A quantitative systems pharmacology model for simulating OFF-Time in augmentation trials for Parkinson’s disease: application to preladenant

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Abstract
The clinical impact of therapeutic interventions in Parkinson’s disease is often measured as a reduction in OFF-time when the beneficial effects of the standard-of-care L-DOPA formulations wanes off. We investigated the pharmacodynamic interactions of augmentation therapy to standard-of-care using a quantitative systems pharmacology (QSP) model of the basal ganglia motor circuit, essentially a computer model of neuronal firing in the different subregions with anatomically informed connectivity, cell-specific expression of 17 different G-protein coupled receptors and corresponding coupling to voltage-gated ion channel effector proteins based on experimentally observed intracellular signaling. The calculated beta/gamma (b/g) power spectrum of the local field potentials in the subthalamic nucleus was previously calibrated on the clinically relevant Unified Parkinson’s Disease Rating Scale (UPDRS). When combining this QSP model with PK modeling of different formulations of L-DOPA, we calculated the b/g fluctuations over a 16 h awake period and used a weighted distance from a specific threshold to determine the cumulative liability of OFF-Time. Prediction of OFF-time with clinical observations of different L-DOPA formulations showed a significant correlation. Simulations show that augmentation with the adenosine $A_{2A}$ antagonist preladenant reduces OFF-time with 6 min for carbidopa/levodopa 950 mg 5-times daily to 37 min for 100 mg L-DOPA – 3 or 5 times daily. Exploring delays between preladenant and L-DOPA intake did not improve the outcome. Hypothetical $A_{2A}$ antagonists with an ideal PK and pharmacology profile can achieve OFF-Time reductions ranging from 9.5 min with DuoDopa to 55 min with low dose L-DOPA formulations. Combination of the QSP model with PK modeling can predict the anticipated OFF-Time reduction of novel $A_{2A}$ antagonists with standard of care. With the large number of GPCR in the model, this combination can support both the design of clinical trials with new therapeutic agents and the optimization of combination therapy in clinical practice.

Keywords OFF-time · Augmentation therapy · Adenosine · Standard-of-care · Dyskinesia

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| A1           | Adenosine 1 receptor |
| A2A          | Adenosine 2A receptor |
| AUC          | Area-under-the-curve (for PK profile) |
| cAMP         | Cyclic adenosine-mono-phosphate (intracellular second messenger) |
| GPe          | Globus Pallidus pars externa |
| GPe          | Globus Pallidus pars interna |
| MSN          | Medium spiny neurons (majority of striatal GABAergic neurons) |
| PD           | Parkinson’s disease |
| PET          | Positron emission tomography |
| PK           | Pharmacokinetics |
| Pyr          | Pyramidal neurons (located in the motor cortex) |
| QSP          | Quantitative systems pharmacology |
| Re           | Reticular neurons |
| STN          | Subthalamic nucleus |
| TC           | Thalamocortical neurons |
| UPDRS        | Unified Parkinson’s disease rating scale |

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Introduction

L-DOPA is still the standard of care for Parkinson’s Disease (PD) patients, but because of the short half-life, patients develop motor response fluctuations such as end-of-dose wearing off. The duration of these motor fluctuations is called OFF-time and greatly affect the quality of life. Traditionally, patients keep a diary of these periods over the day in 30-min intervals, but increasingly wearables are used to document these fluctuations in an objective manner. For that reason, different longer-acting formulations of L-DOPA or dopamine agonists have been developed, but they are often cumbersome and invasive or do not improve much on this readout.

To address this issue, various augmentation strategies where drugs are added to the standard-of-care have been explored with the objective of reducing OFF-time, for example with adenosine A2 antagonists [1] that act on the same pathway as most dopamine agonists. This can lead to complex pharmacodynamic interactions which would necessitate multiple clinical trials with different combinations.

In this report, we use a biophysiologically realistic Quantitative Systems Pharmacology (QSP) computer model to explore different combinations of A2A antagonists with the standard-of-care on OFF-time. This model will be calibrated against clinical data and allows the simulation of multiple clinical trial scenarios.

As an example, we present the calculation for the total OFF-time for a 16 h awake day for the last day of a 72 h simulation for combinations of the A2A antagonist preladenant with various L-DOPA formulations.

Adenosine 2A antagonism can intervene at the intracellular pathway of the D2R on the D2+MSN neurons that project into the indirect pathway [2, 3]. In addition, colocalization of the A2A-R with the A1R on presynaptic Glutamatergic afferents that stimulate the D2+MSN neurons affects the amount of Glutamate released [4].

In patients with deep brain stimulation, the ratio of power in the beta over gamma band (b/g) of local field potentials in the subthalamic nucleus (STN) is strongly correlated to clinical symptoms of bradykinesia and rigidity from the UPDRS clinical scale [5]. Therefore, we use this readout from the QSP model to predict the clinical motor phenotype.

Because of the PK profile of L-DOPA leading to fluctuating dopamine levels during treatment which were different for each formulation and treatment frequency in combination with the PK profile of preladenant, we opted for the use of a 2-dimensional beta/gamma surface or look-up table for pure computational reasons. By calculating a trajectory from the pharmacokinetic profiles associated with the specific simulation condition we can then generate time-dependent pharmacodynamic profiles of the b/g ratio.

One axis reflects the ambient dopamine level in the motor circuit that is affected by the pathological state, the placebo response and various L-DOPA formulations. This leads to modulation of both D1 and D2-R on the direct and indirect pathway. The other axis is based on the pharmacodynamic effect of adenosine A2A antagonism including the engagement of the intracellular c-AMP dependent pathway downstream of the D2R in the indirect pathway that can be modulated also with D2-preferring dopamine agonists in addition to the presynaptic impact on glutamate release.

OFF-time is defined as the duration during which the patient experiences motor fluctuations as a consequence of insufficient dopamine levels during the day. Because lower beta/gamma ratio is directly proportional to Parkinsonian motor outcome, the model readout is based on the weighted accumulated time that the subthalamic nucleus beta/gamma ratio of local field potential is above a certain threshold.

Model description

This approach combines Pharmacokinetic (PK) and Pharmacodynamic (PD) modeling in a disease relevant model of the human basal ganglia motor circuit [6] that drive network activity related to clinical symptoms. As mentioned before, the key QSP biomarker is the calculated power spectrum in the beta and gamma band of local field potentials in the subthalamic nucleus [5].

Receptor competition model

Central target engagement of the drug at a specific dose is simulated using quantitative PET imaging displacement studies with specific radiotracers in a QSP model of the dopaminergic synapse [7]. This model reflects the human dynamics of the various neurotransmitters by calibrating the presynaptic autoreceptor coupling physiology using fast cyclic voltammetry data from rodents and primates and constrain it subsequently by human imaging data. In addition, this allows the derivation of free neurotransmitter levels, presynaptic firing frequencies and basal receptor activations associated with conditions in healthy subjects and Parkinson’s patients. For instance, this leads to a substantial difference between rodent and human dopaminergic dynamics [8].
**Subcortical basal ganglia Parkinson’s disease model**

The Parkinson’s Disease QSP model of subcortical motor circuitry has been described before [6] and is described in detail in the Supplementary information (see Fig. 1). Basically, the model consists of the striatum, STN-GP circuitry, and thalamo-cortical circuitry [9] where we have added neuromodulator receptor effects. The STN-GP circuitry consists of two segments of the globus pallidus (GP\(_e\) and GP\(_i\)) and the subthalamic nucleus (STN) [10]. The thalamus model is extended from [11] where specific receptor effects of interest were added.

Each cell type is modeled with membrane conductances and each compartment obeys the membrane current balance equation of the Hodgkin-Huxley formalism [12]. The membrane potential, \(V\), is computed by numerically integrating the equation \(C_d\frac{dV}{dt} = g_a(V-E_a) + I_{ex}\), where \(C\) is the membrane capacitance, \(g_a\) is the ionic conductance of an a-type ion channel, and \(E_a\) is the reversal potential of an a-type ion channel. The sum is over all types of ion conductances in each model compartment, and \(I_{ex}\) represents an externally applied current from synaptic currents.

The striatum model simulates the processing capacity of medium spiny neurons (MSN) in the ventral striatum or nucleus accumbens [10]. The model calculates the excitability of D\(_1\) positive MSN cells that project to the direct pathway and D\(_2\) positive MSN cells that project to the indirect pathway when driven by afferent cortical projections [13, 9] of STN, GP\(_i\), and GP\(_e\).

The spiking properties of Thalamo-Cortical neurons are caused by a fast sodium channel, Na [14], a fast potassium channel, K [14], a low-threshold Ca channel, iTc [15], a hyperpolarization-activated cation channel, Ih [16, 17], a potassium A channel, K\(_a\) [18], and a potassium leak channel [17].

Synaptic currents are used to calculate frequency band activity of local field potentials. We assume that synaptic currents in pyramidal cells are the major contributing dipole that generates field potentials [19], because their large number dominates the synaptic currents in other types of cells. Gamma power (\(\gamma\)) is then calculated as the integral of the gamma band (35–65 Hz), while beta-power is calculated as the integral over the spectrum (20–35 Hz).

**Receptor effects, pharmacology and disease state**

Membrane conductances and synaptic currents are modulated by actual receptor activation levels as determined

![Fig. 1](left) The model framework for basal ganglion, cortex, and thalamus. Two types of medium spiny neurons in the striatum, D\(_1\) and D\(_2\), project inhibitory (red) synapses to GP\(_i\) (direct pathway) and GP\(_e\) (indirect pathway) respectively. The GPe neurons are reciprocally coupled to themselves and the subthalamic nucleus (STN). The STN projects excitatory (green) synapses to the GP\(_i\) and the GP\(_e\) neurons, which excite thalamocortical (TC) neurons excite reticular (Re) neurons that reciprocally inhibit TC. Sensory input excites TC and TC projects to the cortex containing pyramidal cells (Pyr) and inhibitory basket cells (BC). All cell types receive background excitatory and inhibitory fluctuating inputs that represent random synaptic activity. White rectangles represent membrane currents and colored ovals represent receptor types coupled to the membrane and synaptic currents. See text for currents and receptor types. PD pathology (red arrows) is implemented using DA neuronal cell death, mGluR\(_2,3\) dysfunction at the MSN-GPe indirect pathway connection and dorsal raphe changes; while compensatory changes (green arrows) include changes in the GPe-STN coupling and DA synapse modification, such as D\(_2\) upregulation and DAT downregulation. (Right) Network Activation State diagram where each dot is an action potential for the different brain regions. The left axis refers to the brain region (i.e. PFC, MSN, GPe, etc.). Due to the specific coupling and ion channel kinetics, an oscillation-type behavior arises in the subthalamic Nucleus which can be captured by local field potentials as a specific frequency band in the power spectrum (Color figure online).
using the receptor competition model [8, 10] described above. The percent change in the maximum conductance will determine how the membrane and synaptic currents change as a result of each drug-dose combination and the pathological condition. The modulation of voltage-gated ion channels will lead to a change in spiking activity of the model affecting properties of oscillatory readouts.

Placebo response is robust in most clinical trials in Parkinson’s disease even when the subjects are on stable standard-of-care medications. This is likely due to the pulse of DA release when subjects are expecting a reward, as demonstrated in a healthy volunteer challenge with amphetamine [20]. We have previously calibrated the extent of the dopamine surge associated with the placebo effect as observed in clinical trials.

Adenosine A2A antagonism can intervene at two points in the basal ganglia circuit. D2R activation of the MSN neurons that project into the indirect pathway leads to a decrease in cAMP as a second messenger trough a Gi coupled pathway, while A2A activation leads to an increase in cAMP [2, 3]. Activation of the cAMP pathway leads to enhanced excitatory output of the indirect NoGo pathway. The lower ambient DA as a consequence of Parkinson’s pathology leads to lower reduction and higher level of cAMP formation leading to higher excitatory state of the D2 + MSN neurons, allowing the NoGo pathway to dominate. Blocking the A2A receptor, reduces part of the stimulation on the cAMP and consequently lowers activation of the NoGo pathway. It has to be noted that D2-prefering DA agonists also engage with this same pathway, which has important implications for clinical trial simulation where preladenant is added to standard-of-care.

The second mechanism is based on the colocalization of the A2A-R with the A1R at the level of presynaptic Glu afferents that stimulate the D2 + MSN neurons. Here A2A antagonist are able to reduce the amount of Glu released [4] and therefore mitigate the excess stimulatory drive on the indirect pathway.

**Development of the 2-dimensional Look-up table**

Because we wanted to simulate the effect of a number of different therapeutic interventions with different PK profiles, we opted for the use of a 2-dimensional look-up table (LUT) of extracellular DA levels and “target engagement” levels of the intracellular cAMP pathway downstream of the D2R in the indirect pathway, consisting of engagement of the intracellular cAMP dependent pathway and the presynaptic impact on glutamate release. Maximal reduction of glutamate release is 80% for 100% A2A antagonism, as determined from experimental in vivo microdialysis data [4].

Such a LUT would basically allow to derive the pharmacodynamic effect of STN beta/gamma ratio from the trajectory of the PK profile with the corresponding DA and A2A target engagement along the landscape of this 2-D Look-up table space.

A quadratic function was fitted to the predicted beta/gamma ratio (z) for different levels of cAMP modulation (x) and dopamine deficit (y) in order to smooth the surface

\[ z = b_0 + b_1x + b_2y + b_{12}xy + b_{11}x^2 + b_{22}y^2 \]  \( (1) \)

Coefficients \( b_n \) were fitted using the weighted least squares method with equal weighting of all data points, performed in R version 3.6.2.

**Calculation of the PK profiles**

The PK profiles of the different therapeutic interventions are generated using standard compartmental modeling approaches using published PK models, when available. They are then combined with the 2D surface of the beta/gamma readout to generate a 72 h pharmacodynamic profile of the biomarker (in silico beta/gamma readout) under the various conditions. Where no published PK model was identified, a PK model was built to describe published plasma concentration profiles. Data was digitised using GetData Graph Digitizer 2.22. Simulations were performed in Phoenix 8.0 (Certara L.P.) and R version 3.6.2. Detailed calculations are shown in the Supplementary Information.

**Model readout for the OFF-time and ON-time with dyskinesia**

OFF-time was estimated for the 16-h period of time awake, starting on the third day (48 h) of simulated dosing of the L-dopa formulation with or without preladenant. Note that in clinical trials, OFF-Time is reported in time bins of 30 min. We further assumed that there was b/g threshold (threshold-OFF) above which motor symptoms were clearly present and that the lower b/g, the lower the probability of OFF-Time depending upon the difference with the threshold-OFF. Because of the variability inherent in the clinical readout, especially in the grey zone around the threshold, we assumed this function to be of a Hill-type, rather than a linear function. This can also account for the fact that the probability cannot be negative when the b/g ratio reaches its lowest value. For each time point of predicted beta/gamma ratio z at 30 min intervals, the probability of OFF-time was calculated as follows:

\[ p(t) = \begin{cases} 
1 - \frac{\text{thresholdOFF} - z}{(\text{thresholdOFF} - z) + EC_{50}\text{-off}} & \text{for } z < \text{thresholdOFF} \\
1 & \text{for } z \geq \text{thresholdOFF}
\end{cases} \]  \( (2) \)
The total OFF-time for 16 h awake estimated the sum of the probability for all time points multiplied by the time interval of 0.5 h, plus the placebo effect:

\[ \text{Offtime}(h) = \text{placebo} + \sum_{t} p(t) \times 0.5 \]  

(3)

ThresholdOFF, \( EC_{50-\text{OFF}} \) and the placebo effect are free parameters, calibrated with clinical data.

Similarly, for the calculation of the ON-Time with dyskinesia, ThresholdDYS and \( EC_{50-\text{DYS}} \) are calibrated independently for troublesome and non-troublesome dyskinesia.

\[ p(t) = \begin{cases} 
\frac{\text{thresholdDYS} - z}{(\text{thresholdDYS} - z) + \text{EC}_{50-\text{DYS}}} & \text{for } z < \text{thresholdDYS} \\
0 & \text{for } z \geq \text{thresholdDYS}
\end{cases} \]  

(4)

**Pharmacodynamic effect of therapies**

A baseline DA deficit (Deficit\(_{\text{Baseline}}\)) of 95% and 85% were assumed for severe and mild PD, respectively, based on the loss of signal of PET-imaging DATSCan data [21]. In general, symptoms start when over 70% of DA neurons are lost. With regard to the pharmacodynamic impact of L-DOPA, PET imaging with 11C-raclopride, a D2 tracer, indicated a transient increase in synaptic dopamine levels following dosing of Sinemet 250/25 (250 mg L-dopa, 25 mg carbidopa) of 500% of baseline concentration in severe PD and 150% of baseline concentration for mild PD, corresponding to a change in DA deficit from 95 to 70% in severe PD and from 85 to 62.5% in mild PD [22]. The average plasma L-dopa concentration during this time was calculated as 1.98 mg/L from the pharmacokinetic model. This average L-DOPA concentration was used to calculate the relative change (RelChange) in synaptic dopamine per unit L-DOPA plasma concentration (mg/L) from the PET imaging study. For any new L-DOPA concentration \( CP \), the dopamine deficit over time following administration of L-dopa formulations can then be estimated as follows:

\[ \text{Deficit} = \frac{\text{Deficit}_{\text{baseline}} - (1 - \text{Deficit}_{\text{baseline}}) \times \text{RelChange}}{\text{C}_P} \]  

(5)

An underlying assumption is that there is a direct relationship between synaptic dopamine concentration and L-dopa plasma concentration.

The concentration dependent extent of adenosine A\(_{2A}\) receptor antagonism by preladenant was estimated from PET imaging data in rhesus monkeys [23]. The reported dose resulting in a half-maximal occupancy (ED\(_{50}\)) in the whole striatum was converted the plasma concentration resulting in half maximal occupancy (EC\(_{50}\) mg/L) using the average plasma concentration of preladenant during the time interval of PET imaging, resulting in a plasma EC\(_{50}\) of 3.2 ng/mL. Adenosine A\(_{2A}\) receptor antagonism was assumed equal to the receptor occupancy (RO), defined as:

\[ \text{Antagonism} = \text{RO} = \frac{\text{Bmax} \times \text{C}_P}{\text{EC}_{50} + \text{C}_P} \]  

(6)

where Bmax is the maximal receptor occupancy, which was assumed to be 100%. It is assumed that there is a direct relationship between plasma concentration and adenosine A\(_{2A}\) receptor antagonism.

cAMP modulation in D\(_2\) + MSN neurons was assumed to be proportional to adenosine A\(_{2A}\) receptor antagonism as follows:

\[ \text{cAMP modulation} = a + b \times \text{antagonism} \]  

(7)

where constant a accounts for the contribution of co-administered D\(_2\) receptor agonists to cAMP modulation and was calibrated using the OFF-time for the basal and placebo response data in clinical studies of preladenant in which the majority of all subject (85–96% across all arms) received concomitant dopamine agonists. Constant b accounts for the effect of A2A antagonism to cAMP modulation under D2 receptor agonists, calibrated using the OFF-time for the preladenant active arms in clinical studies. This parameter ranges from 0 to 1 and describes the level of the cAMP modulation downstream of D2R activation/A2aR suppression with various modulators (for instance, L-DOPA, DA agonists and A2A antagonist).

Calibration of parameters was performed by adjusting parameters to minimize the average fold error (AFE) and absolute average fold error (AAFE), measures of precision and bias respectively, between the predicted and the observed outcomes across all studies (n).

\[ \text{AFE} = 10^{\frac{1}{n} \sum \log \left( \frac{\text{predicted}}{\text{observed}} \right)} \]  

(8)

\[ \text{AAFE} = 10^{\frac{1}{n} \sum \left( \log \left( \frac{\text{predicted}}{\text{observed}} \right) \right)} \]  

(9)

**Results**

**PK profiles of relevant medications**

The simulated PK profiles for different L-DOPA formulations and for preladenant are shown in Fig. 2A–D. L-DOPA, Sinemet and Stalevo are shown for 100 and 200 mg doses 5–8 times/day, whereas Rytary is shown for 490 and 980 mg 3–5 times daily. Drug exposure is larger for Rytary over Stalevo than for Sinemet due to longer-acting formulation modifications, by the addition of entacapone as COMT inhibitor in the case of Stalevo and the
extended release formulation in the case of Rytary. As expected, the more invasive DuoDopa formulation where a gel is continuously administered with a portable pump directly in the duodenum or the upper jejunum via a percutaneous endoscopic tube, thereby bypassing the stomach, has a substantially larger exposure of the active component L-DOPA at 2 and 4 mg/L. On the other hand, preladenant PK profile (Fig. 2E) assuming a bid formulation demonstrates linear pharmacokinetics but with substantial peak-to-trough ratios.

Fig. 2 Simulated PK profiles of different L-DOPA formulations over 72 h A L-DOPA Sinemet, B L-DOPA Stalevo, C L-DOPA Rytary, D L-DOPA DuoDOPA, E Preladenant
Two-dimensional Look-up table of beta/gamma readout

The original 2-D surface as modelled directly from the QSP model is presented in Fig. 3A. One axis represents the ambient dopamine concentration, which is a combination of disease pathology, placebo response and standard-of-care medications (i.e. different formulations of L-DOPA). The other axis reflects the impact on the intracellular pathway and subsequent change in the A-type K\textsuperscript{+} channel conductance. This dimension is driven by the presence of D\textsubscript{2}R preferring dopamine agonists and the A\textsubscript{2A} antagonist preladdenant. Because of the fluctuations due to stochasticity, a smoothed version is used as shown in Fig. 3B.

Estimated parameters from Eq. 1 were $b_0 = 0.715$, $b_1 = -0.207$, $b_2 = -0.1251$, $b_{12} = -0.0243$, $b_{22} = 0.0504$. This surface was fitted using a R-package (more information in the Supplementary Information). The quadratic coefficients are only about three times ($b_{22}$ vs $b_2$) or 8 times ($b_{12}$ vs $b_1$) smaller than the linear terms, suggesting a substantial non-linear relationship.

Calibration of the QSP model with clinical data

We first calibrated the prediction of the OFF-time in the QSP model using Eq. 3 and Eq. 2 by changing Model parameters, such as EC\textsubscript{50}, threshold, and the placebo effect so that model predictions capture the reported OFF-time from the clinical trial. A stepwise procedure was taken to calibrate the clinical data as follows. Starting values for placebo effect [24–26] were estimated as the mean value between 0.1 and 1.0 h (0.6 h). We then calibrated of EC\textsubscript{50} to recover OFF-time during DuoDOPA treatment [27].

Assessment of prediction for Sinemet and Rytary clinical arms of [24] was used to refine placebo effect, threshold and EC\textsubscript{50}. Next, we selected the parameter set with best overall correlation with minimal precision and bias over all studies, including the jejunal formulation [25, 26, 28] (Fig. 4A). Final optimized parameters were fixed at 0.752 for Threshold, 0.006 for EC\textsubscript{50} and 0.5 for Placebo effect. All parameters relate to the b/g ratio and are dimensionless. For 6/10 studies the predicted TIME-off was within 10% of the reported value (Fig. 4a), and for all studies the prediction error was less than 10%.

Finally, to derive values for parameters \(a\) (capturing the contribution of co-administered D\textsubscript{2} receptor agonists to cAMP modulation) and \(b\) (proportionality constant relating A\textsubscript{2A} antagonism to cAMP modulation) in Eq. 6, we extended the clinical calibration to include the different formulations of multiple A\textsubscript{2A} antagonists. This was performed using published clinical data of OFF-time in clinical studies of A\textsubscript{2A} antagonists in which the majority of all subject (85–96% across all arms) received concomitant dopamine agonists [29–31] (Fig. 4B). This yielded final values \(a = 0.12\) and \(b = 0.035\). For 13/14 studies, the predicted OFF-time was within 10% of that reported in the clinical study (Fig. 4B).

Calibration of dyskinesia

The calibration of the QSP model for acute dyskinesia is performed assuming there is no L-DOPA induced dyskinesia because this is associated with a different form of pathological change which is beyond the scope of this project. Rather we assume that the transient dyskinesia is
triggered by the actual ‘overshoot’ of dopamine therapy augmented with adenosine A2A antagonism.

Using a similar approach (Eq. 4) as for the OFF-time readout, we calibrated the model with clinical data ON-Time with total dyskinesia, troublesome and non-troublesome dyskinesia. This arises when the beta/gamma ratio after treatment ends up below the predefined threshold from the OFF-time calibration (0.752). Calibration for total dyskinesia yields parameters for Placebo = 0 and EC50 = 0.075. Similarly, when calibrating the model to troublesome dyskinesia, the EC50 is now 0.32.

From these two calibrations, we can calculate non-troublesome dyskinesia as the difference of total dyskinesia and troublesome dyskinesia.

Total ON-time was predicted within 10% and 30% of the reported values for 2 and 14 of 22 study arms, respectively (Fig. 5A). For troublesome dyskinesia, 9 and 13 predictions were within 10% and 30% of the observations, respectively (Fig. 5B), and for non-troublesome dyskinesia 6 and 15 of the predictions were within 10% and 30% of the observed value (Fig. 5C).

Simulated OFF-time with various L-DOPA formulations and augmentation with preladenant

The pharmacokinetic/pharmacodynamic model described above was applied to predict the OFF-time and the ON-Time with troublesome dyskinesia and non-troublesome dyskinesia for different formulations and dosing regimens for mild and severe PD. In particular, doses of 100 and 200 mg L-DOPA, Sinemet and Stalevo (3, 5 and 8 times daily), 380 and 760 mg Rytary (3 and 5 times daily) were simulated in mild PD and 490 and 980 mg Rytary (3 and 5 times daily) were simulated in severe PD. In addition, DuoDOPA titrated to 2 and 4 mg/l at steady state was also simulated for severe PD.

As an example, Fig. 6 shows the pharmacodynamic readout of beta/gamma for two doses of Sinemet (100 and 200 mg) given five times a day. Of note is that the PD profile (beta/gamma) is the inverse of the PK profile, i.e. the higher the plasma concentration, the lower the beta/gamma ratio (and the longer the ON-Time). Lowering b/g ratio, brings the system towards the ‘healthy’ control situation. This value of b/g is then used in the probabilistic function that calculates the OFF-time.

Figure 6 also shows that the impact of preladenant is relatively small and only observable at the trough of the PK profile for the different L-DOPA formulations. In the case of severe PD, OFF-time is dose-dependently reduced by a 10 mg preladenant dose with the effect ranging from 37 min for L-DOPA 100 mg 5 times daily to 17 min for Sinemet, 13 min for Stalevo and 6 min for Rytary and DuoDopa. The impact of preladenant in mild PD is even smaller.

The acute readout of the b/g biomarker in Fig. 6 shows that the biggest improvement of A2A antagonists is at the peak of the L-DOPA formulation when the b/g is already at its lowest point and continues to provide a limited protection when the L-DOPA is cleared from the plasma. The small improvement at any time, but when accumulated over a day, amounts to a duration that ranges from 0.64 h (39 min for the lowest dose of L-DOPA) to 0.02 h (1.2 min for the DuoDopa formulation.

Table 1 shows the effect of preladenant augmentation to different formulations of the standard of care, illustrating the rather modest effect on reducing OFF-time. When comparing the effects of 2 mg vs 10 mg preladenant (a five-fold increase in dose), the increase in OFF-Time increases only between 75% (for Stalevo 200 mg 8 times daily) and 33% (for DuoDopa 2 mg/l). This highlights the strong non-linear relationship between preladenant dose.
and clinical efficacy with the biggest gain coming at the lowest dose of 2 mg daily. This relationship is dependent upon the standard-of-care therapy with the largest and smallest effect noted when combined with Stalevo and DuoDopa respectively. Importantly, augmentation therapy with 10 mg preladenant twice a day to 100 mg L-DOPA 5 times daily (500 mg total daily), decreases the OFF-time to the level observed with L-DOPA 200 mg 8 times a day monotherapy (1600 mg total daily), possibly opening the possibility to reduce L-DOPA induced dyskinesia.

Furthermore, increasing the delay between L-DOPA and preladenant intakes during the day does not improve the outcome, rather it slightly worsens the outcome.

We then simulated the effect of a very high but unrealistic dose of preladenant that is predicted to result in almost complete A2A receptor antagonism. This is also equivalent to the simulation of a hypothetical preladenant analogue with very high affinity for the A2A receptor. In that case, the maximum reduction in off time predicted with any of the standard dose regimens and formulations of L-dopa tested for severe Parkinson’s disease is 55 min for L-DOPA 100 mg 5 times daily to 25 min for Sinemet 100 mg 5 times daily, 10.5 min for Rytary 490 mg three times daily and 9.5 min for Dudopa.

Discussion

This report describes the development and qualification of a mechanism-based Quantitative System Pharmacology (QSP) model that when combined with simulated PK profiles of various therapeutic interventions in Parkinson’s disease can generate predictions of clinically relevant readouts, notably OFF-time and ON-Time with dyskinesia. These outcomes are often collected using patient diaries but can now also be continuously monitored using wearables and are very important for Quality of Life in the treatment of PD patients. In fact, continuous objective measurement of OFF-time with wearables has the potential to optimize treatment strategies [32].

The QSP model is based on the functional anatomy of the basal ganglia, in particular the dorsal motor circuit, uses a clinically accessible biomarker (beta/gamma ratio of local field potentials in subthalamic nucleus) and was
calibrated previously for readouts on the UPDRS scale at the group level using retrospective historical clinical trial data of a large number of different pharmacological interventions and assuming steady-state concentrations of therapeutic interventions [6].

Because of the uncertainty around factors that are not fully captured in the model assumptions or due to insufficient information in the reported clinical protocols, such as the additional comediations, specific genotypes or variability in the PK profile, we opted for a readout that was driven by a probabilistic E\textsubscript{max} function. The parameters of this function were determined by optimization of the correlation between predicted and observed outcomes for a number of reported group average treatment responses.

With regard to the beta/gamma readout, the calibrated threshold of 0.752 is the value above which the probability of OFF-time is 1 and the system is in the OFF-state; the greater the difference between the actual calculated value and this threshold, the lower the probability of OFF-time; the value of 0.006 for EC\textsubscript{50} suggest that the probability at 0.752 – 0.006 = 0.746 is 50%.

Along the same line, the same approach can also be used to generate estimates of the duration of troublesome and non-troublesome dyskinesia as a consequence of the beta/gamma biomarker dropping below a certain threshold. Here the probability is zero for that same threshold of 0.752. With an EC\textsubscript{50} value of 0.07, the lower the actual beta/gamma ratio (the greater the difference from the threshold), the higher the probability becomes with a 50% chance for non-troublesome dyskinesia at 0.752 – 0.07 = 0.682. Similarly the value of beta/gamma for which the probability of troublesome dyskinesia becomes 50% is 0.752 – 0.32 = 0.422.

Comparing to reported data from clinical trials, we achieved a reasonably strong correlation for the OFF-time readout, and for total dyskinesia duration, but a somewhat
lower correlation for troublesome dyskinesia. Different factors might contribute to this observation. First, in line with the greater EC₅₀ for troublesome vs non-troublesome dyskinesia, the magnitude of the duration was much smaller for reported troublesome dyskinesia (usually 1 h or less/day) as compared to the other readouts (2–5 h/day). Second, the interpretation of troublesome vs non-troublesome dyskinesia might suffer from subjective interpretation, while total dyskinesia is easier to define. This is also evidenced by the fact that different trials with very similar L-DOPA formulations and doses report very different readouts of troublesome dyskinesia.

Based on the calibration outlined above, we simulated the effect of preladenant augmentation therapy added to various L-DOPA formulations on OFF-time in a naturalistic setting (i.e., without placebo effect or other standard-of-care medications, such as Dopamine agonists). The outcomes suggest a limited benefit even in the situation where dopamine levels are poorly controlled, such as in 3 times daily L-DOPA at the lowest dose. For other formulations that reduce the fluctuations of L-DOPA, the added benefit of preladenant is much smaller. Also, the effect is smaller in mild PD. This is probably due to the difference in baseline dopamine levels. The simulated results are grossly in line with the outcome of a Phase 2 monotherapy trial [33] and the inconsistent outcomes of augmentation trials [31, 34] leading to the termination of the preladenant clinical development program. Combining preladenant’s PK profile with the relationship to central A₂A receptor occupancy, it follows that peak occupancy is about 90%, but this falls to 60% and 40% 8 and 12 h after dosing respectively [23]. It is not unconceivable that other A₂A antagonists with smaller peak-to-trough relationships, such as istradefylline might show more robust clinical effects. An interesting application of this simulation approach is the dose reduction of the standard-of-care L-DOPA formulation that optimizes clinical efficacy with reduced liability for L-DOPA induced dyskinesia. Historically, placebo response is robust as demonstrated by acute ¹¹C-raclopride PET tracer displacement study in healthy volunteers [20] and the dopamine transporter selective PET tracer ¹¹C-RT132 in Parkinson’s patients [35]. In this report, we choose to adjust the placebo effect based on the clinical trials rather than deriving the increase in dopamine from the PET imaging studies which was shown to predict better the clinical outcome in chronic 12-week studies as opposed to acute outcomes [6].

A major difference between this mechanism-based QSP model and more traditional empirical PK/PD models is the generalizability of the prediction for other pharmacological agents acting on different pathways within the motor basal ganglia circuit or combination therapy with drugs acting on different pathways. In fact, the model suggests a strong non-linear relation between preladenant drug exposure and clinical efficacy, which is dependent upon the formulation of the standard-of-care. Other applications, as illustrated in the

| Preladenant dose                   | 10 mg twice daily | 5 mg twice daily | 2 mg twice daily |
|-----------------------------------|------------------|-----------------|-----------------|
| ‘L-dopa 100 mg 5 times daily’     | −0.64            | −0.54           | −0.4            |
| ‘L-dopa 100 mg 8 times daily’     | −0.62            | −0.52           | −0.39           |
| ‘L-dopa 200 mg 5 times daily’     | −0.58            | −0.49           | −0.37           |
| ‘L-dopa 200 mg 8 times daily’     | −0.53            | −0.45           | −0.33           |
| ‘Sinemet 100 mg 5 times daily’    | 0.27             | −0.23           | −0.17           |
| ‘Sinemet 100 mg 8 times daily’    | 0.19             | −0.16           | −0.12           |
| ‘Sinemet 200 mg 5 times daily’    | 0.16             | −0.14           | −0.1            |
| ‘Sinemet 200 mg 8 times daily’    | 0.09             | −0.08           | −0.06           |
| ‘Stalevo 100 mg 5 times daily’    | 0.22             | −0.18           | −0.14           |
| ‘Stalevo 100 mg 8 times daily’    | 0.15             | −0.13           | −0.09           |
| ‘Stalevo 200 mg 5 times daily’    | 0.12             | −0.1            | −0.08           |
| ‘Stalevo 200 mg 8 times daily’    | 0.07             | −0.06           | −0.04           |
| ‘Rytary 490 mg 3 times daily’     | 0.1              | −0.09           | −0.06           |
| ‘Rytary 490 mg 5 times daily’     | 0.07             | −0.06           | −0.04           |
| ‘Rytary 980 mg 3 times daily’     | 0.05             | −0.04           | −0.03           |
| ‘Rytary 980 mg 5 times daily’     | 0.03             | −0.02           | −0.02           |
| ‘Duodopa 2 mg/L SS’              | −0.09            | −0.08           | −0.06           |
| ‘Duodopa 4 mg/L SS’              | −0.04            | −0.04           | −0.03           |

As expected, the largest effect was observed with the L-DOPA formulation with the lowest drug exposure. The data clearly suggest a non-linear relationship between preladenant dosing and clinical outcome.
results section, are related to the optimization of hypothetical drugs in terms of pharmacokinetic profile and pharmacology as augmentation therapy in Parkinson’s patients. In addition, this approach allows to account for chronopharmacodynamic effects driven by circadian rhythms of membrane expression levels and/or coupling of intracellular pathways that can be well captured by wearables.

Other modeling approaches include a neurocomputational model of a motor task readout coupled with L-Dopa pharmacokinetics [36–38]. While this approach in principle can be extended to include augmentation therapy with adenosine A2A antagonists, the modeled readout (fingertapping) is more difficult to apply in clinical practice as a measure of OFF-time.

Limitations of the QSP model presented here include the level of detail (i.e. number of neurons) in the different basal ganglia subregions. Due to computational constraints the neurons in each basal ganglia subregion, ranges from 4 to 16. The biology of the human basal ganglia is very complex and this computer model excludes possibly important biological processes. However, we would argue that the current level of detail, focused on the specific pharmacology of the treatments, has value for therapeutic applications in clinical practice.

In the QSP model, the ratio of beta/gamma was a more robust outcome as compared to the absolute level of beta power, which often has been used in clinical studies [5]. In most cases in our QSP model, the beta/gamma ratio was driven by the changes in beta power.

The model in its current form, does not include any molecular disease pathway and therefore is unable to simulate the impact of disease-modifying therapies, such as anti-alpha synuclein antibodies [39] or treatments focused on genetic risk factors [40]. However, molecular mechanisms linking these pathological processes to dysfunctional cell biology become increasingly available. As an example, the impact of aggregated a-synuclein on the glibenclamide-sensitive K+ channel [41] can be implemented in the QSP model. Furthermore, the impact of LRRK2 mutations on ligand-gated glutamate channels [42], voltage-gated calcium channels [43] or synaptic plasticity [44] can in principle be added to the existing clinically calibrated QSP model. This would allow to simulate the pharmacodynamic interaction between disease-modifying therapies and the standard of care in clinical trials, both on the UPDRS as well as on OFF-time to be quantified in advance.

Conclusion

We developed a QSP model of a clinical readout in Parkinson’s patients in combination with PK modeling of relevant comedinations. The model was applied to the OFF-time readout and dyskinesia and was calibrated using a number of different L-DOPA formulations. The model was then applied to augmentation trials with adenosine A2A antagonist preladenant and explore different pharmacological profiles and trial scenarios. In summary, this approach might be a new powerful tool for supporting clinical trials with symptomatic and disease-modifying therapies with regard to clinically relevant functional scales that aim to improve quality of life for Parkinson’s disease patients.

Table 1. Decrease in OFF-time (hours) for different doses of preladenant in augmentation therapy with various formulations of L-DOPA as standard of care. As expected, the largest effect was observed with the L-DOPA formulation with the lowest drug exposure. The data clearly suggest a non-linear relationship between preladenant dosing and clinical outcome.

Author contributions RR developed the PK model and RR and EM ran the simulations; EM developed the interface between the PK model and the QSP model; DT and JH provided key insights into defining the relation between the QSP biomarkers and the clinical presentation. PvdG and HG conceived and led the project and wrote the manuscript. All authors reviewed the manuscript.

Declarations

Conflict of interest The authors declare no competing interests.

Supplementary Information

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