptor pharmacology profiles, the D_2 and 5-HT_{2A} receptor occupancy levels of antipsychotics were related to the effective concentrations.
Methods: The PKPD model structure developed earlier (part I) was used to quantify the drug effect using the 3 PANSS subscales. The maximum drug effect sizes (E_{max}) of oral SGAs (risperidone, olanzapine, ziprasidone, and paliperidone) across PANSS subscales were compared with that of haloperidol, while accounting for the placebo effect. Using the estimates of PKPD model parameters, the effective concentrations (C_{eff}) needed to achieve 30% reduction in the PANSS subscales were computed. Calculated effective concentrations were then correlated with receptor pharmacology profiles.
Results: Positive symptoms of schizophrenia responded well to all antipsychotics. Olanzapine showed a better effect towards negative symptoms than the other SGAs and haloperidol. Dropout modelling results showed that the probability of a patient dropping out from a trial was associated with all subscales, but was more strongly correlated with the positive subscale than with the negative or the general subscales. Our results suggest that different levels of D_2 or 5-HT_{2A} receptor occupancy are required to achieve improvement in PANSS subscales.
Conclusions: This PKPD modelling approach can be helpful to differentiate the effect of antipsychotics across the different symptom domains of schizophrenia. Our analysis revealed that olanzapine seems to be superior in treating the negative symptoms compared to other non-clozapine SGAs. The relationship between receptor pharmacology profiles of the antipsychotics and their clinical efficacy is not yet fully understood.

1. Introduction

The "typical" antipsychotic drugs (first generation antipsychotics (FGAs)) such as haloperidol and chlorpromazine are D_2 dopamine receptor antagonists and have been used to treat schizophrenia since more than fifty years. To overcome some of the adverse events (*e.g.* extrapyramidal side effects) of typical antipsychotics and to improve the treatment options for the negative symptoms of schizophrenia, second generation antipsychotics (SGAs) or "atypical" antipsychotics were introduced into the clinic in 1990s. Unlike FGAs, SGAs interact with a broader range of pharmacological receptor types. SGAs with a high affinity mainly towards serotonin and dopamine receptors (mainly 5-HT_{2A} and D_2) were classified as serotonin–dopamine antagonists (Horacek et al., 2006) or serotonin spectrum dopamine modulators (Meltzer and Massey, 2011) (*e.g.* risperidone, paliperidone, ziprasidone, asenapine, and lurasidone). In contrast, SGAs that show an affinity for other receptors such as histaminergic, cholinergic, and α-adrenergic receptors, in addition to serotonin and dopaminergic activity are grouped as multi-acting receptor targeted antipsychotics

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(Horacek et al., 2006) (*e.g.* clozapine, olanzapine and quetiapine). Although there are several SGAs available on the market for the treatment of schizophrenia, several unmet needs remain unaddressed, including a more effective treatment towards the negative symptoms and cognitive impairment in patients with schizophrenia (Leucht et al., 2009).

One of the rating scales frequently used to measure the clinical effect of antipsychotics is the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). It consists of 30 items, where each item is scored from 1 through 7 (1 indicating the absence of the symptom and 7 indicating extremely suffering from the symptom). These 30 items are grouped into 3 subscales; positive (7 items), negative (7 items) and general psychopathology (16 items).

It has been suggested that SGAs are more effective towards negative symptoms than FGAs in schizophrenic patients. However, recently, Leucht et al. (2009) performed statistical meta-analyses of clinical trials in patients with schizophrenia and reported a limited advantage of the newer agents in terms of efficacy towards the negative symptoms. To complement the findings of Leucht et al. (2009) in this paper we present the pharmacokinetic and pharmacodynamic (PKPD) modelling results for 1 FGA and 4 SGAs, using a large pooled dataset of PK and PANSS scores from schizophrenic patients. In this analysis, we also account for the placebo effect, predictors of the placebo effect (*via* covariate analysis) and the dropouts (*via* time-to-event type of hazard models).

To our knowledge, limited quantitative research has been carried out to link the exposure of antipsychotic drugs to the total PANSS score and no literature is available linking the exposure to PANSS subscales *per se*. Hence, we developed a PKPD model using PANSS total score and presented the results in an accompanying research article (part I) (Pilla Reddy et al., 2012, 2013-this issue). In the present paper (part II), the primary objective was to quantify the drug effects towards the 3 PANSS subscales by PKPD modelling of individual-patient level placebo and drug response data. In addition, the relationship between the clinical efficacy, *in vitro* and *in vivo* receptor pharmacology profiles, and the dopamine and serotonin receptor occupancy (D_2RO and 5-HT_{2A}RO) of antipsychotic drugs was investigated with the aim of investigating the hypothesis that SGAs show better negative symptom control than FGAs.

2. Methods

This work was performed within the framework of the Dutch Top Institute Pharma Project: Mechanism-based PKPD modelling platform (http://www.tipharma.com). This modelling platform involves leading global pharmaceutical companies and academic institutions from The Netherlands. PANSS and PK data used in this analysis were provided by Janssen Research and Development (Belgium), Pfizer (USA) and Merck (The Netherlands) and came from a number of double-blind clinical trials of their investigational drugs conducted between 1989 and 2009. Only clinical trial data available to us where scores on all subscales for individual patients were known was for 4 SGAs (olanzapine, risperidone, paliperidone, and ziprasidone) and 1 FGAs (haloperidol). Unfortunately we did not have data for other than haloperidol under FGAs. With available data, we have compared the effect of SGAs with FGA (haloperidol) and also among the SGAs. As the PANSS subscale data was not available for some of the studies, the number of placebo treated patients in the dataset for PANSS subscale analysis (n = 741) were lower than in the dataset used for the PKPD modelling of PANSS total score (n = 1338). All the studies were industry-sponsored Phase II and Phase III clinical trials except for one open-label study of haloperidol. The overview of trial design, summary statistics of the respective PANSS total and subscale scores and dropout rates across the studies used in the development of exposure-response models are shown in part I of the accompanying paper.

Earlier analysis based on the PANSS total scores from the placebo arms of schizophrenia trials identified the best placebo model and several predictors for the placebo effect (Pilla Reddy et al., 2012). In this study, we performed a similar analysis to identify the best performing placebo model and the predictors that are specific for the PANSS subscales. The typical value of the maximum drug effect (E_{max}) for the different drugs was estimated using the PKPD model structure that was developed earlier for the PANSS total score with minor modifications if deemed necessary.

The PKPD model structure is shown in the following equation:

$$\text{PANSS Score} = \text{Baseline PANSS} \times \underbrace{\left[\left(1-P_{max}\times\left(1-e^{-\left(\frac{TIME}{TD}\right)^{POW}}\right)\right)}_{\text{Placebo effect model}} * \underbrace{\left(1-\left(\frac{E_{max}\times C_{ss}}{EC_{50}+C_{ss}}\right)\right)}_{\text{Drug effect model}} * \underbrace{\left(1-e^{-KT\times TIME}\right)}_{\text{Delay in drug effect}}\right]$$

The Weibull placebo model (Pilla Reddy et al., 2011) describes the change of the PANSS score from baseline, which eventually reaches a plateau. P_{max} is the maximum placebo effect, TD is the time to reach 63.2% of the maximum change from baseline, and POW is the shape parameter. In the drug effect model, the PK model-predicted steady-state concentration (C_{ss}) of the antipsychotic drug is related to the PANSS score using an E_{max} model. E_{max} is the maximum drug effect, EC_{50} is the steady-state concentration required to achieve half of E_{max}. KT is the rate constant associated with the time required to obtain the maximum drug effect. The inter-individual variability (IIV) for the model parameters and a residual unexplained variability (RUV) were estimated if possible. Using the estimates of PKPD model parameters, the steady-state effective concentrations (C_{eff}) necessary to reach the 30% reduction in PANSS score from baseline were computed for each drug using the following equation:

$$C_{eff} = EC_{50}/(E_{max}/(1-\text{PANSS}/(\text{Baseline PANSS}*(1-P_{max})))-1).$$

The modelling procedures and calculations of C_{eff} have been described in detail in part I (Pilla Reddy et al., 2013-this issue).

To account for the dropouts, an exponential time-to-event (TTE) hazard model was utilized. In the first part of our study the dropout event was shown to be linked to the PANSS total. However, to understand the contribution of the each PANSS subscale to the total hazard of patients dropping out from a trial, the dropout model parameters were estimated under different scenarios. In the first scenario, each of the PANSS subscale contributions towards the hazard of dropout was analyzed independently:

$$\text{Hazard for the dropout event} = \text{BHAZ} \times \exp(-\text{BETA}_1 \times \text{PANSS subscale})$$

BHAZ is the baseline hazard without influence of predictors, while BETA is a parameter that relates the probability of a patient dropping out to one of the PANSS subscores. In the second scenario, the hazard of a patient dropping out from a trial was estimated by allowing a contribution of each of the subscales:

$$\text{Hazard for the dropout event} = \text{BHAZ}*\exp(-(\text{BETA}_1\times\text{PANSS positive})+(-\text{BETA}_2\times\text{PANSS negative})+(-\text{BETA}_3\times\text{PANSS general})$$

In the final scenario, combinations of two PANSS subscales were explored.

To characterize the relationship between the clinical efficacy (30% reduction in PANSS subscale score from its baseline value) and D_2 (D_2RO) and 5-HT_{2A} serotonin receptor occupancy (5-HT_{2A}RO) levels, we used the following relationship:

$$RO = RO_{max}\times C_{eff}/(Kd + C_{eff})$$

where RO_{max} is the maximum receptor occupancy, Kd is the plasma level of antipsychotic drug associated with 50% of maximum RO. C_{eff} for an antipsychotic drug to produce a 30% change in PANSS subscale score from its baseline value is obtained from our final PKPD model. The values of Kd and RO_{max} for D_2 receptor binding were obtained from literature (de Greef et al., 2011), where an E_{max} model was fitted to D_2RO and plasma concentrations of different antipsychotics from PET studies to estimate Kd and RO_{max}. Since human *in vivo* Kd values for 5-HT_{2A} receptor binding were not available, we used *in vitro* Ki values for calculations, assuming RO_{max} to be 100% (Nucci et al., 2009).

Non-parametric bootstrap and simulation-based visual predictive check (VPC) plots (as described in the part I) (Pilla Reddy et al., 2013-this issue) were used as model evaluation tools.

3. Results

3.1. Placebo effect model

The Weibull placebo model was used to account for the placebo effect. The placebo effect model parameters and predictors that were associated with the placebo effect on the PANSS subscales are reported in Table 1. The positive symptoms exhibited a relatively higher degree of improvement than the negative and the general symptoms. Covariate modelling results indicate that substantial heterogeneity in placebo effect arises from predictors such as study center, study duration and disease condition. There was a large effect of study center on the placebo effect of the negative subscale, *i.e.* studies that were conducted outside USA exhibited a 134% higher placebo effect (P_{max}) for the negative symptoms (improvement). Moreover, higher RUV in non-USA studies was observed for all the PANSS subscales.

3.2. Pharmacokinetic and pharmacodynamic model

Steady-state concentrations (C_{ss}) of antipsychotic drug predicted by the PK model (as described in part I) were related to the scores of the PANSS subscales. A common model (analysis of all atypical antipsychotic drugs together) was developed for PANSS positive and general scales, but it was not possible for the negative symptoms as we encountered numerical difficulties to fit the drug effect model. However, separate analysis (per compound) resulted in successful estimation of the model parameters. Hence, the PD parameters for the negative subscale were estimated separately for each antipsychotic drug. The summary of the PKPD parameter estimates of the different antipsychotic drugs with their 95% bootstrap confidence intervals are depicted in Table 2. The maximum drug effect size (E_{max}) against the positive subscale was high for the antipsychotic drugs when compared to other subscales (Table 2). On the other hand, the post-hoc individual estimate of the effect size (E_{max}) for the negative symptoms was highest for olanzapine (Fig. 1a). Olanzapine appeared numerically superior when compared to other antipsychotic drugs with respect to all symptom domains of schizophrenia. The time course of the PKPD model-predicted change from baseline of PANSS total and its subscale scores for placebo and antipsychotic drugs is displayed in Fig. 1b. All antipsychotics exhibited a greater overall symptom reduction than placebo. Different time course trajectories between the PANSS subscales were observed. The positive symptoms of schizophrenia responded well to all antipsychotics. The improvement in negative symptoms was not as large as seen with the other symptom domains. All SGAs and haloperidol reduced the overall negative symptoms significantly more than placebo treatment. Our analysis showed a delay ($t_{1/2}$ E_{max} = 0.693/KT) in achieving half of the maximum drug effect towards the negative symptoms of more than 3 weeks for ziprasidone and olanzapine, while it was about 5 days for haloperidol, risperidone, and paliperidone. The IIV of the EC_{50} parameter could not be estimated for the positive and general scales; hence, the IIV was fixed to a nominal value of 50% CV. The IIV for the EC_{50} of the negative subscale could be estimated and was found to be large for all antipsychotic drugs. Table 3 summarizes the typical drug effect parameters across the PANSS total and subscale scores that were subsequently used to calculate the effective concentrations and respective effective doses required to achieve 20 or 30% reduction in PANSS scores from the baseline score.

3.3. Dropout model

The parameter BETA that describes the relationship between the observed PANSS score and the hazard of a patient dropping out from a trial was estimated to be highest for the PANSS positive subscale and lowest for the PANSS negative subscale (Table 4). This indicates that the probability of a patient dropping out from a trial increases

Table 1
Placebo model parameter estimates (with bootstrap 95% CIs)[a].

Parameters	PANSS positive	PANSS negative	PANSS general
Weibull placebo model parameters			
Baseline PANSS (BASL)	22.8 (22.4–23.2)	23.9 (23.5–24.3)	45.3 (44.6–45.9)
TD (days) (time to reach 63.2% of maximum change from baseline)	15 (13–18)	19 (14.8–36.8)	15 (13–18)
P_{max} (maximum placebo effect)	0.094 (0.058–0.125)	0.052 (0.032–0.076)	0.048 (0.028–0.066)
POW (shape parameter)	1.26 (1.06–1.53)	1.39 (1.51–1.99)	1.32 (1.13–1.54)
Covariates on placebo model parameters[b]			
BASL-DIS (acute *vs.* chronic)[c]	−0.15 (−0.19 to −0.11)	–	–
P_{max}-DIS (acute *vs.* chronic)	−1.15 (−1.57 to −0.82)	–	–
P_{max}-USA (USA *vs.* non-USA)	–	1.34 (0.49–3.13)	–
RUV-REG (qd *vs.* bid)	–	−0.20 (−0.29 to −0.09)	–
RUV-DUR (short *vs.* long)	−0.28 (−0.44 to −0.04)	–	–
RUV-DIS (acute *vs.* chronic)	0.43 (0.18–0.73)	–	0.31 (0.1–0.55)
RUV-US (USA *vs.* non-USA)	0.29 (0.15–0.44)	0.64 (0.46–0.87)	0.40 (0.22–0.60)
Random effects (IIV and RUV)			
IIV BASL (CV %)	23 (21–24)	22 (20–23)	18 (16–19)
IIV P_{max} (SD)	0.24 (0.22–0.27)	0.17 (0.15–0.24)	0.21 (0.19–0.23)
IIV- RUV (CV %)	28 (21–35)	37 (28–46)	30 (28–40)
RUV (SD)	1.94 (1.75–2.14)	1.75 (1.51–1.99)	2.9 (2.5–3.4)

[a] 95% CI from 1000 bootstrap samples; bid = twice daily; CI = confidence interval; CV: coefficient of variation; DIS: disease type; DUR: study duration; qd = once daily; IIV = inter-individual variability; POW = shape parameter; RUV = residual unexplained variability; USA = location of study site (in or outside the USA); PANSS = Positive and Negative Syndrome Scale; and SD = standard deviation.
[b] Parameter-covariate relationship represents a proportional increase in the parameter value by the covariate.
[c] Chronic patients had 15% lower PANSS positive BASL score.

Table 2
Model parameter estimates (with bootstrap 95% CIs) obtained from the PKPD models using the time course of PANSS scores[a].

PKPD model	Haloperidol	Risperidone	Olanzapine	Ziprasidone	Paliperidone
PANSS positive subscale					
BASL PANSS positive	23.3 (22.9–23.6)	22.4 (22.4–22.6)	22.4 (22.4–22.6)	22.4 (22.4–22.6)	22.4 (22.4–22.6)
E_{max}	0.41 (0.25–0.69)	0.32 (0.28–0.38)	0.43 (0.30–0.78)	0.19 (0.13–0.32)	0.33 (0.28–0.39)
EC_{50} (ng/ml)	1.2 (0.22–3.12)	9.4 (3.4–21.7)	12.4 (1.2–43.3)	25.5 (2.5–130)	5.84 (1.6–12.3)
KT (1/day)	0.11 (0.07–0.18)	0.048 (0.039–0.057)	0.048 (0.039–0.057)	0.048 (0.039–0.057)	0.048 (0.039–0.057)
IIV E_{max} (SD)	0.30 (0.22–0.44)	0.25 (0.19–0.29)	0.25 (0.19–0.29)	0.25 (0.19–0.29)	0.25 (0.19–0.29)
RUV as SD (additive)	2.2 (2.0–2.3)	2.0 (1.9–2.1)	2.0 (1.9–2.1)	2.0 (1.9–2.1)	2.0 (1.9–2.1)
PANSS negative subscale					
BASL PANSS negative	24.1 (23.7–24.4)	24.7 (24.3–25)	23.8 (23.5–24.2)	23.6 (23.3–23.8)	23.8 (23.5–24.1)
E_{max}	0.21 (0.11–0.38)	0.14 (0.09–0.15)	0.33 (0.22–0.52)	0.17 (0.06–0.33)	0.15 (0.12–0.20)
EC_{50} (ng/ml)	6.4 (3.7–13.9)	18.5 (3.3–34)	10.1 (2.2–25)	62 (12–191)	17.3 (11.7–57)
KT (1/day)	0.19 (0.14–0.27)	0.16 (0.12–0.21)	0.028 (0.016–0.05)	0.0073 (0.004–0.015)	0.13 (0.10–0.22)
IIV E_{max} (SD)	0.25 (0.22–0.38)	0.24 (0.20–0.26)	0.40 (0.22–0.38)	0.30 (0.26–0.44)	0.27 (0.22–0.35)
IIV EC_{50} (CV%)	269 (162–443)	311 (251–425)	141 (65–313)	192 (138–347)	226 (170–243)
RUV as SD (additive)	2.3 (2.2–2.5)	2.3 (2.2–2.3)	2.2 (2.2–2.3)	2.0 (1.9–2.1)	2.0 (1.9–2.2)##
PANSS general subscale					
BASL PANSS general	45.1 (44.6–45.6)	44 (43.7–44.2)	44 (43.7–44.2)	44 (43.7–44.2)	44 (43.7–44.2)
E_{max}	0.27 (0.17–0.48)	0.19 (0.16–0.23)	0.34 (0.25–0.55)	0.12 (0.07–0.20)	0.24 (0.20–0.30)
EC_{50} (ng/ml)	2.58 (0.73–6.31)	3.97 (0.49–11.1)	12.2 (2.7–37)	36.4 (13.2–131)	3.07 (0.23–10)
KT (1/day)	0.15 (0.09–0.23)	0.035 (0.021–0.045)	0.035 (0.021–0.045)	0.035 (0.021–0.045)	0.035 (0.021–0.045)
IIV E_{max} (SD)	0.25 (0.19–0.38)	0.22 (0.18–0.32)	0.22 (0.18–0.32)	0.22 (0.18–0.32)	0.22 (0.18–0.32)
RUV as SD (additive)	3.8 (3.6–4.0)	3.6 (3.5–3.7)	3.6 (3.5–3.7)	3.6 (3.5–3.7)	3.6 (3.5–3.7)

[a] 95% CI from 1000 bootstrap samples; BASL = Baseline; E_{max} = maximum drug effect; EC_{50}: 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; and SD = standard deviation. IIV EC_{50} for positive and general scale was fixed to 50% CV, as it was not estimable.

exponentially with the deterioration of positive symptoms. When interaction between the PANSS subscales was allowed, the net contribution of the positive subscale for the hazard of dropout remains high, but the opposite effect was observed with the PANSS negative subscale *i.e.* a decrease in probability of patient dropping out with an increase in observed PANSS negative scores. Based on the change in NONMEM objective function value (ΔOFV), the dropout model associated with only the PANSS positive score and the dropout model associated with all subscales (*i.e.* model with interaction between all subscales) were selected to perform the model-based simulations to evaluate the predictability of the joint model (PKPD model and dropout model).

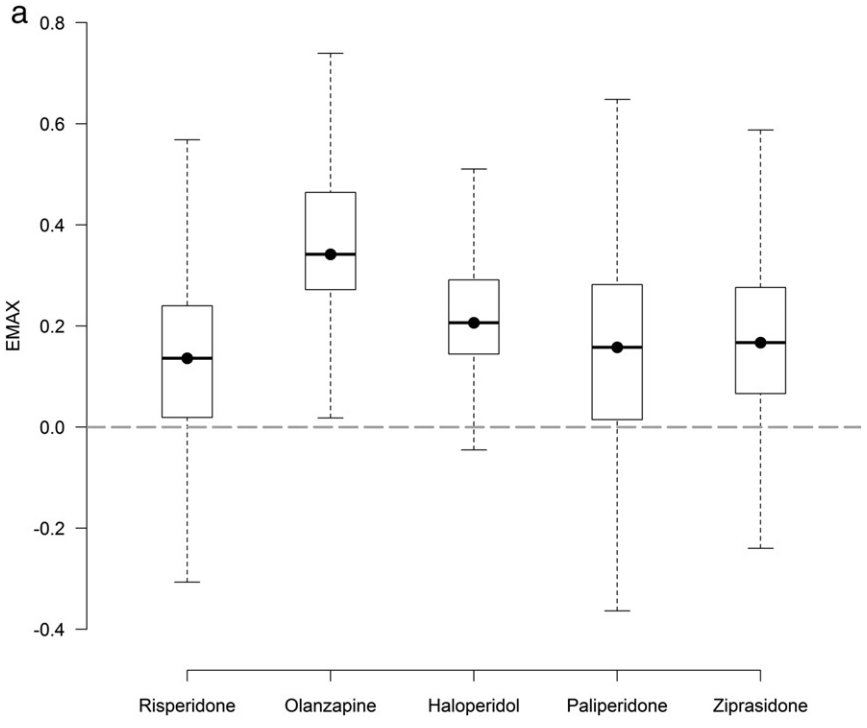

Fig. 1. a. Box plot showing the post-hoc estimates of maximum drug effect on PANSS negative symptoms by antipsychotics on top of the placebo effect. b. Model predicted percentage change from baseline in PANSS total and its subscales for the placebo and for each drug based on the original dataset but assuming no dropout (missing PANSS scores due to a dropout from a trial were predicted using the PKPD model). Green = total PANSS, Blue = positive subscale, Red = negative subscale, Orange = general subscale.

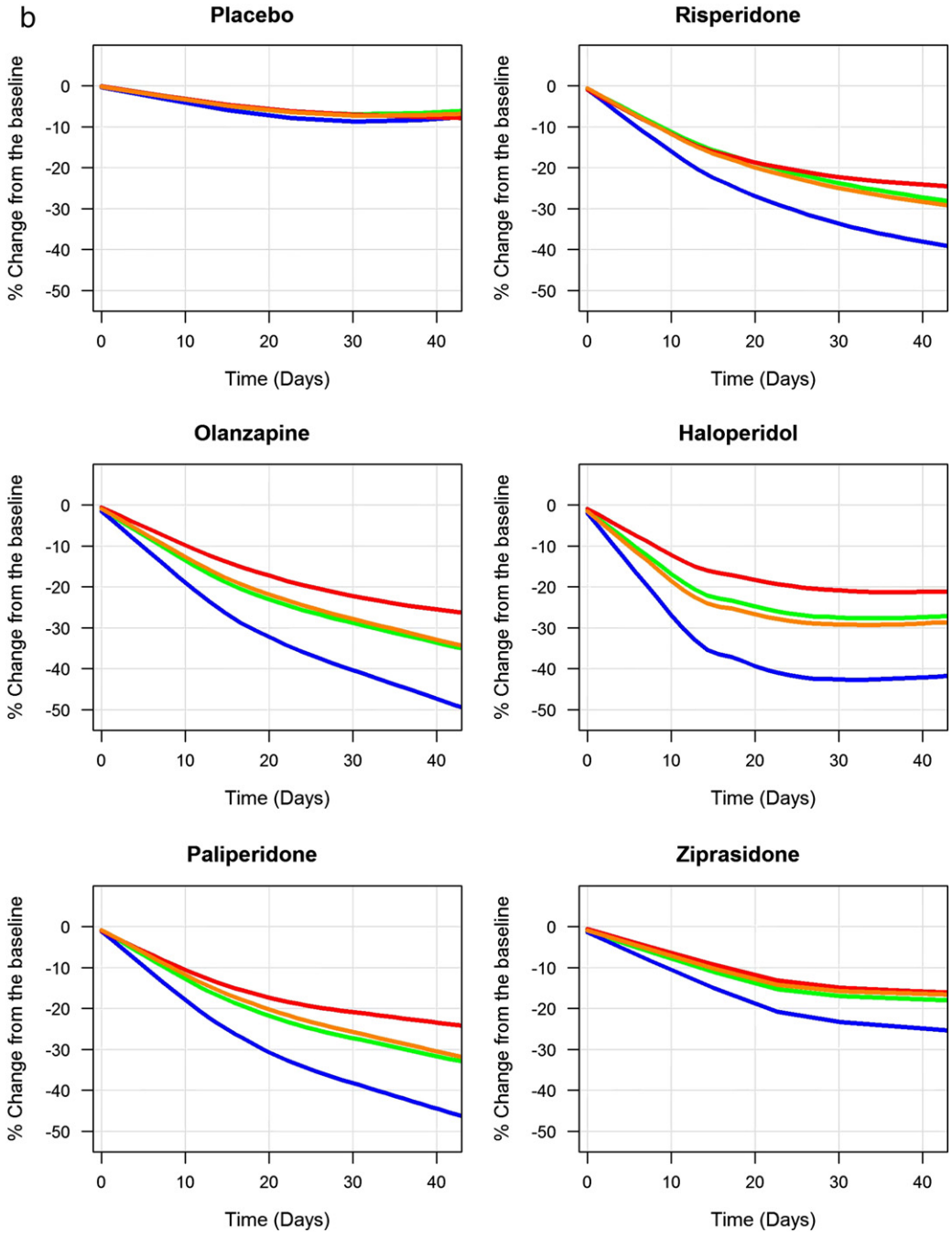

Fig. 1 (*continued*).

3.4. Model evaluation

The bootstrap re-sampling technique and model-based simulations respectively were used as model evaluation tools to check the stability and predictability of the model. The median parameter estimates obtained from the bootstrap replicates were in agreement with those obtained with the final PKPD model using the original dataset (data not shown). However, the bootstrap 95% confidence intervals of EC_{50} for some drugs vary more than 2-fold from the median typical value (Table 2). Monte-Carlo simulation-based visual predictive check (VPC) plots indicated that the PKPD models of PANSS subscales were able to describe the time course of each subscale well. Table 2 and Fig. 2 show the robustness and predictive power of the developed PKPD model, respectively. VPC plots for the joint PKPD model including dropout are shown in Fig. 2a and b. Based on VPC plots, the dropout model with interaction seems to be better in describing the change in PANSS positive scores following the placebo treatment (97.5th percentiles of the simulated data of Fig. 2b). This finding may not be surprising as placebo arms had higher dropout rates (~65%, mainly due to lack of efficacy) than the drug treatment arms (~35%) allowing the dropout model with interaction to perform better for the placebo treatment.

3.5. Relationship between the clinical efficacy and in vitro and in vivo receptor profiles

Tables 5a and 5b summarize the *in vitro* and *in vivo* pharmacodynamic characteristics of antipsychotics, respectively. Olanzapine has the lowest 5-HT_{2A}/D_2 receptor affinity ratio compared to other SGAs. Based on C_{eff} values obtained from the model of PANSS total scores, the calculated D_2RO of antipsychotic drugs was in the range of 50–79%,

Table 3
Calculated effective antipsychotic dose and concentrations for PANSS total, and its subscales at 20 and 30% reduction in PANSS score from baseline.

	PKPD model estimated parameters				Effective C_{ss} (ng/ml)		Corresponding dose: effective dose (mg/day) = Css∗CL/F	
	Baseline score	P_{max}	E_{max}	EC_{50}	20% decrease in PANSS	30% decrease in PANSS	20% decrease in PANSS	30% decrease in PANSS
Haloperidol								
PANSS total	91.6	0.081	0.31	3.6	0.84	2.7	1.8	5.6
Positive subscale	23.4	0.099	0.41	1.2	0.17	0.54	0.4	1.2
Negative subscale	24.1	0.047	0.21	6.4	5.8	31	12	65
General subscale	45.1	0.048	0.27	2.58	1.19	3.2	2.51	7.1
Risperidone								
PANSS total	91.1	0.073	0.23	3.72	1.38	5.3	0.20	0.8
Positive subscale	22.5	0.094	0.32	9.42	1.68	6.0	0.24	0.9
Negative subscale	24.1	0.051	0.14	18.5	42.1	#	6.3	#
General subscale	44	0.052	0.19	3.97	7.21	#	1.1	#
Olanzapine								
PANSS total	91.1	0.073	0.39	24.8	4.89	13.8	2.58	7.3
Positive subscale	22.5	0.094	0.43	12.4	1.52	4.9	0.80	2.6
Negative subscale	24.1	0.051	0.33	10.1	4.9	13.4	2.61	6.38
General subscale	44	0.052	0.34	12.2	3.72	9.2	1.96	4.9
Ziprasidone								
PANSS total	91.1	0.073	0.22	39.7	15.6	63.1	20.26	81
Positive subscale	22.5	0.094	0.19	25.5	8.70	48.3	11.27	63
Negative subscale	24.1	0.051	0.17	62	82.8	#	113	#
General subscale	44	0.052	0.12	36.4	#	#	#	#
Paliperidone								
PANSS total	91.1	0.073	0.23	6.89	2.55	9.8	0.86	3.3
Positive subscale	22.5	0.094	0.33	5.84	1.00	3.5	0.34	1.2
Negative subscale	24.1	0.051	0.15	17.3	30.0	#	10.4	#
General subscale	44	0.052	0.24	3.07	3.20	22.6	1.05	7.6

PANSS total parameters are from part I (Pilla Reddy et al., 2013-this issue); # 20% or 30% decrease in PANSS from baseline PANSS score was not attained. Effective Css (C_{eff}) = EC_{50}/(E_{max}/(1 − PANSS/(Baseline PANSS∗(1 − P_{max}))) − 1); % change in score is given by = PANSS − Baseline PANSS/(Baseline PANSS − number of PANSS items[a]) P_{max} = maximum placebo effect; E_{max} = maximum drug effect; EC_{50}: steady-state concentration required to achieve half of E_{max}.
[a] Number of PANSS items: PANSS total: 30; PANSS positive: 7; PANSS negative: 7; PANSS general:16.

which is close to the antipsychotic D_2RO therapeutic window of 60–80%. The level of D_2RO required for improving the positive symptoms was in the range of 42–74%.

Olanzapine was quite different in terms of *in vivo* PD characteristics when compared to other SGAs with the lowest D_2RO for both the positive (42%) and for the negative symptoms (42%). Haloperidol was distinct from SGAs with a lower 5-HT_{2A}/D_2 receptor affinity ratio and low 5-HT_{2A}RO levels. In line with the reported in literature (Kapur et al., 1996), Tables 5a and 5b show that haloperidol predominately binds to the dopamine (D_2) receptors, while olanzapine moderately binds to D_2 and 5-HT_{2A} receptors, which makes it atypical in terms of receptor profiles. This atypical receptor profile of olanzapine may be related to improvement of the negative symptoms of schizophrenia.

4. Discussion

SGAs are claimed to exhibit a broad efficacy spectrum with lesser side effects than FGAs. One of the assertions while marketing these SGAs is "better negative symptom control than FGAs" (Sernyak and Rosenheck, 2007). SGAs are different from conventional typical antipsychotics in many ways including their receptor binding properties, efficacy and safety profiles. The available SGAs might be effective against different symptom domains other than positive symptoms depending on their receptor binding profile (Grunder et al., 2009). It has been hypothesized that either a higher 5-HT_{2A}/D_2 affinity ratio or a high selectivity towards the 5-HT_{2A} receptors contributes to the improved efficacy towards the negative symptoms in schizophrenia (Kapur and Remington, 1996).

Table 4
Results of joint modelling of PANSS scores and the dropout events.

Parameters (% RSE)	Scale							
	PANSS total	Positive	Negative	General	Positive + negative + general	Positive + negative	Positive + general	Negative + general
BHAZ:								
Placebo (1/day)	0.0005 (9)	0.00119 (7)	0.00438 (8)	0.00057 (9)	0.00066 (10)	0.00112 (9)	0.00053 (9)	0.00076 (9)
Risperidone (1/day)	0.00031 (10)	0.00072 (7)	0.00219 (9)	0.00038 (9)	0.00046 (10)	0.00068 (9)	0.00036 (9)	0.00053 (9)
Olanzapine (1/day)	0.00046 (11)	0.00096 (10)	0.00304 (10)	0.00054 (11)	0.00061 (12)	0.0009 (12)	0.00049 (11)	0.00072 (11)
Ziprasidone (1/day)	0.00022 (8)	0.00054 (7)	0.00157 (8)	0.00023 (9)	0.0003 (9)	0.00051 (9)	0.00024 (9)	0.00031 (9)
Paliperidone (1/day)	0.00057 (9)	0.00119 (8)	0.00409 (9)	0.00067 (9)	0.00074 (9)	0.00113 (9)	0.0006 (9)	0.00087 (9)
BETA	−0.0352 (3)	NE	NE	NE	NE	NE	NE	NE
$BETA_1$ (positive)	NE	−0.111 (3)	NE	NE	−0.0703 (5)	−0.11 (3)	−0.0746 (5)	NE
$BETA_2$ (negative)	NE	NE	−0.0443 (6)	NE	0.0312 (13)	−0.00382 (86)	NE	0.0422 (9)
$BETA_3$ (general)	NE	NE	NE	−0.0672 (4)	−0.0479 (6)	NE	−0.0342 (7)	−0.0831 (7)
OFV	112,211	112,102	112,952	112,212	111,940	112,101	111,980	112,138
ΔOFV	–	−109	+741	+1	−271	−110	−231	−73

NE: not estimated; ΔOFV: Change in OFV in relation to the PANSS total model; 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.

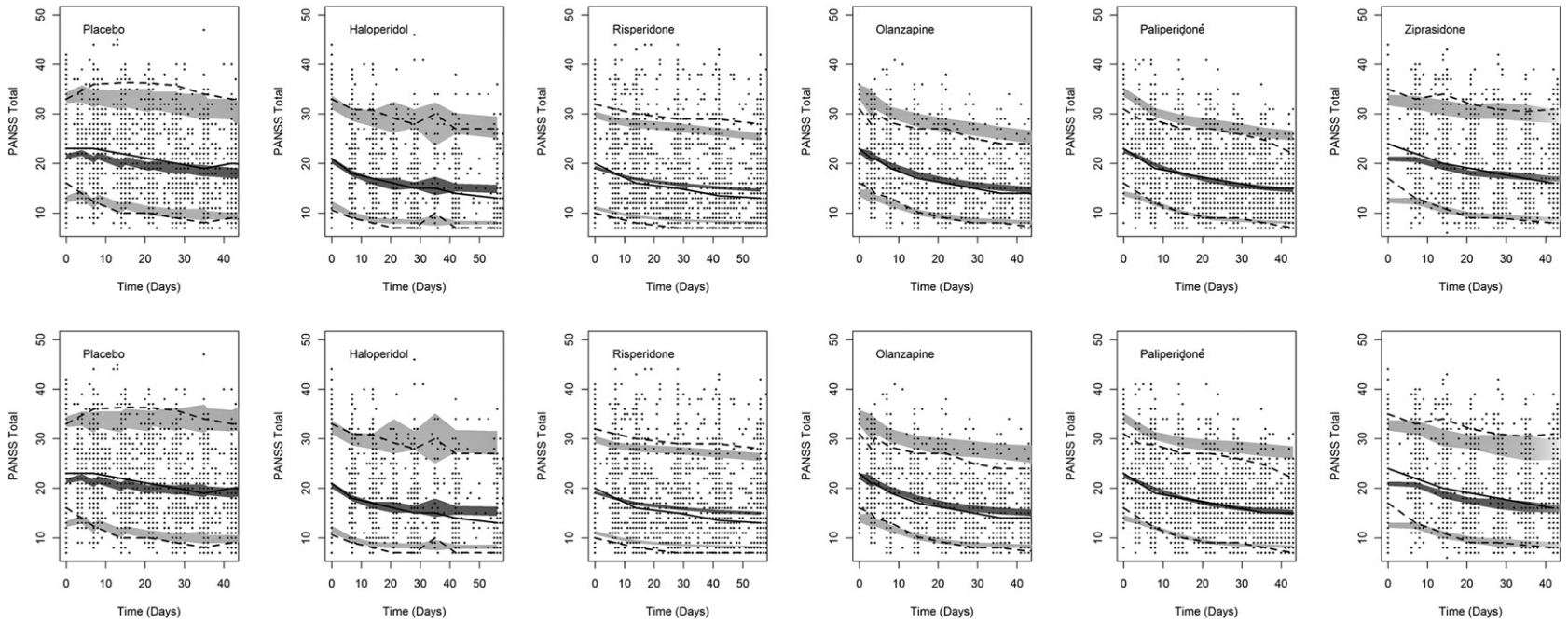

Fig. 2. Depicts the visual predictive check (VPC) plots of the PKPD model for different antipsychotics with the dropout model using observed PANSS positive scores (top panel) and the dropout model using observed scores of all subscales *i.e.*, positive + negative + general (bottom panel). The gray shaded areas represent the 95% confidence intervals of the corresponding 2.5th, 50th and 97.5th percentiles of the simulated data, the black dashed lines represent the 2.5th and 97.5th percentiles of the observed data and the black solid line represents the median of the observed data. Black dots represent the observed PANSS scores.

Table 5a
In vitro pharmacodynamic characteristics of antipsychotics.

Antipsychotic drug	D_2 (k_{off}: min^{-1}) Kapur and Seeman (2000)	*In vitro* receptor affinity (K_i in nM)				
		D_2	5-HT_{2A}	5-HT_{1A}	5-HT_{2C}	5-HT_{2A}/D_2
Haloperidol	0.017	2	119	2832	4475	59.5
Risperidone	0.026	4.9	0.48	420	33	0.10
Olanzapine	0.039	72	4.9	2720	14	0.07
Ziprasidone	0.073	4	0.73	112	4.1	0.18
Paliperidone	0.026[a]	2.1	1	590	NA	0.48

Lower 5-HT_{2A}/D_2 affinity ratio indicates higher the selectivity towards 5-HT_{2A}, k_{off} = dissociation constant for D_2 receptor.
[a] Same as that of risperidone.

The 5-HT_{2A} antagonism may confer atypicality on antipsychotic drugs with relatively weaker D_2 antagonism because of the ability of 5-HT_{2A} receptors to modulate the activity of dopaminergic neurons differentially in different regions of the brain (Meltzer et al., 2003).

A meta-analysis of clinical studies using a central tendency statistical approach may account for some sources of variability in efficacy but may not provide sufficient information from a drug development perspective about the efficacy, potency, and safety of a drug. Nevertheless, it may provide information about the potential of a drug to be effective against the given condition. On the contrary, population-based PKPD modelling using non-linear mixed effect approach is very well suited to handle the different sources of variability that eventually helps to strengthen the claim for efficacy and provides quantitative estimates of time course and magnitude of drug action. PKPD modelling allows estimating the effectiveness of SGAs after accounting for the differences related to methodological aspects, exposure, placebo effect, and dropout rates. Investigations into the PANSS subscales and components of the PANSS using advanced methodological approaches such as modelling and simulations could provide a means for a better understanding of diverse therapeutic aspects of SGAs. For this reason, we applied a PKPD modelling approach using the data obtained for the different PANSS subscales to differentiate between antipsychotic drugs with respect to their effect on different domains of schizophrenia reflected by the different PANSS subscales. In addition, the relationship between the clinical efficacy, *in vitro* and *in vivo* receptor pharmacology profiles was explored. The comparison of the time course of the effect of the drugs on the different subscales showed appreciable differences. All antipsychotic drugs were more effective than placebo during the first 2 weeks of the study (Fig. 1b). In our PKPD analysis, the time required to achieve half of the maximum drug effect (E_{max}) for positive and general symptoms for SGAs was found to be about 2–3 weeks. Some neuronal remodelling changes in the brain may be responsible for this gradual increase to the maximum drug effect (Horacek et al., 2006). On the contrary, this time delay to achieve half of the maximum drug effect was less than one week with haloperidol treatment. This faster improvement with haloperidol treatment may be due to its quick blockade of the D_2 receptor to cause an antipsychotic action and slow k_{off} rates from D_2 receptors (Stahl, 2008).

The negative subscale appears to have a lower magnitude of improvement when compared to other subscales (Fig. 1b). The delay in achieving the maximum drug effect for the negative symptoms was reported before in the literature (King, 1998a, 1998b). With our data, haloperidol, risperidone, and paliperidone showed slightly faster onset of drug effect or improvement for the negative symptoms than ziprasidone and olanzapine.

Joint modelling of PANSS total scores with dropout events using the placebo data and antipsychotic drugs showed that the relationship between the chance of a patient dropping out of a trial increases with lack of improvement in schizophrenia symptoms (Pilla Reddy et al., 2012, 2013-this issue). When the results were analyzed for the different PANSS subscales it appeared that the probability of a dropout was more strongly associated with worsening of positive symptoms (BETA = −0.11) than of negative and general symptoms. Although dropout modelling using only the PANSS for the negative symptoms showed that the hazard of dropout increases with worsening of negative symptoms (BETA = −0.044), the increase in NONMEM OFV by 741 units relative to PANSS total indicates a poor association between the negative subscale and the dropout event. When interaction between the PANSS subscales was allowed in the model, an opposite effect was observed with the PANSS negative subscale *i.e.* a decrease in probability of a patient dropping out was found to be correlated with an increase in observed PANSS negative scores. The physiological reason for this finding is difficult to understand, but it may be hypothesized that this effect could be due to secondary effects of an improvement of positive and general symptoms, or a reduction of co-morbid symptoms of depression or anxiety, or an alleviation of the extrapyramidal effects by co-medication (*e.g.* anti-cholinergic agents). Moreover, less improvement in negative symptoms may lead to hospitalization of the patient, which may result in lower dropout rates. We did not have co-medication information for all the trials to explore the effect of adjunctive therapy for the improvement of negative symptoms. However, Ahadieh et al. (2011) reported that adjunct therapy in schizophrenia does affect the improvement in the time course of PANSS negative symptoms.

It has been suggested that complex pharmacological interactions between several receptors are important for atypicality. Table 5a supports the hypothesis that the affinity (ki) ratio of serotonergic activity to dopaminergic activity (Meltzer et al., 1989, 2003) plays a role to some extent in mediating the efficacy of atypical antipsychotics (*e.g.* olanzapine). The calculated D_2RO levels required for the improvement in PANSS total score were in the range of 50–79%, which is more or less in line with suggested D_2RO range (Uchida et al., 2011). However, our data suggest that different levels of D_2 and 5-HT_{2A} receptor occupancy are required to achieve improvement in PANSS subscales (Table 5b). Relatively high affinity towards serotonin receptor subtypes could potentially enable a compound to produce antipsychotic efficacy at lower levels of D_2 occupancy (de Greef et al., 2011).

Recently, Frankle et al. (2011) showed the relationship between the 5-HT_{1A} receptor binding and the improvement in negative symptoms following ziprasidone dosing (n = 6). However, in our analysis,

Table 5b
Relationship between the effective concentrations (C_{eff}) and the receptor occupancy levels.

Antipsychotic drug	RO_{max} D_2RO de Greef et al. (2011)	Kd: D_2 (ng/ml) de Greef et al. (2011)	Kd: 5-HT_{2A} (ng/ml) Nucci et al. (2009)	C_{eff} (ng/ml)			D_2RO (%)			5-HT_{2A} RO (%)		
				Total	Positive	Negative[a]	Total	Positive	Negative	Total	Positive	Negative
Haloperidol	92	0.53	13.5	2.7	0.54	5.8	77	46	84	17	4	30
Risperidone	91	4.43	0.07	5.3	6	42.7	50	52	83	99	99	100
Olanzapine	88	5.29	1.25	13.8	4.9	4.9	63	42	42	92	80	80
Ziprasidone	98	15.4	1.97	63.1	48.3	83	79	74	83	97	96	98
Paliperidone	90	4.6	0.09	9.8	3.5	30	61	39	78	99	97	100

[a] Corresponds to 20% decrease in PANSS score from baseline as the maximum improvement of >20% with PANSS score never attained. RO_{max} = maximum receptor occupancy, Kd = plasma level of antipsychotic drug associated with 50% of maximum RO; C_{eff} = drug concentration to produce a 30% reduction in PANSS score; D_2RO = dopamine 2 receptor occupancy; 5-HT_{2A} RO = serotonin 2A receptor occupancy.

ziprasidone exhibited a low effect towards the negative symptoms raising the question about the role of 5-HT_{1A} receptors towards the improvement of negative symptoms.

This pooled analysis of the efficacy of several SGAs and one FGA concludes that atypical antipsychotics are not superior to the high potency typical antipsychotic haloperidol with respect to improvement of the scores for the diverse subscales of the PANSS. However, olanzapine due to its different pharmacological profiles compared to other SGAs is shown to result in a better negative symptom management. The strength of our pooled PKPD analysis is that we could compare the differences in efficacy within the atypical antipsychotics and with the typical antipsychotic haloperidol. Extrapolation to other antipsychotics namely, asenapine (Friberg et al., 2009), quetiapine (Kimko et al., 2000) and lurasidone using their respective efficacy PD parameters from literature by means of $C_{eff} = EC_{50}/(E_{max}/(1 - PANSS/(Baseline\ PANSS \times (1 - P_{max}))) - 1)$ resulted in C_{eff} and effective doses (data not shown), which were in line with reported in literature or regulatory documents.

Adverse events such as extrapyramidal side effects were not taken into account despite the fact that they potentially could negatively influence the efficacy outcomes. Therefore, the value of this PKPD analysis can be further improved by integration of adverse event modelling results. The relationship between receptor pharmacology profiles of the antipsychotics and their clinical efficacy is not yet fully understood. In this regard, PKPD modelling could be a valuable tool to characterize the relationship between D_2RO and clinical effects of antipsychotic drugs and to predict the optimal human dose for new antipsychotic drugs.

In this modelling work, we have taken into consideration of factors such as the drug's affinity and intrinsic activity at the site of action, drug concentration and underlying internal and external factors of the patient to determine the effective dose and concentration that lead to better antipsychotic efficacy. Such an analysis enhances the key decisions in drug development such as dose selection, study design, product positioning, in-licensing, and early go/no-go decisions. In conclusion, this PKPD modelling work may be helpful to differentiate the effects of antipsychotic drugs across the different symptom domains of acute and chronic schizophrenia, accounting for placebo effect and dropouts. Our analysis revealed that olanzapine seems to be superior in treating the negative symptoms compared to other non-clozapine SGAs.

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Contributors

Venkatesh Pilla Reddy performed the PK–PD analysis (under the supervision of Johannes Proost and Magdalena Kozielska) and drafted the manuscript. Ahmed Abbas Suleiman and Martin Johnson collected the literature data and performed preliminary PK analysis. An Vermeulen, Jing Liu and Rik de Greef shared the data and gave critical inputs for the analysis. Johannes Proost, Geny M.M. Groothuis and Meindert Danhof critically revised and approved the final manuscript.

Conflict of interest

An Vermeulen is an employee of Janssen Research & Development (Beerse, Belgium). Jing Liu is an employee of Pfizer Global Research and Development (Groton, CT, USA). Rik de Greef is an employee of Merck Sharp & Dohme (Oss, the Netherlands). None of the other authors have any conflicts of interest that are directly relevant to the content of this study.

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