Translational PKPD modeling in schizophrenia
Pilla Reddy, Venkatesh

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Translational PKPD modelling in schizophrenia: linking receptor occupancy of antipsychotics to efficacy and safety

Venkatesh Pilla Reddy,1 Magdalena Kozielska,1 Martin Johnson,1 An Vermeulen,2 Jing Liu,3 Rik de Greef,4 Geny M.M. Groothuis,1 Meindert Danhof,2 and Johannes H. Proost.1

Submitted

1Division of Pharmacokinetics, Toxicology and Targeting, University of Groningen, Groningen, the Netherlands
2Advanced PKPD Modelling and Simulation, Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium
3Clinical Pharmacology, Pfizer Global Research and Development, Groton, CT, USA
4Clinical PKPD, Merck Research Labs, Merck Sharp & Dohme, Oss, the Netherlands
5Division of Pharmacology, Leiden/Amsterdam Center for Drug Research, Leiden, the Netherlands

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ABSTRACT

**Purpose:** To predict the dopamine D<sub>2</sub> receptor occupancy (D<sub>2</sub>RO) of antipsychotics and to link predicted D<sub>2</sub>RO with clinical endpoints to understand the relationship between the D<sub>2</sub>RO and the clinical effects of antipsychotics.

**Methods:** Pharmacokinetic-Pharmacodynamic (PKPD) models were developed to predict the D<sub>2</sub> receptor occupancy window of antipsychotics. **Step 1:** Patient-specific steady-state concentration was calculated using post-hoc Bayesian estimates of clearance obtained from a PK model. **Step 2:** D<sub>2</sub>RO was predicted with empirical and semi-mechanistic models using observed D<sub>2</sub>RO or *in vitro* data. **Step 3:** D<sub>2</sub>RO was linked to the clinical endpoints of efficacy (Positive and Negative Syndrome Scale, PANSS) and safety (extrapyramidal symptoms, EPS). **Step 4:** Effective D<sub>2</sub>RO for clinical efficacy and minimal EPS events were computed using model parameters.

**Results:** Predicted D<sub>2</sub>RO was in agreement with clinically observed D<sub>2</sub>RO at relevant antipsychotic doses. The effective D<sub>2</sub>RO required to achieve a 30% reduction in PANSS from baseline score was in the range of 50-70%. Above 80% D<sub>2</sub>RO, incidence of EPS increased sharply. The interplay between D<sub>2</sub> and 5-HT<sub>2A</sub> receptors may be related to a lower EPS incidence.

**Conclusions:** This modelling framework provides a valuable tool to characterize the relationship between D<sub>2</sub>RO and clinical effects of antipsychotics. Furthermore, may be helpful to extrapolate the D<sub>2</sub>RO-PANSS/EPS relationship to new drugs with the same mechanism of action.
INTRODUCTION

Dopaminergic function has a key role in the treatment of schizophrenia, and, as a result, for the selection and development of new antipsychotics (APs). The dopamine D₂ receptor is strongly associated with the potential modulation of schizophrenic symptoms as measured with rating scales such as the Positive and Negative Syndrome Scale (PANSS). In recent years, ATAPs were claimed to manage the negative or cognitive symptoms better than TAPs.[1] Furthermore, several atypical antipsychotics (ATAPs) were shown to exhibit less extrapyramidal side effects (EPS) compared to typical antipsychotics (TAPs).[2] Better negative symptoms control and less EPS side effects with ATAPs were hypothesized to be due to their effects on various other receptors like 5-HT₂A, 5-HT₁A, 5-HT₂C, and D₄ receptors.[3] Binding of ATAPs to the above-mentioned receptors other than D₂ may lead to a beneficial increase in endogenous dopamine release at mesocortical and striatal dopaminergic neurons that could eventually lead to the improvement in negative symptoms and a lower incidence of EPS side effects. Moreover, fast dissociation from the D₂ receptors, preferential extrastriatal and high extrasympathetic D₂RO by ATAPs were also considered to be important for these effects.[4-6]

The brain D₂RO of APs can be used as a potential biomarker to characterize both penetration of the drug into the brain as well as its binding to the (target) receptor through imaging techniques such as positron emission tomography (PET). However, these imaging studies are low throughput, high cost, and highly labor intensive. Consequently, sample sizes are usually too small to permit extensive or longitudinal analyses of receptor occupancy vs. drug efficacy. Understanding this relationship would be of great value in the clinical setting in terms of choosing the dose and dosing schedule. In this regard, translational pharmacokinetic-pharmacodynamic (PKPD) modelling could be a better tool to not only predict and characterize the time course of drug effects but also to separate drug-specific and system-specific factors contributing to the pharmacodynamics of a drug. Using such a model-based approach, one can accommodate the diverse drug-related features (e.g., physico-chemical properties, in vitro efficacy and safety profile and ADME properties) and the system-related features (e.g., receptor density, transduction process, and disease progression) which can increase the efficiency in drug development of APs.[7]

This paper describes a pharmacokinetic-pharmacodynamic (PKPD) modelling approach to link D₂RO to PANSS scores (D₂RO-PANSS) and to link D₂RO to EPS events (D₂RO-EPS) for different APs with the following objectives:

i) to investigate different methods to predict human D₂RO and ii) to define the relationship between the D₂RO and clinical response, as described by the change in PANSS score, and the incidence of EPS adverse events in patients suffering from schizophrenia. In this study, we included the following currently available ATAPs: risperidone, olanzapine, ziprasidone, paliperidone extended release, and a recent
Phase II test compound (JNJ-37822681). Haloperidol was used as a reference TAP to compare the efficacy and safety profile of various ATAPs with that of a TAP.

**METHODS**

**Clinical Data**
This PKPD modelling work was performed within the framework of the Dutch Top Institute Pharma project: Mechanism-based PKPD modelling platform. Three pharmaceutical companies that are members of this mechanism-based PKPD platform, namely, Janssen Research and Development- Belgium, Merck Sharp & Dohme Limited- the Netherlands and Pfizer Global Research and Development – USA, contributed the data used in this analysis. The data for D₂RO-PANSS analysis included the individual-level pharmacokinetic (PK; plasma concentrations) and PD (PANSS) data from 4999 patients. The APs included in the D₂RO-PANSS analysis were haloperidol, risperidone, olanzapine, ziprasidone, and paliperidone. The data for the D₂RO-EPS included PK and EPS-related AEs data (n=2630) that were reported spontaneously by patients over the study period. The important AEs documented were akathisia, hyperkinesia, dystonia, Parkinsonism, tardive dyskinesia, hypokinesia, and tremor. The model was developed without discriminating between the different types of EPS AEs. The APs included in D₂RO-EPS analysis were haloperidol, olanzapine, paliperidone, ziprasidone, and JNJ-37822681. Table 1 summarizes the trial designs of the APs that were used in this study. In vitro dissociation rate constants for APs at the human cloned dopamine D₂ and 5-HT₂A receptors and other relevant in vitro properties such as human plasma/brain protein binding information were collected from literature.[3,8-13]

**Pharmacokinetics**
Population PK parameters (clearance; CL/F) were obtained either from models developed in-house or from models published in the literature.[14-17] Patient-specific steady-state concentration (Cₜₚ) was calculated using the dosing regimen and the empirical Bayesian estimate of clearance (CL/F) obtained by fitting the PK model to the measured plasma concentrations in the NONMEM VII software.[18] For patients in whom pharmacokinetics were not assessed or available, the population PK parameter estimates of CL/F were used for the predictions of Cₜₚ. The predicted individual Cₜₚ were then used to predict the D₂RO of the drugs, which were subsequently linked to the time-course of the PANSS or EPS severity levels. Cₜₚ and D₂RO were set at zero for the placebo treatment arms.

**Dopamine D₂ Receptor Occupancy**
Individual D₂RO levels were predicted for the patient population (in whom the PANSS and EPS data were available) treated with different APs. Three different methods, empirical to semi-mechanistic in nature, were utilized.
Method I: Human D₂RO predictions based on PET Kᵰ values
In method I, an Eᵢₘₐₓ model as shown in Eq (1) was used to predict D₂RO.

\[
D₂RO = \frac{D₂RO_{max} \times C_{ss}}{(K_d + C_{ss})} \tag{Eq. 1}
\]

Where D₂RO is the model predicted D₂ receptor occupancy, C_{ss} is the predicted steady-state concentration, and K_d is the apparent dissociation constant, which is the plasma concentration required to occupy 50% of the available brain D₂ receptors at steady state. D₂RO_{max} is the maximal receptor occupancy that can be achieved. D₂RO_{max} and K_d can be estimated by fitting Eq. (1) to a series of D₂RO data measured by PET at different plasma concentrations of the AP drug. D₂RO_{max} was fixed to 100% assuming that the AP drug can occupy all available dopamine D₂ receptors. Once the K_d value of the drug is known, it is possible to calculate the time course for D₂RO for each patient from the steady-state plasma concentration of the drug. In this approach, each subject’s calculated C_{ss} was converted into D₂RO based on the parameters of the Eᵢₘₐₓ model (Kᵰ) that were reported in the literature \[10,19\] (see Table 2). The literature K_d values were in line with the values that were obtained by fitting the literature data (e.g. paliperidone) via non-linear mixed effects modelling.

Method II: Human D₂RO predictions using a dynamic k_{on}-k_{off} PKPD model
The Bayesian modelling approach in NONMEM was utilized to estimate the receptor binding parameters, such as k_{on}, k_{off}, and K_d, using D₂RO data from PET studies where \[^{[11C]} \text{raclopride}\] was used as the radioligand. An earlier developed physiology-based PKPD model structure\[^{[20,21]}\] was used to predict the D₂RO time profile of different APs by accounting for their distribution in the brain and association to and dissociation from D₂-receptors in the striatum. As shown in Figure 1b, this model consists of the following brain compartments: brain-vascular, brain-extravascular, striatum-free, and striatum-bound. The PK model-predicted plasma C_{ss} was used as an input to the brain-vascular compartment, which is assumed to be connected to the central compartment by the human cerebral blood flow. From the brain-vascular compartment, only the unbound drug crosses the blood-brain barrier (BBB), and is transported into the brain-extravascular compartment; this process is governed by the brain-extravascular clearance (CL_{bev}). Furthermore, the drug is rapidly transported from the brain-extravascular compartment to the striatal compartment where it can reversibly bind to the D₂ receptors. The receptor association and dissociation processes were described using k_{on} as the receptor association rate constant (nM⁻¹h⁻¹), and k_{off} as the receptor dissociation rate constant (h⁻¹). K_d (nM) can be estimated or derived using the relationship (K_d = k_{off}/k_{on}). Dopamine D₂ receptor density in striatum was parameterized as B_{max} (nM) and assumed to be equal to 28 nM.\[^{[22]}\] The volumes of brain-vascular and brain-extravascular compartments were assumed to be equal to the physiological values in human: 0.15 L and 1.4 L, respectively.\[^{[23]}\] The volume
Table 1. Overview of clinical trials in subjects with schizophrenia included in the development of the clinical translational PKPD model

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Trial Phase</th>
<th>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>
<th>EPS Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCH-303</td>
<td>2004</td>
<td>III</td>
<td>6 weeks</td>
<td>Oral/QD</td>
<td>Acute</td>
<td>Paliperidone ER 6,9,12 mg,</td>
<td>373</td>
<td>93 (0.6)</td>
<td>-19.5</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Olanzapine 10 mg</td>
<td>128</td>
<td>94 (0.9)</td>
<td>-19.9</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>125</td>
<td>93 (1)</td>
<td>-4.1</td>
<td>54</td>
<td>8</td>
</tr>
<tr>
<td>SCH-304</td>
<td>2004</td>
<td>III</td>
<td>6 weeks</td>
<td>Oral/QD</td>
<td>Acute</td>
<td>Paliperidone ER 6,12 mg,</td>
<td>219</td>
<td>92 (0.8)</td>
<td>-16.4</td>
<td>52</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Olanzapine 10 mg</td>
<td>105</td>
<td>94 (1.2)</td>
<td>-18.1</td>
<td>52</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>101</td>
<td>94 (1.2)</td>
<td>-7.6</td>
<td>66</td>
<td>6</td>
</tr>
<tr>
<td>SCH-305</td>
<td>2004</td>
<td>III</td>
<td>6 weeks</td>
<td>Oral/QD</td>
<td>Acute</td>
<td>Paliperidone ER 3,9,15 mg,</td>
<td>356</td>
<td>93 (0.7)</td>
<td>-16.8</td>
<td>36</td>
<td>21</td>
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<td></td>
<td>Olanzapine 10 mg</td>
<td>125</td>
<td>92 (1.1)</td>
<td>-18.1</td>
<td>30</td>
<td>7</td>
</tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>Placebo</td>
<td>118</td>
<td>93 (1.1)</td>
<td>-2.9</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>INT-2</td>
<td>1989</td>
<td>III</td>
<td>8 weeks</td>
<td>Oral/BID</td>
<td>Chronic</td>
<td>Risperidone 0.5, 2, 4, 6, 8 mg</td>
<td>1136</td>
<td>90 (0.5)</td>
<td>-16.4</td>
<td>25</td>
<td>NA</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Haloperidol 5 mg</td>
<td>226</td>
<td>87 (1.1)</td>
<td>-14.8</td>
<td>28</td>
<td>NA</td>
</tr>
<tr>
<td>INT-3</td>
<td>1992</td>
<td>III</td>
<td>8 weeks</td>
<td>Oral/BID</td>
<td>Chronic</td>
<td>Risperidone 1, 3, 5, 8 mg,</td>
<td>335</td>
<td>91 (1.0)</td>
<td>-11.7</td>
<td>45</td>
<td>NA</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Haloperidol 10 mg</td>
<td>82</td>
<td>92.5 (2.0)</td>
<td>-5.0</td>
<td>60</td>
<td>NA</td>
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<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>83</td>
<td>91 (1.9)</td>
<td>3.5</td>
<td>70</td>
<td>NA</td>
</tr>
<tr>
<td>128-114</td>
<td>1994</td>
<td>III</td>
<td>6 weeks</td>
<td>Oral/BID</td>
<td>Acute</td>
<td>Ziprasidone 40, 80 mg</td>
<td>210</td>
<td>95 (1.5)</td>
<td>-14.6</td>
<td>42</td>
<td>26</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>92</td>
<td>93.5 (2.3)</td>
<td>-6.5</td>
<td>51</td>
<td>20</td>
</tr>
<tr>
<td>128-115</td>
<td>1995</td>
<td>III</td>
<td>6 weeks</td>
<td>Oral/BID</td>
<td>Acute</td>
<td>Ziprasidone 20,60,100 mg</td>
<td>251</td>
<td>90 (1.0)</td>
<td>-8.7</td>
<td>45</td>
<td>29</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Haloperidol 10 mg</td>
<td>85</td>
<td>94 (1.8)</td>
<td>-15.0</td>
<td>44</td>
<td>59</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>83</td>
<td>91 (1.8)</td>
<td>-0.4</td>
<td>67</td>
<td>20</td>
</tr>
<tr>
<td>128-303</td>
<td>1995</td>
<td>III</td>
<td>54 weeks</td>
<td>Oral/BID</td>
<td>Chronic</td>
<td>Ziprasidone 20,40,80 mg</td>
<td>219</td>
<td>83 (1.2)</td>
<td>-6.6</td>
<td>55</td>
<td>NA</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>75</td>
<td>88 (2.2)</td>
<td>-0.7</td>
<td>81</td>
<td>NA</td>
</tr>
<tr>
<td>128-307</td>
<td>1997</td>
<td>III</td>
<td>54 weeks</td>
<td>Oral/QD</td>
<td>Chronic</td>
<td>Ziprasidone 40,60 mg</td>
<td>126</td>
<td>90 (1.3)</td>
<td>-2.4</td>
<td>53</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>64</td>
<td>87.5 (2.1)</td>
<td>8.5</td>
<td>75</td>
<td>NA</td>
</tr>
<tr>
<td>SCH-2002</td>
<td>2009</td>
<td>II</td>
<td>6-12 weeks</td>
<td>Oral/BID</td>
<td>Acute</td>
<td>JNJ-37822681, 10, 20, 30 mg</td>
<td>301</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Olanzapine 15 mg (QD)</td>
<td>90</td>
<td>92 (1.2)</td>
<td>-25.7</td>
<td>22</td>
<td>15</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>98</td>
<td>90.4 (1.0)</td>
<td>-4.8</td>
<td>46</td>
<td>6</td>
</tr>
<tr>
<td>LMU</td>
<td>NA</td>
<td>Open</td>
<td>4 weeks</td>
<td>Oral/QD</td>
<td>Acute</td>
<td>Haloperidol 2.5-40 mg</td>
<td>80</td>
<td>106 (2.4)</td>
<td>-41.8</td>
<td>42</td>
<td>95</td>
</tr>
</tbody>
</table>

ROA: Route of Administration, QD: Once Daily; BID: Twice Daily; SE: Standard Error; *Mean change in PANSS from baseline using last observation carried forward (LOCF); NA: Not Applicable; # subjects corresponds to PANSS data
of striatum-free and striatum-bound compartments was assumed to be equal to 0.15 L.\[^{[23]}\] The clearance from the brain-vascular compartment was assumed to be equal to the cerebral blood flow in humans, which is 36 L/h.\[^{[24,25]}\] The brain-extravascular and striatum-free compartments were assumed to be equilibrating rapidly. This was achieved by fixing the clearance between brain-extravascular and striatum-free compartments to a high value. In addition, an active efflux clearance (CL\(_{\text{efflux}}\)) and active influx clearance (CL\(_{\text{influx}}\)) component between brain-vascular and brain-extravascular compartments were included in this model to accommodate for active drug transport into or from the brain, where appropriate.

The Bayesian modelling approach has been shown to be a useful tool when the data carries little information.\[^{[26]}\] In such cases, this approach allows the use of informative priors (a prior is the distribution of a parameter based on previous information) in the model. In our analysis, informative prior distributions for K\(_d\) were derived from human \textit{in vivo} PET studies after correcting for molecular weight and plasma protein binding of the drug. The prior distribution information for other parameters was based on the results of preclinical translational work.\[^{[27]}\] The k\(_{\text{on}}\)-k\(_{\text{off}}\) model was then fitted to the available D\(_2\)RO data in order to obtain parameter estimates. The model parameters estimated by this model were CL\(_{\text{efflux}}\), CL\(_{\text{influx}}\), K\(_d\), k\(_{\text{off}}\), CL\(_{\text{bev}}\), and residual unexplained error (RUV).

For all drugs, prediction of the D\(_2\)RO using the Bayesian fitting procedure was performed and the predicted D\(_2\)RO was plotted and compared graphically with the observed D\(_2\)RO data (results not shown) to ascertain the predictive power of the k\(_{\text{on}}\)-k\(_{\text{off}}\) model. Simulations based on the k\(_{\text{on}}\)-k\(_{\text{off}}\) model parameters (as shown in Table 2), were carried out to predict the D\(_2\)RO for patients where the PANSS and EPS data were available.

\textbf{Method III: Prediction of endogenous dopamine release and its D\(_2\)RO based on \textit{in vitro} information}

Method III was undertaken to test the hypothesis of improvement in the negative symptoms and lower EPS occurrence rates by ATAPs. It was reported that these properties were due to the higher affinities to 5-HT\(_{2A}\) receptors than to D\(_2\) receptors. In addition, the 5-HT\(_{2A}\) antagonistic property of ATAPs leads to an increase in endogenous dopamine release allowing to elicit its normal function in the prefrontal cortex and the striatum. In this method, D\(_2\)RO of endogenous dopamine in the presence of APs was used as a driving force for the change in PANSS scores from baseline instead of the D\(_2\)RO of the APs themselves. By this means, one could quantify the level of endogenous dopamine required to be present at the different dopaminergic pathways (for instance, for the improvement in the negative symptoms, a higher dopaminergic activity at the meso-cortical pathway seems to be important). \textit{In vitro} dissociation constant values from D\(_2\) and 5-HT\(_{2A}\) receptors, unbound plasma and brain fraction, andCss of the different APs were used\[^{[8]}\] to quantify the D\(_2\)RO of endogenous dopamine in the presence and absence of APs.
Table 2: *In vitro, in vivo*, physiological values and model parameter estimates used in human D₂RO predictions.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Haloperidol</th>
<th>Olanzapine</th>
<th>Paliperidone</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
<th>JNJ-37822681</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population Pharmacokinetic Model: $C_{ss} = [\text{Dose}/\tau/(CL/F)]$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CL/F$ (L/h) (% RSE)</td>
<td>88 (6)</td>
<td>21.7 (3)</td>
<td>14.1 (3)</td>
<td>4.66 (9)*</td>
<td>54.3 (4)</td>
<td>27.1 (4)</td>
</tr>
<tr>
<td>Method I: Human D₂RO predictions based on human PET Kd values (assuming 100% ROmax)</td>
<td></td>
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<tr>
<td>Apparent $K_a$ (ng/ml)</td>
<td>0.56</td>
<td>11.7</td>
<td>6.65</td>
<td>8.64</td>
<td>33.2</td>
<td>14.9</td>
</tr>
<tr>
<td>Method II: Dynamic $k_{on}/k_{off}$ model</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>$CL_{influx}$ (L/h)</td>
<td>23.8 (16)</td>
<td>3.01 (7)</td>
<td>52.4 (51)</td>
<td>11.5 (44)</td>
<td>26.6 (51)</td>
<td>21.3 (1)</td>
</tr>
<tr>
<td>$K_a$ (nM)</td>
<td>0.395 (30)</td>
<td>0.842 (52)</td>
<td>1.23 (34)</td>
<td>2.28 (31)</td>
<td>2.12 (16)</td>
<td>5.7 (2)</td>
</tr>
<tr>
<td>$k_{off}$ (h⁻¹)</td>
<td>1.72 (42)</td>
<td>1.22 (37)</td>
<td>0.361 (45)</td>
<td>1.32 (46)</td>
<td>5.59 (7)</td>
<td>26.3 (1)</td>
</tr>
<tr>
<td>$CL_{efflux}$ (L/h)</td>
<td>130 (38)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Metabolite-CL (L/h)</td>
<td>-</td>
<td>-</td>
<td>106 (47)</td>
<td>57.4 (40)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Metabolite -CL efflux (L/h)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>64.1 (40)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RUV-D, RO (%)</td>
<td>18.5</td>
<td>59.6</td>
<td>9.5</td>
<td>16.2</td>
<td>1.37</td>
<td>1</td>
</tr>
<tr>
<td>Method III: Dopamine release model using <em>in vitro</em> receptor pharmacology data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraction unbound in plasma</td>
<td>0.07</td>
<td>0.0800</td>
<td>0.253</td>
<td>0.12</td>
<td>0.019</td>
<td>0.123</td>
</tr>
<tr>
<td>Fraction unbound in brain</td>
<td>0.011</td>
<td>0.034</td>
<td>0.0755</td>
<td>0.0699</td>
<td>0.0170</td>
<td>0.03</td>
</tr>
<tr>
<td><em>In vitro</em> D₂, Ki (nM)</td>
<td>0.40</td>
<td>2.7</td>
<td>2.0</td>
<td>2.1</td>
<td>1.2</td>
<td>47.3</td>
</tr>
<tr>
<td><em>In vitro</em> 5-HT₂A, Ki (nM)</td>
<td>46</td>
<td>1.6</td>
<td>0.16</td>
<td>0.16</td>
<td>3.3</td>
<td>2896</td>
</tr>
<tr>
<td>Endogenous dopamine synthesis</td>
<td>120 nM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$K_a$ value for dopamine</td>
<td>300 nM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RSE – relative standard error; RUV- residual unexplained variability; $CL_{influx}$ – influx clearance at BBB; $CL_{efflux}$ – efflux clearance at BBB; $CL_{bev}$ – passive clearance across BBB. *clearance value for active moiety
Fig. 1. Brief overview of methods used for predicting the $D_2$RO
Where $\Phi_{e0}$ and $C_{e0}$ are the % D$_2$RO of endogenous dopamine and the concentration of endogenous dopamine in the absence of drug treatment, respectively.$^{[28]}$ $K_{de}$ is the \textit{in vitro} dissociation constant of dopamine for the D$_2$ receptors.$^{[29]}$

$$\Phi_e = \frac{C_e}{C_e + K_{de} (1 + C_R / K_{d_{D2}})} \times 100 \quad (\text{Eq. 3})$$

In Eq (3), $\Phi_e$ is the % D$_2$RO of endogenous dopamine in the presence of drug; $C_e$ is the concentration of endogenous dopamine in the presence of drug (obtained from Eq (6)). $C_R$ and $K_{d_{D2}}$ represent the concentration of unbound drug in the vicinity of D$_2$ receptors and the dissociation constant of the AP drug from the D$_2$ receptors, respectively.

$$\Phi_{D2} = \frac{C_R}{C_R + K_{d_{D2}} (1 + C_e / K_{de})} \times 100 \quad (\text{Eq. 4})$$

$\Phi_{D2}$ is the % D$_2$RO of AP drug in the presence of endogenous dopamine

$$\Phi_{5HT} = \frac{C_R}{C_R + K_{d_{5HT}}} \times 100 \quad (\text{Eq. 5})$$

$\Phi_{5HT}$ is the % 5-HT$_{2A}$RO of AP drug; $K_{d_{5HT}}$ is the dissociation constant of an AP drug from the 5-HT$_{2A}$ receptors.

Assuming that the release of endogenous dopamine in the dopaminergic pathways by the APs is proportional to the 5-HT$_{2A}$RO of the AP, $C_e$ in the Eq (3) can be expressed by the following equation (i.e. assumed to be a simple linear function).

$$C_e = C_{e0} + C_{emax} \times \Phi_{5HT} / 100 \quad (\text{Eq. 6})$$

where $C_{e0}$ is the endogenous dopamine level at normal physiological conditions (120 nM). $C_{emax}$ is a model parameter that represents the maximum increase in concentration of endogenous dopamine in relation to 5-HT$_{2A}$ binding ($\Phi_{5HT}$) at the prefrontal cortex or at the striatum. The predicted $C_e$ based on Eq (6) is used in Eq (3) to calculate the % D$_2$RO of endogenous dopamine.

**D$_2$RO-PANSS Model**

The PKPD model structure to link predicted human D$_2$RO (methods I and II) to the PANSS scores is shown in Eq (7):
LINKING RECEPTOR OCCUPANCY OF ANTIPSYCHOTICS TO EFFICACY AND SAFETY

The Weibull placebo model describes the change of the PANSS score from baseline following the placebo treatment, which eventually reaches a plateau. $P_{\text{max}}$ is the maximum placebo effect, TD is the time to reach 63.2% of the maximum effect, and POW is the shape parameter.

An $E_{\text{max}}$ model was used to quantify the drug effect, which was assumed proportional to the placebo effect. The derivation of the equations that were used to describe the relationship between $C_{ss}$, $D_{2\text{RO}}$, and the drug effect is shown in appendix A. $E_{\text{max}}$ is the maximum drug effect. $RO_{50}$ is the parameter that describes the steady-state $D_{2\text{RO}}$ required to achieve half of $E_{\text{max}}$. KT is a rate constant associated with the time required to achieve the maximum drug effect. Q and $Q_{50}$ are a function of RO and $RO_{50}$ as shown in the drug effect model of Eq (7). The Q transformation allows Q to have a value from zero to infinity for $D_{2\text{RO}}$ from 0 to 100%.

For both the $D_{2\text{RO}}$-PANSS and $D_{2\text{RO}}$-EPS model (see $D_{2\text{RO}}$-EPS model section below), an $E_{\text{max}}$ model with a single $E_{\text{max}}$ parameter for all drugs was applied, assuming no observed differences in $E_{\text{max}}$ between the different APs. As an alternative, to address the observed differences in the drug effect for the different APs, an $E_{\text{max}}$ model with a different $E_{\text{max}}$ value for each drug was also considered. The % bias for the model parameters of these two models were estimated using the stochastic simulation and estimation method in NONMEM via PsN interface. The inter-individual variability (IIV) for the model parameters and a residual unexplained variability (RUV) were also estimated.

Using the estimates of the $D_{2\text{RO}}$-PANSS model parameters, the steady-state effective $D_{2\text{RO}}$ (Eff$_{D2\text{RO}}$) necessary to reach a 30% reduction in the PANSS scores from baseline were computed for each drug using the following equation (8):

$$\text{Eff}_{D2\text{RO}} = \frac{Q \times 100}{1 + Q}; \text{where } Q = \frac{Q_{50}}{\left(\frac{E_{\text{max}}}{\text{PANSS}} \cdot \frac{1}{1 - BL \cdot (1 - P_{\text{max}})} \right)}$$

(Eq. 8)

Approximately 64% of the reported studies in the literature calculated the percentage change in PANSS from baseline score without 30 points correction, which may lead to erroneous results. It has been recently recommended to subtract 30 PANSS points while calculating the % change in PANSS score from baseline, as 30 is the lowest possible value of PANSS, since each item is rated between...
1 and 7. Therefore, the effective $D_2$RO was calculated under two circumstances. First, as the % reduction of PANSS scores from baseline with subtracting 30 points: 

$$\% \text{ change in PANSS} = \frac{\text{PANSS} - \text{Baseline PANSS}}{\text{Baseline PANSS} - 30} \times 100,$$

and secondly, without subtracting for 30 points: 

$$\% \text{ change in PANSS} = \frac{\text{PANSS} - \text{Baseline PANSS}}{\text{Baseline PANSS}} \times 100.$$ 

Simulations were performed to quantify the uncertainty in the $D_2$RO-PANSS response curve. For this exercise the covariance matrix of the $D_2$RO-PANSS model parameters, which describes the uncertainty and correlations in the parameter estimates, was used for estimating the confidence intervals (CIs) around the typical trend. 

Method III was undertaken to test the hypothesis of improvement in the negative symptoms by the extent of dopamine release owing to $5-HT_{2A}$ antagonism in the prefrontal cortex. In this model, the drug effect was added as an inhibitory response, where the clinical effect is decreasing with increasing $D_2$RO by endogenous dopamine as shown in Eq (9).

$$\text{Drug effect} = E_{\text{max}} \times \left(1 - \frac{Q^y}{(Q_{50}^y + Q^y)}\right) \times (1 - e^{-K\times t})$$

(Eq. 9)

where $Q = \frac{\Phi_e}{100 - \Phi_e}$; $Q_{50} = \frac{\Phi_{e50}}{100 - \Phi_{e50}}$.

Where $\Phi_e$ is the % $D_2$RO of endogenous dopamine in the presence of drug and $\Phi_{e50}$ is the $D_2$RO of endogenous dopamine at 50% of the maximum drug effect.

**$D_2$RO-EPS Model**

An earlier developed compartmental Markov model structure was used to describe the probability of EPS incidence as a function of model predicted $D_2$RO of APs. EPS compartmental model structure with possible transitions (no EPS, mild EPS and pooled moderate/severe, defined as compartment 1, 2, and 3, respectively). Eq (10) was used to link the model predicted $D_2$RO (using method I and II) to EPS.

$$\text{KF}_{xy} = \text{Base}_{xy} \times e^{- (k_{xy} \times \text{time})} \times \exp[(E_{\text{max}} \times Q^y) / (Q_{50}^y + Q^y)]$$

(Eq. 10)

$$\text{KB}_{xy} = \text{Base}_{xy} \times e^{- (k_{xy} \times \text{time})}$$

(Eq. 10a)

where $Q = RO / (100 - RO_{50})$; $Q_{50} = RO_{50} / (100 - RO_{50})$.

$\text{KF}_{xy}$ is the forward transition probability rate constant at a given time and treatment; $\text{KB}_{xy}$ is the backward transition probability rate constant at time t;
Base_{xy} is the transition probability rate constant at the start of the study; \( x \): presents EPS state; \( y \) is the future EPS state; \( k_{xy} \) is the transition rate constant depicting EPS occurrence with time; \( t_{1/2} \) is the half-life describing the change in \( KF_{xy} \) or \( KB_{xy} \) with time. Drug Effect is the effect of AP drug on \( KF_{xy} \); \( E_{max} \): represents the maximum drug effect on the transition rate from state \( x \) to state \( y \); \( RO_{50} \) is the model parameter that corresponds to D\(_2\)RO required for 50% of the \( E_{max} \) effect (for more details see Chapter 9; Pilla Reddy et al.\(^{[34]}\) The drug effect was added only to the forward rate transitions constants (\( KF_{12} \) and \( KF_{23} \)). The level of D\(_2\)RO at which the rate of EPS occurrence increases was calculated from the D\(_2\)RO-EPS model.

In method III, the extent of the EPS was related linearly \[^8\] to the degree of the dopamine release using equations 11 and 12.

\[
\begin{align*}
\text{EPS} &= \alpha \times \left( \Phi_{e0} - \Phi_e \right)/\Phi_{e0} \\
C_e &= C_{e0} + C_{emax} \times \Phi_{5HT}/100
\end{align*}
\]

(Eq. 11)

(Eq. 12)

where \( \alpha \) is the scaling factor for the EPS (i.e. the extent of EPS induced by APs is proportional to the rate of decrease in D\(_2\)RO of endogenous dopamine); \( \Phi_{e0} \) and \( \Phi_e \) are the % D\(_2\)RO of endogenous dopamine in the absence and in the presence of drug, respectively. \( C_{e0} \) is the endogenous dopamine level at normal physiological conditions (120 nM). \( C_{emax} \) is a model parameter that represents the maximum increase in concentration of endogenous dopamine in relation to 5-HT\(_{2A}\) binding (\( \Phi_{5HT} \)) in the striatum. The EPS indices for APs at different doses were calculated using Eq (11).

**Model Evaluation**

Monte-Carlo simulations were used as a model evaluation tool to check the predictability of the model. Simulations were performed for the PKPD model by simulating 1000 datasets identical in structure and covariate values to the original dataset. For the D\(_2\)RO-EPS model the lower and upper prediction intervals of the proportions of patients at each EPS state (no EPS, mild and moderate) at each planned visit or observation were constructed using 100 simulated replicates of the initial dataset and compared with the corresponding observed proportions. Corresponding visual predictive check plots (VPCs) were constructed both for PANSS scores and for EPS severity data.

**RESULTS**

Individual post-hoc values of CL/F from the drug-specific PK model were used to calculate the \( C_e \) for each individual. Subsequently, D\(_2\)RO was predicted using three different methods as described in the Methods section. The *in vitro* and *in vivo* PK, and PKPD model parameter estimates for the various drugs and the
values for the endogenous dopamine synthesis and receptor affinity that were used in human D$_2$RO predictions are shown in Table 2. The predicted D$_2$RO levels were linked to the time course of PANSS scores and the severity levels of EPS using the PKPD models as described in the methods section.

**D$_2$RO-PANSS model**

The estimated parameter values (with % RSE) of the D$_2$RO-PANSS model using the three methods I, II, and III are shown in Table 3. There was no statistically significant difference in NONMEM OFV observed between these three models. The model parameters were found to be similar between methods I and II. The PKPD models (methods I and II) assume no observed differences in Emax between the APs and hence estimate a single Emax parameter. We also explored a model (method I) with different, drug specific Emax parameters, which resulted in a marginal drop of NONMEM OFV (-29 units with four additional parameters) when compared to single E$_{\text{max}}$ model. A model with a single E$_{\text{max}}$ resulted in a lower % bias (<20%) than a model with different E$_{\text{max}}$ values (data not shown).

With method III, the estimate of dopamine release in response to AP drug treatment was found to be different when linked to the PANSS totalscore (1940 nM) and PANSS positive subscale (677 nM). However, a model with linking dopamine D$_2$RO to the PANSS negative subscale resulted in a parameter identifiability problem. The D$_2$RO of endogenous dopamine at 50% of the maximum drug effect (Φe$_{50}$) was found to be 61% and 32%, respectively for the PANSS total and PANSS positive scale (data not shown).

Covariates for the placebo effect (disease condition, study duration, study year, geographic region) were also taken into account in this model. Previously, we demonstrated that dropouts from a study did not influence the estimation of the PKPD model parameters. However, it was shown to be important when designing a new clinical trial via simulations.$^{[16,30]}$ Figure 2a shows the VPCs for the D$_2$RO-PANSS model (Method I) after accounting for the dropouts (via a dropout model-based last observed PANSS score), indicating that the D$_2$RO-PANSS model adequately describes the time course of the PANSS scores.

Effective D$_2$ROs were calculated for the different drugs and presented in Table 5. The Eff$_{D2RO}$ window for a 30% reduction in PANSS scores from baseline was in the range of 50-69%. Simulations including uncertainty in the parameter estimates (CL/F, baseline PANSS, P$_{\text{max}}$, E$_{\text{max}}$, RO$_{50}$) were performed for the D$_2$RO-PANSS and exposure-PANSS models. The plot of the change in PANSS from baseline vs. D$_2$RO (Figure 3a) and dose (Figure 3b) of APs shows that the clinical effect increases with increasing D$_2$RO or dose. For some drugs (risperidone, paliperidone and ziprasidone), no further improvement in efficacy with increasing dose was observed.
**D₂RO-EPS Model**

An earlier developed Markov model\[^{34}\] was extended by including the mechanistic components like D₂RO predictions based on $k_{on} - k_{off}$ rates of the APs (method II) and the dopamine release (method III). The estimated parameter values (with %RSE) of the D₂RO-EPS model using a single Emax parameter are shown in Table 4. The model with dopamine release (method III) was capable to satisfactorily predicting the proportions of the patients experiencing each of the EPS states across time, except for JNJ-37822681 (Figure 2b). The model with inclusion of endogenous dopamine release (method III) resulted in a lower NONMEM OFV. Figure 4 (left panel) depicts the relationship between the model predicted D₂RO of endogenous dopamine, D₂RO of AP drug, and the 5-HT\(_{2A}\)RO vs. doses that were tested in a trial. The 5-HT\(_{2A}\)RO was lowest for haloperidol and JNJ-37822681. However, JNJ-37822681 exhibited less EPS side effects, which may be explained by its fast $k_{off}$ rates (26.3 h\(^{-1}\)). The right panel of figure 4 shows the EPS index for the different APs. It was evident that haloperidol, even at lower doses (≤ 12 mg/day), resulted in a higher EPS incidence than the ATAPs.

**Table 3.** Parameter estimates obtained with the three different methods to model the D₂RO-PANSS relation.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
<th>Parameters (% RSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameters</strong></td>
<td><strong>Description</strong></td>
<td><strong>Method I</strong></td>
</tr>
<tr>
<td>Baseline PANSS (BL)</td>
<td>Baseline PANSS score</td>
<td>91.5 (1)</td>
</tr>
<tr>
<td>$P_{\text{max}}$</td>
<td>Placebo effect</td>
<td>0.0728 (7)</td>
</tr>
<tr>
<td>KT (1/day)</td>
<td>Delay in drug effect</td>
<td>0.047 (2)</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>Maximum drug effect</td>
<td>0.254 (1)</td>
</tr>
<tr>
<td>RO(_{50})</td>
<td>D₂RO to achieve half of $E_{\text{max}}$</td>
<td>56.2 (1)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Shape parameter</td>
<td>1 FIX</td>
</tr>
<tr>
<td>$\Phi_{\text{tp50}}$</td>
<td>Dopamine D₂RO to achieve half of $E_{\text{max}}$</td>
<td>-</td>
</tr>
<tr>
<td>$C_e$</td>
<td>Endogenous dopamine release (nM)</td>
<td>-</td>
</tr>
<tr>
<td>IIV $P_{\text{max}}$ (SD)</td>
<td>Additive inter-individual variability for $P_{\text{max}}$</td>
<td>16 (2)</td>
</tr>
<tr>
<td>IIV BL (CV %)</td>
<td>Exponential inter-individual variability for baseline PANSS</td>
<td>21 (2)</td>
</tr>
<tr>
<td>IIV $E_{\text{max}}$ (SD)</td>
<td>Additive inter-individual variability for $E_{\text{max}}$</td>
<td>25 (4)</td>
</tr>
<tr>
<td>RUV as SD (additive)</td>
<td>Residual variability for the PANSS score</td>
<td>8.3 (1)</td>
</tr>
<tr>
<td>OFV</td>
<td>NONMEM Objective Function Value</td>
<td>184075</td>
</tr>
</tbody>
</table>

PANSS data was not available for JNJ-37822681. Hence, JNJ-37822681 was not included in the D₂RO-PANSS model.
a)
Fig. 2. (a) Visual predictive checks for the adequacy of the D_{2}RO-PANSS model (Method I). Shaded area depicts the 95% prediction interval for the simulated PANSS and black solid line represents median PANSS scores from the original data. The grey shaded areas represent the 95% confidence intervals of the corresponding 2.5^{th}, 50^{th} and 97.5^{th} percentiles of the simulated data. The black dashed line represents the 2.5^{th}, 97.5^{th} percentiles of the observed data. (b) Visual predictive checks showing the proportions of patients at each EPS state on planned visits in the observed data (red lines) with the corresponding 95% prediction intervals (light blue region) as constructed from 100 simulations for different antipsychotics using the D_{2}RO-EPS model (method III).
DISCUSSION

Brain $D_2$RO of AP drugs of 60–80% is a prerequisite for an optimal clinical effect in schizophrenic patients. Therefore, it is important to select a dose and dosing regimen that will provide an adequate exposure that subsequently maintains the target $D_2$RO in the range of 60-80%.

Recently we have shown a quantitative relationship between plasma AP drug levels and clinical efficacy and EPS side effects using a PKPD model. The predictive power of this PKPD model may increase when it is based on parameters that are closely related to the site of drug action implying that a further improvement in the conventional exposure-response models may be accomplished by integrating the RO information and the clinical effects. Therefore, the first objective of our translational work was to assess the ability of the PKPD model to predict the receptor occupancy in humans following administration of APs. Mechanism-based PKPD models combined with physiological parameters have the ability to predict human PKPD properties using prior information from in vitro and preclinical studies, followed by linking to the clinical endpoints. The second objective was to develop a PKPD modelling approach to investigate the link between predicted $D_2$RO and PANSS and EPS respectively of APs to elucidate the “occupancy window” that provides an optimal clinical efficacy with minimal adverse events. For this, we used retrospective data from clinical trials with different APs conducted during the last two decades.

Data of RO, and clinical endpoints (PANSS/EPS) in the same patients were difficult to obtain. In an attempt to overcome this limitation, we used plasma concentration, PANSS, and EPS data from different well-designed clinical trials in combination with PET imaging studies and PKPD models for determining the effective $D_2$RO and the safe $D_2$RO range.

The apparent plasma $K_d$ values for each AP drug can be obtained from PET studies. Use of these $K_d$ values to calculate $D_2$RO is a simplistic method and ideally, the unbound plasma concentration should be used for this purpose. This approach assumes a rapid equilibration of plasma and brain concentrations at the receptor sites and binding to the receptors. In many cases, these assumptions may not hold, e.g. for drugs that are P-glycoprotein substrates rapid equilibration between plasma and brain does not occur. In such cases, $k_{on}$-$k_{off}$ models can be used to estimate the true association-dissociation rate constants. Another limitation of using PET $K_d$ values is that any time delay between a plasma concentration and its corresponding $D_2$RO is usually ignored. This time delay may be ignored in case of steady state conditions or alternatively, $k_{on}/k_{off}$ or effect compartment models can be used to account for this delay.

In this study we adopted the PET Kd values that were reported from PET studies that used the most common ligand $[^{11}C]$raclopride, because different imaging methods or different methods of quantification of the radiotracer binding resulted in different Kd values (data not shown). In our analysis, only striatal
Table 4: Parameter estimates obtained with the three different methods to model the $D_2$RO-EPS relation.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
<th>Method I &lt;=Visit 4 &gt; Visit 4</th>
<th>Method II &lt;=Visit 4 &gt; Visit 4</th>
<th>Method III &lt;=Visit 4 &gt; Visit 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base$_{12}$ (day$^{-1}$)</td>
<td>Transition (no EPS to mild EPS) probability rate constant at the start of the study</td>
<td>0.0187 (8) 0.0196 (8) 0.0282 (7)</td>
<td>0.0187 (8) 0.0196 (8) 0.0282 (7)</td>
<td>0.0187 (8) 0.0196 (8) 0.0282 (7)</td>
</tr>
<tr>
<td>Base$_{21}$ (day$^{-1}$)</td>
<td>Transition (mild EPS to no EPS) probability rate constant at the start of the study</td>
<td>0.134 (7) 0.078 (10) 0.144 (7) 0.0906 (9)</td>
<td>0.134 (7) 0.078 (10) 0.144 (7) 0.0906 (9)</td>
<td>0.134 (7) 0.078 (10) 0.144 (7) 0.0906 (9)</td>
</tr>
<tr>
<td>Base$_{23}$ (day$^{-1}$)</td>
<td>Transition (mild EPS to moderate/severe EPS) probability rate constant at the start of the study</td>
<td>0.369 (15) 0.078 (10) 0.373 (15) 0.077 (10) 0.484 (14) 0.0906 (9)</td>
<td>0.369 (15) 0.078 (10) 0.373 (15) 0.077 (10) 0.484 (14) 0.0906 (9)</td>
<td>0.369 (15) 0.078 (10) 0.373 (15) 0.077 (10) 0.484 (14) 0.0906 (9)</td>
</tr>
<tr>
<td>Base$_{12}$ (day$^{-1}$)</td>
<td>Transition (moderate/severe EPS to mild EPS) probability rate constant at the start of the study</td>
<td>0.134 (7) 0.134 (7) 0.144 (7)</td>
<td>0.134 (7) 0.134 (7) 0.144 (7)</td>
<td>0.134 (7) 0.134 (7) 0.144 (7)</td>
</tr>
<tr>
<td>$t_{1/2}$ for KF$_{12}$ (days)</td>
<td>Half-life describing the change with time (no EPS to mild EPS)</td>
<td>8.9 (3) 8.9 (3) 8.9 (3)</td>
<td>8.9 (3) 8.9 (3) 8.9 (3)</td>
<td>8.9 (3) 8.9 (3) 8.9 (3)</td>
</tr>
<tr>
<td>$t_{1/2}$ for KF$_{23}$ (days)</td>
<td>Half-life describing the change with time (mild EPS to moderate/severe EPS)</td>
<td>2.7 (9) 2.7 (9) 7 (4) 2.8 (10) 9.2 (4)</td>
<td>2.7 (9) 2.7 (9) 7 (4) 2.8 (10) 9.2 (4)</td>
<td>2.7 (9) 2.7 (9) 7 (4) 2.8 (10) 9.2 (4)</td>
</tr>
<tr>
<td>$t_{1/2}$ for KB$<em>{21}$ and KB$</em>{12}$ (days)</td>
<td>Half-life describing the change with time for backward transitions</td>
<td>20 (9) 14 (10) 18 (8)</td>
<td>20 (9) 14 (10) 18 (8)</td>
<td>20 (9) 14 (10) 18 (8)</td>
</tr>
<tr>
<td>Covariate effect</td>
<td>Effect of residence in Eastern Europe on KB$<em>{21}$ and KB$</em>{12}$</td>
<td>1.08 (20) 0.89 (20) 0.89 (15)</td>
<td>1.08 (20) 0.89 (20) 0.89 (15)</td>
<td>1.08 (20) 0.89 (20) 0.89 (15)</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>$E_{\text{max}}$ represents the maximum drug effect on the transition rate from state x to state y</td>
<td>1.73 (30) 2.53 (30)</td>
<td>1.73 (30) 2.53 (30)</td>
<td>1.73 (30) 2.53 (30)</td>
</tr>
<tr>
<td>$RO_{50}$ (%)</td>
<td>$D_2$RO required for 50% of $E_{\text{max}}$ effect</td>
<td>86.5 (6) 92 (2)</td>
<td>86.5 (6) 92 (2)</td>
<td>86.5 (6) 92 (2)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Shape parameter</td>
<td>1.3 (35) 1.3 (35)</td>
<td>1.3 (35) 1.3 (35)</td>
<td>1.3 (35) 1.3 (35)</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Slope for dopamine release</td>
<td>-</td>
<td>-</td>
<td>2.25 (5)</td>
</tr>
<tr>
<td>$C_{\text{EMax}}$</td>
<td>Endogenous dopamine release (nM)</td>
<td>-</td>
<td>-</td>
<td>893 (6)</td>
</tr>
<tr>
<td>OFV</td>
<td>NONMEM Objective Function Value</td>
<td>7963</td>
<td>7895</td>
<td>7834</td>
</tr>
</tbody>
</table>

EPS data was not available for risperidone. Hence, risperidone was not included in the $D_2$RO-EPS model.
Fig. 3. Predicted $D_2$ RO and dose response of antipsychotics on PANSS total change from baseline PANSS score. The solid line reflects median predicted $D_2$ RO or dose response. The shaded area reflects uncertainty of the prediction. Black dots reflect the median value of actual outcomes from the respective trials and doses. PANSS$_{(0-6)}$ denotes % change with subtraction of 30 points and PANSS$_{(1-7)}$ denotes % change without subtraction of 30 points. Only percentage change in PANSS with 30 points correction is shown for the dose response (bottom panel).
Fig. 4. Left panel plot representing the interplay between the receptor affinities of APs and D_{2}R_{O} by endogenous dopamine (method III). Red: Antipsychotic drug’s D_{2}R_{O}; Blue: Endogenous dopamine D_{2}R_{O}; Green: Antipsychotic drug’s 5-HT_{2}R_{O}. Right panel represents the EPS index for different antipsychotics, calculated based on equation.
D$_2$RO data were utilized. Although recently, the role of D$_2$ binding in striatum and temporal cortex in clinical efficacy has been indicated\([4]\), the region of binding is of less concern in the present study, as all ATAPs that were included in our analysis exhibited a similar D$_2$RO occupancy irrespective of the region of interest\([39, 40]\).

It has been hypothesized that differences in the dissociation rate (as expressed by $k_{off}$) of APs from the D$_2$ receptor may lead to functionally different types of dopamine blockade and, thereby, differentiation in clinical effects between APs\.[9]\ To investigate this hypothesis a series of D$_2$RO measurements should be performed in patients, which may be difficult in clinical studies. However, to overcome this limitation, we used an earlier developed rat physiology-based PKPD model to predict the dopamine D$_2$RO in human striatum following the administration of different AP drugs. A Bayesian fitting procedure with prior information was used to estimate dynamic $k_{on}/k_{off}$ PKPD model parameters from sparse and limited PET PK-D$_2$RO data. This model did not include information at the 5-HT$_2A$ binding, as the PET RO information at the 5-HT$_2A$ receptor was not available.

Several studies demonstrated that ATAPs generally have a much lower affinity for D$_2$ been hypothesized to be involved in for the therapeutic effect of APs\.[41-45]\ Method III (endogenous dopamine release approach) was specifically applied.

<table>
<thead>
<tr>
<th>Approach</th>
<th>Haloperidol</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Ziprasidone</th>
<th>Paliperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Dose (mg/day)</td>
<td>PKPD</td>
<td>5.6</td>
<td>0.8</td>
<td>7.3</td>
<td>82</td>
</tr>
<tr>
<td>Effective Conc. (ng/ml)</td>
<td>PKPD</td>
<td>2.7</td>
<td>5.2</td>
<td>13.8</td>
<td>63</td>
</tr>
<tr>
<td>Effective D$<em>2$RO (%) using different E$</em>{max}$ model</td>
<td>D$_2$RO-PANSS</td>
<td>50</td>
<td>62</td>
<td>51</td>
<td>69</td>
</tr>
<tr>
<td>Effective D$<em>2$RO (%) using single E$</em>{max}$ model</td>
<td>D$_2$RO-PANSS</td>
<td>61 (Method I); 58 (Method II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D$<em>2$RO$</em>{50}$ (%) for EPS incidence</td>
<td>D$_2$RO-EPS</td>
<td>86.5 (Method I); 92 (Method II)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effective Conc = EC$_{50}/(E_{max}/(1-PANSS/(Baseline PANSS*(1-P$_{max}$))))-1)$; % change in score is given by $=PANSS -Baseline PANSS/(Baseline PANSS- 30); Effective dose (mg/day) = Effective Conc. *CL/F; Eff$_{D2RO} = Q*100/(1+Q) Q is obtained by $Q = Q_{50}/((E_{max}/(1-PANSS/(BL*(1-P_{max}))))-1)$.\[89, 103\]
to model the interplay between D₂ and 5-HT₂A receptors. Earlier, an interesting model to predict the risk of EPS by incorporating dopamine release, but using literature data was reported.[8] We extended this original concept involving the endogenous dopamine and 5-HT₂A RO for both the efficacy and safety endpoints using a larger and individual-level dataset.

With method III, dopamine release in response to 5-HT₂A binding of APs was found to be different when linked to different clinical endpoints (i.e. PANSS and EPS). A possible reason could be the different serotonin 5-HT₂A receptor expression levels at cortical and substantia nigra pathways.[46] Indeed a three-fold higher 5-HT₂A receptor expression in cortex than in striatum was reported,[46] which could explain the differences in dopamine release.

There is a debate whether ATAPs differ in clinical efficacy. We recently found that there are some differences when linking exposure to PANSS scores.[17] We extended this analysis using D₂RO as a predictor to evaluate the efficacy of a number of APs. For this, two models were considered. The first drug effect model assumes that there are observed differences in maximum drug effect between the APs and therefore, a different E_{max} value per drug was estimated. The second model assumes no differences in E_{max} between the APs and estimates a single E_{max} parameter. Results revealed that the model with different drug-specific E_{max} values resulted in a marginal drop of NONMEM OFV, indicating that both scenarios are indeed plausible. Nevertheless, the model with a single E_{max} value is more suited for predictions in support of trial optimization of new drugs for which E_{max} of the drug is not known. A single RO_{50} parameter was estimated to determine the level of D₂RO to produce a half-maximal effect, which was in the range of 53-56% (Table 3).

The EFF_{D₂RO} levels based on the model with different E_{max} values are shown in Table 5. Recently, Leucht et al.[32] and Obermeier et al.[33] suggested the need to use the correction for 30 points of PANSS score to avoid wrong interpretation of the results while calculating the % change in PANSS scores from baseline. Hence, we calculated the effective D₂RO levels for both scenarios (i.e with correction - PANSS_{(0-6)} or without correction - PANSS_{(1-7)}). The required effective D₂RO levels are in the range of 70-85% to achieve a 30% change in PANSS score from baseline without the 30 points subtraction, while it was in the range of 50-69% with subtraction of 30 PANSS points (Figure 4).

The significant positive correlation (Figure 3) between D₂RO and PANSS suggests that higher doses could be used to treat severe symptoms of schizophrenia (as seen in haloperidol pharmacotherapy).[16] However, beyond 86% of D₂RO, a steep increase in the EPS incidence was observed (Figure 5) implying that doses that yield a D₂RO of > 86% are less beneficial to the patients.

The rationale for using steady-state D₂RO was because the plasma concentrations used were average steady-state levels, as we did not have information on peak levels. It may be expected that clinical improvement in schizophrenia relate to the both steady-state D₂RO levels and peak levels. On the
contrary, EPS events might be linked to peak D₂RO levels but the time of day of onset of the event was not available for most of the compounds.

A compound-independent PKPD model using individual-level D₂RO of different compounds is suited for predictions of efficacy and safety of other drugs and designing the development of new compounds via trial simulations. For these reasons, a model with a single Eₘₐₓ and single RO₅₀ was preferred over a model with different Eₘₐₓ and RO₅₀. We also estimated separate RO₅₀ for each drug (per-compound analysis), which turned out to be in the range of (50-69 %) between drugs (results not shown). The parameter estimates of both the efficacy and safety model were precisely estimated. RO₅₀ was estimated to be 56 and 86.5% for PANSS and EPS, respectively. The estimate of RO₅₀ (from D₂RO-EPS model) of 86.5% is in accordance with the findings of other studies reporting that high D₂RO (>80% following AP drug treatment) results in a higher risk to develop EPS. Several studies seem to indicate that the dopaminergic pathway is involved in the mediation of EPS in humans. Moreover, it was reported that EPS in humans could be caused by a) slow receptor off rates (kₚₚ) or higher affinities to D₂ [47], b) low affinity to 5-HT₂ receptors [43], c) higher striatal than extrastriatal D₂RO [48], and d) low extra-synaptic binding of APs [6]. Our analysis showed that ATAPs produce a lower incidence of EPS than the high-potency TAP haloperidol even at lower doses (Figure 4; EPS index plots). The investigational drug JNJ-37822681 exhibited a lower EPS rate, probably due to its fast dissociation property from the binding site (which was also reflected in the poor VPC of JNJ-37822681 with D₂RO-EPS model using the dopamine release approach and in the left panel of Figure 4 with no change in baseline dopamine D₂RO and negligible 5-HT₂ₐ RO).

Recently, we developed a quantitative framework utilizing the preclinical information to define the optimal doses for achieving human therapeutic D₂RO. [20,21] This modelling approach was prospectively utilized in this paper to predict the D₂RO in humans and was subsequently linked to the clinical effect. This work demonstrates the benefit of an efficient and integral use of all the available information from different sources, but also provides a quantitative framework for testing a scientific hypothesis, that is, ATAPs are less prone to induce EPS or improve negative symptom control (e.g. olanzapine [36]) owing to their 5-HT₂ₐ receptor inhibition. Interestingly, the dopamine release model confirms that JNJ-37822681 is a fast kₚₚ compound which may be due to its lower affinity towards the D₂ and 5-HT₂ₐ receptors [19].

A clear benefit of the newer drugs (e.g paliperidone and JNJ-37822681) over haloperidol in terms of incidence of EPS was seen in our previous analysis. Comparing recently marketed compounds (e.g. paliperidone) with an emerging new drug (JNJ-37822681) or with the existing treatment options (ziprasidone), by using semi-mechanistic PKPD modelling approaches could enable a better understanding of these drugs at the receptor pharmacology level. Similar to clozapine and quetiapine, the lower incidence of EPS of JNJ-37822681 could be due to easier displacement of these drugs from the D₂ receptor by endogenous dopamine release.
Fig. 5. An illustration of the increase in probability of patients to experience EPS with increasing $D_2$RO occupancy using the $E_{\text{max}}$ model and the earlier reported EPS linear model. Both the linear (left panel) and $E_{\text{max}}$ (right panel) models indicate that the EPS probability steeply increases with a $D_2$RO above 80%.
Based on the EPS model, an increase in EPS occurrence rate, as a function of exposure or $D_2$RO, can be predicted. Figure 5 shows the probability of experiencing EPS as a function of $D_2$RO. It is clear from the analysis that a $D_2$RO above 80% sharply increases the incidence of EPS. A recent meta-analysis of in vivo receptor imaging data\(^4\) demonstrated that both TAPs and ATAPs produce high $D_2$RO in the temporal cortex, whereas only the TAPs produced a high $D_2$RO in the striatum. It is possible that lower levels of $D_2$RO with ATAPs, due to their affinity to other receptors, in the striatum cause some adaptive changes resulting in protection against psychotic relapses.\(^4^9\) Moreover, lower levels of $D_2$RO with ATAPs in the striatum could explain some of the differences in EPS rates between haloperidol and ATAPs.

The difference in occupancy of dopamine $D_2$ receptors with clozapine between striatal and extrastriatal regions has been reported as 'limbic selectivity'. This feature was considered one of the reasons for the low risk of EPS and a possible explanation for the effects seen on negative symptoms.\(^4^8\) However, recently it has been reported that there were less differences between striatal and extra-striatal $D_2$RO occupancy for other ATAPs that were used in this analysis.\(^3^9,4^0,5^0\) and this justifies the use of striatal $D_2$RO in this analysis.

The incidence of side effects could be a possible confounder when analyzing the correlation between AP drug plasma levels and efficacy. We did not model efficacy and safety endpoints simultaneously to account for the possible interaction between these two clinical endpoints due to the complexity of the models. However, modelling the link between efficacy with reasons of patient dropping out from a trial is in progress, which will consider efficacy, safety, and other reasons for drop out.

**CONCLUSIONS**

The relationships between $D_2$RO, PANSS, and EPS scores were elucidated using PKPD models with semi-mechanistic components and showed the qualitative and quantitative link between $D_2$RO and efficacy (PANSS) and safety (EPS) endpoints. The use of the $D_2$RO-PANSS/EPS relationship rather than plasma drug exposure-PANSS/EPS relationship allows the introduction of $D_2$RO as a compound-independent variable, which may later be used to extrapolate the $D_2$RO-PANSS/EPS relationship to new drugs with the same mechanism of action. This approach can potentially be expanded to new targets as well.

**ACKNOWLEDGMENTS**

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APPENDIX A

General equation derived from drug - receptor association and dissociation, defining receptor occupancy RO (in %) as a function of drug concentration C:

\[ \text{RO} = \frac{C}{(K_d + C)} \times 100 \]  

(A1)

The drug effect E may be described by the sigmoidal \( E_{\text{max}} \) model:

\[ E = E_{\text{max}} \times \frac{C^\gamma}{(EC_{50^\gamma} + C^\gamma)} \]  

(A2)

To relate the drug effect to receptor occupancy, equation (A2) may be modified to:

\[ E = E_{\text{max}} \times \frac{\text{RO}^\gamma}{(\text{RO}_{50}^\gamma + \text{RO}^\gamma)} \]  

(A3)

Equation (A3) may be used to relate the drug effect to receptor occupancy in PKPD modelling. However, the maximum value of RO is 100%, and therefore the maximum value of E will not reach \( E_{\text{max}} \) (except for low values of \( \text{RO}_{50} \) or high values of \( \gamma \)). This limitation can be avoided by a transformation of RO. Equation (A1) can be rewritten to:

\[ C = K_d \times \text{RO} / (100 - \text{RO}) \]  

(A4)

At 50% of the maximum effect:

\[ EC_{50} = K_d \times \text{RO}_{50} / (100 - \text{RO}_{50}) \]  

(A5)

Equation (A5) shows the relationship between \( K_d \) and \( EC_{50} \). After defining:

\[ Q = \frac{\text{RO}}{100 - \text{RO}} \]  

(A6)

\[ Q_{50} = \frac{\text{RO}_{50}}{100 - \text{RO}_{50}} \]  

(A7)

The transformation of RO to Q guarantees that E reaches \( E_{\text{max}} \) if RO approaches 100%. Substitution of equations (A4)-(A7) in equation (A2):

\[ E = E_{\text{max}} \times \frac{Q^\gamma}{(Q_{50}^\gamma + Q^\gamma)} \]  

(A8)

Equation (A8), (A6) and (A7) can be used to relate the drug effect to receptor occupancy. The transformation of RO to Q guarantees that E reaches \( E_{\text{max}} \) if RO approaches 100%. Although equations (A2) and (A8) are identical if equation (A1) applies, i.e., at equilibrium in receptor binding, equation (A8) may be used also in models where non-equilibrium conditions are considered, i.e., with models describing receptor association and dissociation using \( k_{\text{on}} \) and \( k_{\text{off}} \).
Abbreviations:
C: drug concentration; RO: receptor occupancy; Kd: equilibrium dissociation constant (Kd = koff/kon); E: drug effect; E\text{\_max}: maximum drug effect; EC\text{\_50}: drug concentration at 50% of the maximum drug effect; RO\text{\_50}: receptor occupancy at 50% of the maximum drug effect; \gamma: steepness of concentration-effect relationship; Q: transformation of RO according to equation (A6); Q\text{\_50}: transformation of RO\text{\_50} according to equation (A7)

APPENDIX B
Calculations of effective $D_2$RO (EFF $D_2$RO) to achieve targeted % change in PANSS score from baseline

PANSS scores corresponding to targeted % change in PANSS score from baseline score were calculated based on the following equation, correcting for a minimum PANSS total score of 30.

\[
\text{% change in PANSS Total} = \frac{(\text{PANSS} - \text{Baseline PANSS})}{\text{Baseline PANSS} - 30} \times 100 \quad (B1)
\]

Rearranging the above equation (B1),

\[
\text{PANSS} = -\frac{\text{% change in PANSS Total}}{100} \times (\text{Baseline PANSS} - 30) + \text{Baseline PANSS} \quad (B2)
\]

The corresponding PANSS value (B2) is obtained using the estimate of baseline PANSS from the final $D_2$RO-PANSS model and knowing the desired % change in PANSS score from baseline.

E.g. with a targeted 30% reduction from baseline with a baseline PANSS score of 90:

\[
\text{PANSS} = -(30/100) \times (90 - 30) + 90 \quad \text{will yield a PANSS score of 72.}
\]

Above calculated PANSS was then plugged into the equation describing the change in score from baseline in $D_2$RO-PANSS model:

\[
\text{PANSS} = \text{Baseline PANSS} \times (1 - \text{Placebo effect}) \times (1 - \text{Drug effect}) \quad (B3)
\]

Assuming maximum (at the end of the trial) placebo and drug effect and shape parameter to be 1, the equation (B3) becomes

\[
\text{PANSS} = \text{Baseline PANSS} \times (1 - P_{\text{max}}) \times (1 - E_{\text{max}} \times Q_{50}/(Q + Q_{50})) \quad (B4)
\]

After rearrangement of the above equation, we obtain Q, which is function of $D_2$RO,

\[
Q = Q_{50}/(E_{\text{max}}/(\text{Baseline PANSS}/(1 - P_{\text{max}})) - 1) \quad (B5)
\]
In the $D_2$RO-PANSS model, $D_2$RO was linked to PANSS score via Q transformation:

$$Q = \frac{RO}{100-RO}$$  \hspace{1cm} (B6)

Rearrange (B6) to get RO (i.e. $Eff_{D2RO}$)

$$Eff_{D2RO} = \frac{Q*100}{1+Q}$$  \hspace{1cm} (B7)

Impute the value of Q obtained from equation (B5) in equation (B7) to obtain $EFF_{D2RO}$. 
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