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ORIGINAL ARTICLE

Prediction of Efficacy of Vabicaserin, a 5-HT$_{2C}$ Agonist, for the Treatment of Schizophrenia Using a Quantitative Systems Pharmacology Model

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A quantitative systems pharmacology model that combines *in vitro*/preclinical neurophysiology data, human imaging data, and patient disease information was used to blindly predict steady-state clinical efficacy of vabicaserin, a 5-HT$_{2C}$ full agonist, in monotherapy and, subsequently, to assess adjunctive therapy in schizophrenia. The model predicted a concentration-dependent improvement of positive and negative syndrome scales (PANSS) in schizophrenia monotherapy with vabicaserin. At the exposures of 100 and 200 mg b.i.d., the predicted improvements on PANSS in virtual patient trials were 5.12 (2.20, 8.56) and 6.37 (2.27, 10.40) (mean (95% confidence interval)), respectively, which are comparable to the observed phase IIa results. At the current clinical exposure limit of vabicaserin, the model predicted an ~9-point PANSS improvement in monotherapy, and <4-point PANSS improvement adjunctive with various antipsychotics, suggesting limited clinical benefit of vabicaserin in schizophrenia treatment. In conclusion, the updated quantitative systems pharmacology model of PANSS informed the clinical development decision of vabicaserin in schizophrenia.

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Vabicaserin (SCA-139) is a novel 5-HT$_{2C}$ agonist.[1] The 5-HT$_{2C}$ agonism has been hypothesized to have therapeutic potentials in a wide range of psychiatric disorders based on evidence from preclinical animal models.[2,3] Unlike most agents currently developed for the treatment of schizophrenia, vabicaserin does not directly involve targeting dopamine receptors. Vabicaserin has *in vitro* functional selectivity for 5-HT$_{2C}$ over 5-HT$_{2A}$, 5-HT$_{2B}$, and other receptors.[1] Vabicaserin decreases dopamine levels of nucleus accumbens without affecting striatal dopamine in rodents. This profile is consistent with potential efficacy in the treatment of psychotic symptoms of schizophrenia.[4,5] Chronic administration of vabicaserin significantly decreases the number of spontaneously active mesocorticolimbic dopamine neurons without affecting nigrostriatal dopamine neurons, consistent with the effects of atypical antipsychotics.[4] Unlike atypical antipsychotics, acute administration of 5-HT$_{2C}$ agonists in rodents reduces mesocorticolimbic dopaminergic activity,[4] suggesting that vabicaserin could have a rapid onset of action. Vabicaserin also increases extracellular glutamate content in medial prefrontal cortex of rats, an effect which may provide improved cognitive function.[5] Results from preclinical studies also suggest that 5-HT$_{2C}$ agonists could be effective in improving mood disorders and cognitive impairment associated with schizophrenia, without producing extrapyramidal side effects or weight gain.[4] Therefore, vabicaserin offers the possibility of a new antipsychotic medication with broader efficacy (e.g., cognitive symptoms) as well as improved safety and tolerability over existing antipsychotic agents. However, in a recent phase IIa clinical trial, vabicaserin demonstrated only moderate efficacy in schizophrenia as monotherapy.[5] These results raised questions regarding whether additional clinical studies in monotherapy and in adjunctive therapy of schizophrenia should be conducted.

Given the limitations of animal models in predicting efficacy in schizophrenia, such as fundamental differences in neurotransmitter circuitry between rodents and humans and the incomplete representation of the full human pathology,[6] a quantitative systems pharmacology model of schizophrenia was used to predict the clinical efficacy of vabicaserin in monotherapy and subsequently to assess the potential efficacy in adjunctive therapy in schizophrenia. The model was blinded to the phase IIa data to reduce prediction bias.

The quantitative systems pharmacology model of schizophrenia is a computer-based mechanistic disease modeling platform that combines *in vitro*/preclinical neurophysiology information with human imaging, postmortem, and clinical data.[7,8] The model has successfully predicted the efficacy on total positive and negative syndrome scales (PANSS) of a phase II study of the novel investigative drug JNJ37822681, a highly selective low-affinity dopamine D$_2$ antagonist, in schizophrenia.[9] The model has also predicted the relative, but not the absolute, clinical effect of another antipsychotic drug, ocaperidone.[9]

The purpose of this study was to utilize a quantitative systems pharmacology model to predict steady-state clinical efficacy of vabicaserin as a monotherapy and, subsequently, to estimate the efficacy of vabicaserin as an adjunctive therapy in schizophrenia and to inform whether additional clinical studies with vabicaserin are warranted. To accomplish this, the previously developed quantitative systems pharmacology model of PANSS[7–9] was extended to incorporate 5-HT$_{2C}$ receptor effects in three ways: (i) effect on dopamine firing frequency, (ii) effect on cholinergic striatal interneurons, and (iii) effect

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on γ-aminobutyric acid (GABA) interneurons. The model was then recalibrated to determine the best coupling parameters for these mechanisms. The computer-based quantitative systems pharmacology model also incorporated polypharmacology of the existing antipsychotics that sometimes involves an interaction with 5-HT_{2C} receptors, which may interact in a nonlinear fashion with vabicaserin. The model was blinded to the previously generated vabicaserin phase IIa efficacy data[5] in schizophrenia monotherapy to minimize prediction bias.

RESULTS

Model-predicted 5-HT_{2C} agonist effects on striatal dopamine neuron firing

The effect of full 5-HT_{2C} receptor agonism on striatal dopamine firing was calibrated based on literature data on the interventions (knockout,[10] antagonism,[11] and agonism[12]) on 5-HT_{2C} receptor and subsequent effects on striatal dopamine levels. The activation levels of 5-HT_{2C} receptors and the reductions in dopamine firing were determined using the receptor competition model (top-left oval in **Figure 1**, modified from previously published models[7–9,13]). The model-predicted relationship between dopamine firing frequency and either free dopamine levels in the synaptic cleft or tracer binding at the postsynaptic D_2 receptors was determined to be –1.9% dopamine firing change per 1% 5-HT_{2C} receptor activation increase. This average value of –1.9% for the slope is within the biologically relevant range of –1.6 to –3.2% derived from published preclinical data.[10–12,14]

Recalibration of the updated PANSS model

As the new 5-HT–mediated physiology was added to the model platform, and because many antipsychotics that have been clinically tested show pharmacological effects toward some of the newly introduced receptors, the updated PANSS model (version 2.3.1) was recalibrated as compared with the previous version.[7–9] As shown in **Figure 2**, the recalibration resulted in a strong correlation between the observed and the model-predicted PANSS (r^2 = 0.6861).

Model-predicted effect of vabicaserin as monotherapy

Figure 3 shows the model-predicted change in PANSS relative to a range of normalized 5-HT_{2C} receptor activation from 0.5- to 1.5-fold of the normal baseline receptor activation (63%). At 5-HT_{2C} receptor activation levels less than 0.9-fold of the normal baseline, the model predicted worsening of PANSS. At 5-HT_{2C} receptor activation levels greater than and equal to the normal baseline levels (≥onefold), the model predicted monotonic improvements of PANSS. The improvement of PANSS was predicted to saturate when 5-HT_{2C} receptor activation is greater than 1.4-fold of its normal baseline activation, i.e., at greater than 90% of total 5-HT_{2C} receptor activation.

The predicted changes of PANSS over a range of vabicaserin free drug concentrations are also shown in **Figure 3**. At 18 nmol/l of vabicaserin, the highest average unbound steady-state concentration achieved but not well tolerated in all populations,[15] the model predicted ~9-point improvement in PANSS. A maximal anticipated clinical improvement of 12 points for PANSS was predicted to be achieved with 5-HT_{2C} receptor activation greater than 1.4-fold of the normal baseline value, which would require a free vabicaserin concentration of ≥35 nmol/l.

Model-predicted effect of vabicaserin adjunctive with antipsychotics

The potential additional improvements on PANSS by vabicaserin adjunctive to other antipsychotics in schizophrenia were predicted by the recalibrated PANSS model. In

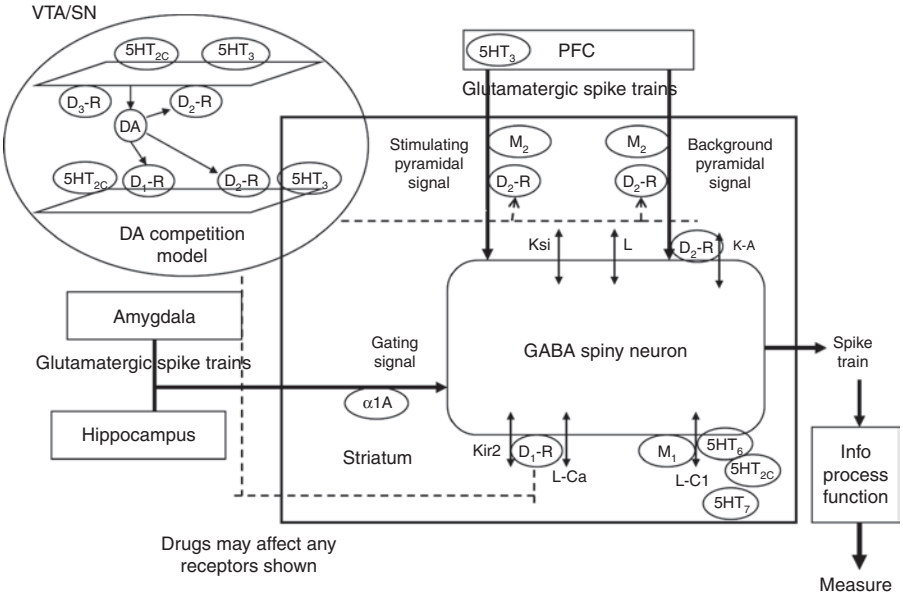

Figure 1 Detailed model of the pharmacology in the ventral striatum that is related to the clinical PANSS outcome. 5-HT_{2C} receptor activation in the VTA affects dopaminergic firing and together with 5-HT_3 has direct effects on D_1 and D_2 receptor activations, whereas 5-HT_{2C}, 5-HT_6, and 5-HT_7 all affect muscarinic cholinergic M_1 receptor tone on MSN neurons through their effect on cholinergic interneurons and 5-HT_{2C} affects GABA interneurons which reduces excitability of the MSN. DA, dopamine; GABA, γ-aminobutyric acid; MSN, medium spiny neuron; PANSS, positive and negative symptoms scale in schizophrenia; VTA, ventral tegmentum area.

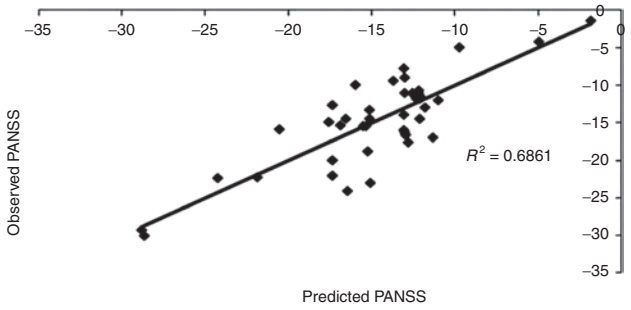

Figure 2 Calibration between model-predicted and clinically reported PANSS responses for 42 drug–dose combinations with the updated PANSS model, including the specific neurophysiology of 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors. PANSS, positive and negative symptoms scale in schizophrenia.

general, the model predicted <4-point additional improvements of PANSS (black-shaded areas in **Figure 4**, except for placebo) when vabicaserin was added to the standard-of-care antipsychotics as cotreatments with haloperidol, olanzapine, asenapine, or zotepine. No improvement was predicted with ziprasidone, aripiprazole, quetiapine, risperidone, or paliperidone at the unbound exposure of 18 nmol/l, the current clinical exposure limit of vabicaserin. The gray-shaded areas in **Figure 4** represent the predicted PANSS improvements by either placebo or the standard care of antipsychotics alone ranging from 10 to 23 points, which are generally consistent with the reported clinical efficacy of these antipsychotics.[16,17]

Virtual patient trial simulation with vabicaserin

To gain confidence in the model, a comparison of the model prediction of virtual trials with the observed phase IIa clinical study results in vabicaserin monotherapy was performed. The predicted mean improvements of PANSS and the 95% confidence intervals of the 10 virtual trials were averaged for the 100 and 200 mg b.i.d. of vabicaserin, respectively, and are shown in **Table 1**. The predicted mean (95% confidence interval) improvements of PANSS from the 10 virtual trials were 5.12 (2.20, 8.56) and 6.37 (2.27, 10.40) for 100 and 200 mg b.i.d. of vabicaserin, respectively. These quantitative systems pharmacology–predicted average effects are in general agreement with the actual observed clinical improvements of PANSS in the phase IIa study (last observation carried forward mean (95% confidence interval)), 8.57 (1.98, 15.15) and 5.91 (–0.84, 12.2), at 100 and 200 mg b.i.d. of vabicaserin, respectively.[5] It is important to note that the typical SDs on PANSS improvements range from 20 to 30 points in the literature.[17] Therefore, the differences between predicted and observed PANSS improvements are relatively minor, and the 95% confidence intervals of the predicted PANSS improvements are within the corresponding observed 95% confidence intervals at 100 and 200 mg b.i.d. of vabicaserin, respectively. Although the simulations do not fully recapitulate the apparent higher mean response at the lower dose, the apparent numerical difference on the observed mean PANSS improvements at 100 and 200 mg b.i.d. of vabicaserin was likely an artifact of data variability.

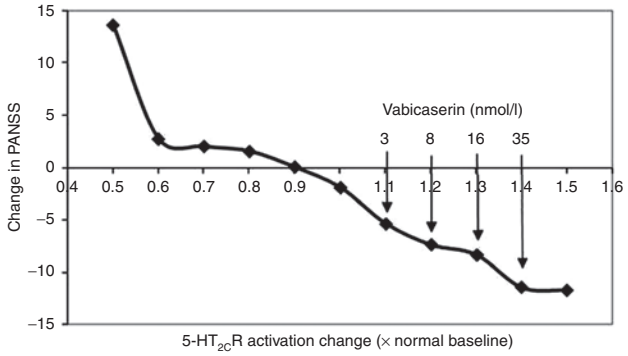

Figure 3 Effect of relative changes (normalized to the baseline value) in 5-HT_{2C} receptor activation on the model-predicted changes in PANSS by vabicaserin as a monotherapy. PANSS, positive and negative symptoms scale in schizophrenia.

DISCUSSION

This report describes the implementation of 5-HT_{2C} receptor neurophysiology and the impact of 5-HT_{2C} activation changes by vabicaserin in the updated quantitative systems pharmacology model of schizophrenia, the output of which correlates with the observed PANSS improvements in a phase IIa clinical study. Vabicaserin is a relatively specific 5-HT_{2C} modulator with modest additional effect on 5-HT_{2B}. The 5-HT_{2C} receptor is an interesting novel target in schizophrenia because the therapeutic effects of its modulation are presynaptic on the dopaminergic projections to the striatum and the human pathology is thought to be presynaptic, rather than postsynaptic.[18] Almost all of the currently marketed antipsychotics interact with the postsynaptic dopamine D_2 receptor on striatal medium spiny neurons, thus providing a unique mechanism of action for vabicaserin and potential for differentiation from existing therapeutic agents.

In this updated PANSS model, the neurophysiology of 5-HT_{2C} was implemented at two different levels: (i) modulation of dopaminergic ventral tegmentum area (VTA) firing and (ii) modulation of striatal cholinergic tone. The coupling factor of a 1.9% decrease in dopamine firing per 1% change in 5-HT_{2C} receptor activation is at the lower range of a number of previously published data on the *in vivo* coupling, which ranges from 1.6 to 3.2% decreases in dopamine firing rate per percent 5-HT_{2C} receptor activation change.[10–12,14] However, this relationship is within the calculated range (1.3–2.3%) from preclinical and *in vitro* experiments with vabicaserin,[19] which gives a greater confidence to the determination of the relationship between 5-HT_{2C} receptor activation and changes in VTA dopamine firing.

The effects of different serotonergic receptor levels, such as 5-HT_{2C}, 5-HT_6, and 5-HT_7 on striatal cholinergic and GABA interneurons,[19–21] were further implemented into the model using preclinical data. The coupling parameters for the new neurophysiological model are constrained with calibration using human clinical data.[7] Although intuitively increased 5-HT_{2C} receptor activation could worsen PANSS through its effect on the Cl^- leak,[22] the model incorporates the increased 5-HT_{2C} receptor activation through its effect on D_2 receptor activation and muscarinic M_1 receptor

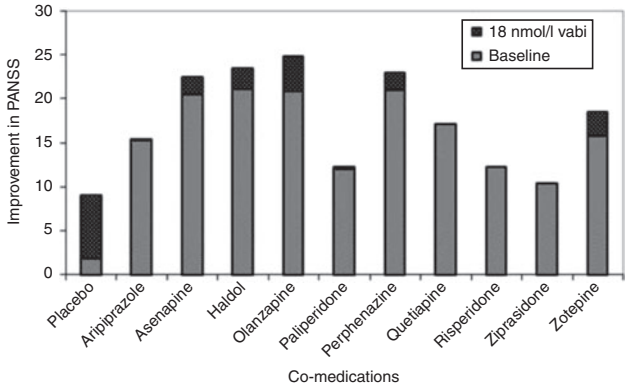

Figure 4 Model-predicted PANSS improvements by vabicaserin adjunctive with various antipsychotic co-medications (black-shaded areas, except for placebo). The antipsychotics are used at their relevant clinical doses as baseline (gray-shaded areas, except for placebo). PANSS, positive and negative symptoms scale in schizophrenia.

Table 1 Summary of model-predicted PANSS improvements in virtual trial simulations using 10 trials of 200 subjects at vabicaserin doses of 100 and 200 mg b.i.d. and in comparison to the observed phase IIa clinical study results

Groups	Vabicaserin (100 mg b.i.d.)	Vabicaserin (200 mg b.i.d.)
Model-predicted PANSS improvement, mean (95% CI)	5.12 (2.20, 8.56)	6.37 (2.27, 10.40)
Observed PANSS improvement in phase IIa, LOCF mean (95% CI)	8.57 (1.98, 15.15)	5.91 (–0.84, 12.2)

CI, confidence interval; LOCF, last observation carried forward; PANSS, positive and negative symptoms scale in schizophrenia.

activation, resulting in a monotonic dose–response prediction on PANSS improvement.

In the prediction of the changes of PANSS vs. 5-HT_{2C} receptor activation by vabicaserin monotherapy in **Figure 3**, fixed-effect simulations were performed without random variability as the objective was to understand the underlying trend of the relationship. At the clinical exposure limit of 18 nmol/l free vabicaserin, the predicted PANSS improvement was ~9 points, which is lower than the typical reported efficacy of marketed antipsychotics,[16] and the exposure was not well tolerated in all subject populations.

In the subsequent virtual trial simulations to predict the PANSS improvement by vabicaserin in the phase IIa study, the variability of observed vabicaserin exposures and the 30% variability around the biological coupling parameters were incorporated into the simulations. The predicted mean and 95% confidence intervals of PANSS improvements from 10 virtual trials of 200 subjects/trial are in the range of corresponding observed values at 100 and 200 mg b.i.d. of vabicaserin, respectively. It is noted that the observed PANSS improvements were based on last observation carried forward imputation because there were significant dropouts due to adverse events, and thus, the observed cases may not adequately represent the underlying treatment effect of vabicaserin. The wide ranges of 95% confidence intervals of the observed PANSS improvements by vabicaserin might be due to the intrinsic variability of the PANSS end point[17] and further amplified by the wide variability of vabicaserin exposure. Therefore, the apparent higher mean PANSS improvement of 8.57 points at 100 mg b.i.d. than the mean value of 5.91 points at 200 mg b.i.d. was likely an artifact of data variability with ~70 subjects in each group, and this difference is considered minimal and not statistically significant given the wide ranges and the overlap of the 95% confidence intervals of (1.98, 15.15) and (–0.84, 12.2) at 100 and 200 mg b.i.d. of vabicaserin, respectively. Overall, the model predicted the observed ranges of PANSS improvements at the two vabicaserin dose levels. In addition, the model-predicted mean placebo effect was 1.8, which is consistent with the observed mean placebo response of 2.7 in the phase IIa study. The virtual trial simulation results provided confidence on the updated PANSS model and the model predictions.

Although the predicted mean PANSS improvements by vabicaserin monotherapy were higher than the predicted mean placebo effect, the values were much lower than the predicted response by olanzapine (23 points), which is also consistent with the observed phase IIa clinical results. The predicted vabicaserin mean treatment effects at 100 and 200 mg b.i.d. were also lower than that typically observed for currently marketed antipsychotics in monotherapy,[16] suggesting that vabicaserin monotherapy may not provide comparable efficacy as currently marketed antipsychotics.

The overall effect of vabicaserin in adjunctive therapy is a result of a number of nonlinear interactions and is therefore difficult to predict in an intuitive and qualitative way. For example, some antipsychotics are relatively strong 5-HT_{2C} receptor antagonists, whereas others affect muscarinic receptors or presynaptic 5-HT_{1B} receptors that drive free 5-HT levels and other 5-HT receptor activation levels.[23] The prediction of adjunctive treatment effects was performed using fixed-effect simulations as the main objective was to predict the mean improvements on PANSS for vabicaserin with cotreatment with antipsychotics. In general, the model predicted additional PANSS improvements of <4 points with all antipsychotics, although slightly better with haloperidol, olanzapine, quetiapine, or zotepine than the improvements with other antipsychotics. However, the predicted improvements of <4 points in vabicaserin adjunctive therapy is generally considered to be clinically nondetectable.

It is acknowledged that there are some limitations for this mechanism-based computer model. The current PANSS model does not take into account the specific downstream interactions of the direct and the indirect pathway but mathematically combines the output of a D_1 receptor–positive medium spiny neuron (MSN) and a D_2 receptor–positive MSN neuron.[7] In principle, a more elaborate basal ganglia model could be developed following earlier work.[23–25] The calibration of this model with the clinical data was quite successful, probably because all antipsychotics modulate D_2 receptors, an effect driven by the MSN neurons.[7] However, the effect of vabicaserin as a modulator of VTA dopamine firing is upstream of the dopaminergic hyperactivity and is therefore closer to the pathology.[18] This also suggests that effects of vabicaserin are in the same global circuit as the antipsychotics. Therefore, there is a high level of confidence that the predicted clinical effect of vabicaserin based upon this model is a reasonable approximation of the biological system.

It is also noted that this simulation is based on a model that is calibrated with the average outcome for a group of patients on the same drug–dose combinations and therefore does not take into account the individual variability within each group.

Another limitation of the current PANSS model is the lack of time–course changes over the 4–12-week duration of the trial. However, the main purpose of this project was to predict (quasi–)steady-state treatment effect on PANSS. Extensive literature exists showing that the onset of antipsychotic treatment effects on PANSS occurs rapidly within the first two weeks of treatment,[26] quasi–steady-state reaches after 4–6 weeks of treatment.[27–29] The model was calibrated with data from 4- to 12-week trials, which is sufficient to answer the key question of (quasi–)steady-state treatment effect on PANSS in this study.

In conclusion, the updated PANSS model was implemented using published knowledge of the subcortical neuroanatomy and neurophysiology and was supplemented with insights from the schizophrenia pathology as determined from human patient populations. This computer model was calibrated using a large collection of published clinical data with 42 drug–dose combinations, including compounds that were effective in preclinical animal models, but failed in clinical studies.[7–9] In addition, the correlation between the model-predicted and model-reported clinical outcomes has been shown to be two- to threefold better than the correlation between the D_2 receptor occupancy and the same clinical data.[7]

The model predicts that the 5-HT_{2C} receptor activation–mediated dopamine reduction in the ventral striatum, at the exposures achieved in the reported clinical study, is likely to be of insufficient magnitude to provide clinical improvement as a stand-alone medication to the same magnitude as postsynaptic D_2 receptor antagonists. The model also predicts that vabicaserin would provide minimal additional improvement in PANSS in adjunctive therapy with antipsychotics. Virtual trial simulations using the updated PANSS model predicted the ranges of the observed clinical results of vabicaserin and the controls by placebo and olanzapine, which provides confidence on the model and on the decision making based on the model predictions. This case study provides an example that quantitative systems pharmacology model of biophysically realistic and humanized brain circuits may be a novel approach for quantitative clinical efficacy predictions in neuroscience disease areas.

METHODS

The PANSS model has been extensively described previously.[7–9] Basically, the level of functional antipsychotic concentration was derived from a simulation of the raclopride positron emission tomography displacement studies in humans, and this intrasynaptic concentration was subsequently used to estimate the impact of the drug on other receptor activation level using the appropriate affinities and dynamics of the neurotransmitters. These modified postsynaptic receptor activation levels on a number of neurotransmitter systems impacted the appropriate ion-channel conductances throughout the circuit, modulated the membrane potential, and therefore changed the firing dynamics. The model was then calibrated by adjusting six biological coupling parameters using published changes in PANSS from 42 retrospective drug–dose combinations to optimize the correlation between the model predictions and the published clinical trial data.

Pharmacology of antipsychotics

Table 2 illustrates the affinities for D_2 receptor (D_2R), 5-HT_{2C} receptor (5-$HT_{2C}R$), 5-HT_{1B} receptors (5-$HT_{1B}R$), and clinically relevant unbound concentrations of a large number of antipsychotics. These values were used to predict the co-medication effects of vabicaserin.

Pharmacology of 5-HT_{2C}

The following preclinical data were utilized to calibrate the effect of full 5-HT_{2C} receptor agonism on striatal dopamine firing. Microdialysis in 5-HT_{2C} receptor knockout mice suggest a 25% increase in dopamine levels in the ventral striatum,[10] whereas treatment with the 5-HT_{2C} receptor antagonist SB 206553 reduces the binding of ^{11}C-raclopride in rats by 20% in ventral striatum.[11] Furthermore, treatment with the 5-HT_{2C} receptor agonist Ro 60–0175 into the medial prefrontal cortex in rats decreases accumbal dopamine outflow by 40%.[12] On the basis of these experimental studies, the effects of the interventions (knockout, antagonism, and agonism) on 5-HT_{2C} receptor activation levels were determined using the receptor competition model[7,13] and the reductions in dopamine firing associated with observed changes in either raclopride binding or free dopamine levels.

Preclinical data on vabicaserin

The following preclinical data on vabicaserin were used to predict PANSS improvement by vabicaserin. In rodents,

Table 2 Pharmacology of various antipsychotics against D_2, 5-HT_{2C}, and 5-HT_{1B} receptors relevant in the calculation of the effect of vabicaserin on antipsychotic-mediated clinical outcomes ranked in order of increasing ratio of 5-$HT_{2C}R/D_2R$ affinities

Drug	D_2R (nmol/l)	5-$HT_{2C}R$ (nmol/l)	Ratio 5-$HT_{2C}R/D_2R$	5-$HT_{1B}R$ (nmol/l)	Clinical exposure (nmol/l)
Clozapine	220	5.59	0.025	398	250
Ziprasidone	5.2	0.9	0.173	2.5	32
Zotepine	8	4.2	0.525	67	50
Olanzapine	27.3	17	0.623	509	90
Chlorpromazine	5.5	6.1	1.119	1,498	35
Sertindole	4.3	6	1.40	60	25
Asenapine	2	10	5.00	55	13
Paliperidone	9.4	48	5.11	17.5	60
Quetiapine	406	2,500	6.16	2,050	800
Melperone	180	2,100	11.7	N/A	440
Risperidone	3.1	49	15.8	6	20
Remoxipride	295	5,500	18.6	N/A	1,400
Aripiprazole	3.3	76	23.0	830	115
Iloperidone	3	146	48.7	89	22
Perphenazine	1.4	130	92.9	N/A	9
Flupenthixol	0.8	102	127	N/A	5
Pimozide	5.1	874	171	N/A	35
Fluphenazine	0.32	579	1,809	334	5
Haloperidol	1.21	4,474	3,698	210	8

All affinity values are in nmol/l and derived from the standardized Psychoactive Drug Screening Database.[31] Functional brain concentration (clinical exposure) derived previously is for an average clinical dose (e.g., 6 mg/day risperidone).[7] Aripiprazole is a special case as it acts as a D_2 partial agonist with 20% maximum efficacy.[13]

17 mg/kg i.p. decreased striatal DA levels by 39%. Dopamine VTA firing was decreased by 40, 50, and 65%, respectively, at 3, 10, and 17 mg/kg i.p. Dopamine synthesis was reduced by 27 and 44%, respectively, at 3 and 10 mg/kg s.c. DOPA (3:4-dihydroxyphenylalanine) synthesis was lowered by 39% at 3.2 mg/kg and ventral striatal raclopride was increased by 30 and 40%, respectively, at 10 and 17 mg/kg s.c. Dorsal striatum raclopride was increased by 17% at the highest dose of 17 mg/kg s.c.[19] The free vabicaserin levels in the brain, in the plasma, and in cerebrospinal fluid in rats were within 1.5-fold of each other (unpublished data). *In vitro* data also showed free equilibrium in permeability assay, suggesting that vabicaserin is not a human P-gp substrate. Based on these data, it was reasonable to assume that free vabicaserin concentration in the brain is the same as the free concentration in plasma.[30]

Implementation of the updated PANSS model with 5-HT$_{2C}$

The details of incorporating direct 5-HT$_{2C}$ receptor mechanisms from the VTA dopamine firing and the cholinergic interneurons in the updated PANSS model are described below.

Using the receptor competition model together with the preclinical data on vabicaserin[19] (see above) in combination with published data on the effect of 5-HT$_{2C}$ modulation on DA activity,[2,10–12] a mathematical function was derived to describe the effect of 5-HT$_{2C}$ receptor activation on dopamine firing frequency and therefore the effects on striatal D$_1$ and D$_2$ receptor activation. Next, the effect of serotonin neurotransmission (including 5-HT$_{2C}$) on striatal cholinergic interneurons was derived. From preclinical studies[19] and assuming that the antagonists RS102221 (5-HT$_{2C}$), SB258585 (5-HT$_6$), and SB 269970 (5-HT$_7$) were used at maximal concentrations, the data suggest a maximal reduction in M$_1$ receptor activation of 33.1% for total 5-HT$_{2C}$ block, 50.5% for total 5-HT$_6$ block, and 82.3% for total 5-HT$_7$ block. Although we did not model explicitly cholinergic interneurons in the striatum, their effects on MSN neurons were implemented using the following equation:

$$M_1^{5HT2C} = 1 - 5HT2C_{M1adj} \times \left[\left(1 - \frac{5HT2C_{Act}}{5HT2C_{Con}}\right) + 1.5\left(1 - \frac{5HT6_{Act}}{5HT6_{Con}}\right) + 2.5\left(1 - \frac{5HT7_{Act}}{5HT7_{Con}}\right)\right]$$

where 5HT2C$_{M1adj}$ is a coupling parameter that is determined during recalibration, 5HTX$_{Act}$ is the activation of the 5-HTX receptor with drug, and 5HTX$_{Con}$ is the activation of the 5-HTX receptor in control situations. The different coefficients reflect the effects of total 5-HTX receptor block on M$_1$ activity, relative to 5-HT$_{2C}$ receptor. M$_1$ receptor activation changes the conductance of the leak-chloride current in the MSN as follows:

$$\Delta g_{Cl} = 0.3\frac{M_1^{Con} - M_1^{5HT2C} M_1^{Act}}{M_1^{Con}}$$

where M_1^{Con} is the activation of the M$_1$ receptor in control situations and M_1^{Act} is the activation of the M$_1$ receptor with drug. Notice that when all 5-HT receptors are at their control activations, $M_1^{5HT2C} = 1$ so that there is no effect on M_1^{Act}.

Furthermore, 5-HT$_{2C}$ receptor affects GABA interneurons in the striatum.[21] Because there are no explicit GABA interneurons in the simulation, we model their effects as an impediment to the excitability of the MSN by modifying the chloride conductance. Increased GABA interneuron firing increases the background chloride conductance in the MSN as:

$$g_{Cl} = \left\{1 - 5HT2C_{Adj}^{GABA}\left(1 - \frac{5HT2C_{Act}}{5HT2C_{Con}}\right)\right\} \cdot \hat{g}_{Cl} \cdot \Delta g_{Cl}$$

where in general, X$_{Act}$ and X$_{Con}$ are actual and baseline control receptor activation levels, $5HT2C_{Adj}^{GABA}$ is a coupling parameter that is determined during recalibration, and $\hat{g}_{Cl}$ is the default chloride leak conductance.

Clinical trial with vabicaserin

The phase IIa clinical study of vabicaserin in schizophrenia was published previously.[5] Briefly, vabicaserin was evaluated in a 6-week randomized, double-blind, placebo-controlled phase IIa study with olanzapine as an active comparator. Hospitalized subjects with acute exacerbations of schizophrenia were enrolled and randomized into one of the four treatment arms: vabicaserin 100 or 200 mg b.i.d., olanzapine 15 mg/day, or placebo for a 6-week treatment. Blinded, independent central raters performed the PANSS and the Clinical Global Impression–Severity scale (CGI-S) assessment via videoconferencing at screening, baseline and each of the 6 weekly postbaseline visits. Central rated PANSS positive was the primary end point, PANSS and PANSS negative were secondary end points. The observed improvements of PANSS (last observation carried forward mean (95% confidence interval)) were 8.57 (1.98, 15.15) and 5.91 (–0.84, 12.2) at 100 and 200 mg b.i.d., respectively. Vabicaserin concentration data was collected between 10 and 15 h after the dose was given. The average total plasma concentration and SD were 3.93 ± 3.30 and 8.58 ± 8.43 ng/ml, for the doses of 100 and 200 mg b.i.d., respectively.

Simulation of virtual patient trial

Vabicaserin plasma concentration distribution was described by a γ distribution based on the observed concentration data. This distribution was used to generate the vabicaserin plasma levels of virtual patients. The plasma levels were then converted to nmol/l brain concentrations by using a factor of 0.968 (nmol/l)/(ng/ml). This conversion is based on the free fraction in plasma protein binding and the molecular weight of vabicaserin and assuming free equilibrium in brain penetration as described in the "Preclinical data on vabicaserin" section. The corresponding brain concentration determined for every virtual patient was applied to determine the predicted improvements on PANSS. It is worthwhile to note that at steady-state twice-daily dosing, the peak-to-trough ratio of vabicaserin concentrations is less than twofold,[15] and therefore, the observed concentration data is a reasonable representation of steady-state vabicaserin exposure.

A total of 4,000 virtual patients with individual drug levels and subsequent brain target engagement levels generated from the observed mean plasma level and variability were simulated for 10 trials of 200 patients each with vabicaserin daily doses of 100 and 200 mg b.i.d. In addition, Gaussian distributions with variability of 30% around the biological coupling parameters determined from the calibration were used for the prediction of individual PANSS improvements.

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Author Contributions. J.L. and H.G. wrote the manuscript. J.L., A.O., T.A.C., and H.G. designed the research. J.L., A.S., P.R., and H.G. performed the research. J.L., A.O., T.A.C., A.S., P.R., and H.G. analyzed the data.

Conflict of Interest. A.S., P.R., and H.G. are employees of In Silico Biosciences, a company providing mechanism-based computer simulation solutions for neuroscience research and development. J.L., A.O., and T.A.C. are employees of Pfizer.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ There are limited examples of systems pharmacology approaches that incorporate relevant brain targets and circuits, knowledge of schizophrenia pathology, and polypharmacology of treatments.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ This study confirmed the predictive capability of humanized quantitative systems pharmacology computer simulations with the actual phase IIa clinical results of a novel 5-HT_{2C} agonist, vabicaserin. This study provides predictions regarding the potential lack of utility of vabicaserin treatments in schizophrenia as monotherapy and as antipsychotic augmentation, which guided the early clinical development decision of vabicaserin.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ This case study provides an example that the quantitative systems pharmacology model of biophysically realistic and humanized brain circuits may be a novel approach for quantitative clinical efficacy predictions in neuroscience disease areas.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ The quantitative systems pharmacology model of biophysically realistic and humanized brain circuits may provide an alternative approach to traditional animal models in selecting novel targets in neuroscience discovery and development.

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