Quantitative Systems Pharmacology Model to Quantify Benefits of DAAO Inhibition in Schizophrenia

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Introduction

- Evidence indicates that hypofunctioning of N-methyl-D-aspartate receptor (NMDAR)-mediated transmission and a reduction in its primary co-agonist, D-serine, may contribute to the pathophysiology of schizophrenia
- Inhibition of D-amino acid oxidase (DAAO), an enzyme responsible for D-serine degradation, results in increased D-serine in plasma and CSF and may lead to improvement in negative symptoms scores

Objectives

- To develop a QSP model that integrates D-serine life cycle, DAAO activity and NMDAR signaling at the synaptic cleft with drug PK and trafficking between periphery, brain and CSF
- To assess clinical benefits of DAAO inhibitors by relating predicted increases in NMDAR signaling to clinical outcome scores (PANSS-negative and SANS)

Methods: Model Qualification

- Rosa's PhysioPD™ Platforms are an efficient approach to Quantitative Systems Pharmacology (QSP)
- PhysioPD Platforms combine **engineering approaches** and **scientific data analysis** to clarify complex physiology and drug interactions

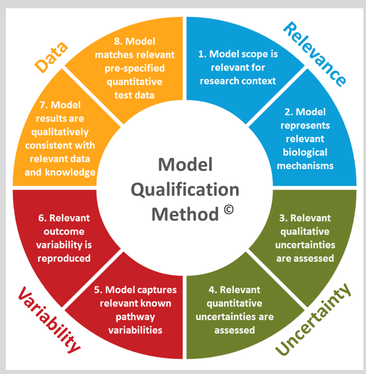

Figure 1. The Platform was qualified with Rosa's Model Qualification Method[1] (MQM)

- PhysioPD Platforms are qualified in accordance with Rosa's Model Qualification Method[1] (MQM) (Figure 1)

Methods: Virtual Patients

- Uncertainty about the details of the biological pathways was documented and explored using Virtual Patients (VPs)
- Each VP was created to explore a specific uncertainty by varying an assumption of the QSP model
- The goal of the VP exploration was to create eight different versions of the model, all consistent with data, to assess how DAAO inhibitors (sodium benzoate) may compare to D-serine oral administration under different assumptions
- The VP cohort was used to examine the mechanistic impacts of possible variability or uncertainty on the predicted efficacy of the drug therapies tested

VP	Mechanistic Change from Reference VP (VP R)
1	**10x** GluN1-2x2x EC50
2	**0.1x** GluN1-2x2x EC50
3	**0.5x** GluN1-2x2x EC50
4	Increased D-serine production in the glia, balanced by increased peroxisome uptake
5	Decreased flux of D-serine from whole brain, balanced by increased glial vesicular release
6	Increased vesicle maximum capacity
7	**10x** Equib Cleft Concentration via increased glial vesicular release

PhysioMap

The Schizophrenia PhysioPD™ Platform represents a cerebellar tripartite synapse, that is the primary site of DAAO inhibition in the brain, plus plasma and CSF compartments

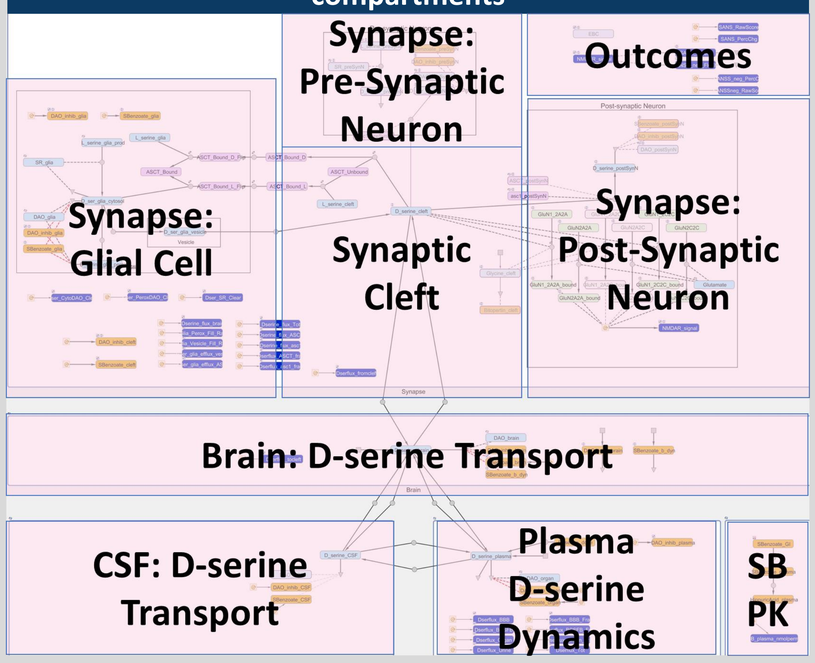

Figure 2. The Schizophrenia PhysioMap includes a synapse in the cerebellum, a general brain compartment, CSF, and plasma.

- A Schizophrenia PhysioPD Research Platform, a graphical and mathematical model, was developed to describe D-serine trafficking and NMDAR signaling in the brain and clinical outcome (Figure 2)
- In vitro, animal, and human data from published sources were used to construct the model to represent the best current scientific understanding of the included mechanisms
- PK and mechanisms of action for D-serine administration (oral source of D-serine) and sodium benzoate (SB, a moderate DAAO inhibitor) were represented

Results: Whole System Behavior

- Clinical data from 5 trials with sodium benzoate and D-serine administration were used to test whole-system behavior and establish relationships to clinical scores
- Available clinical data are sparse, and matching these data should not be construed as "validation" of the QSP model
- VPs displayed a range of responses to oral D-serine or sodium benzoate administration that are consistent with the responses seen in literature (Figure 3)

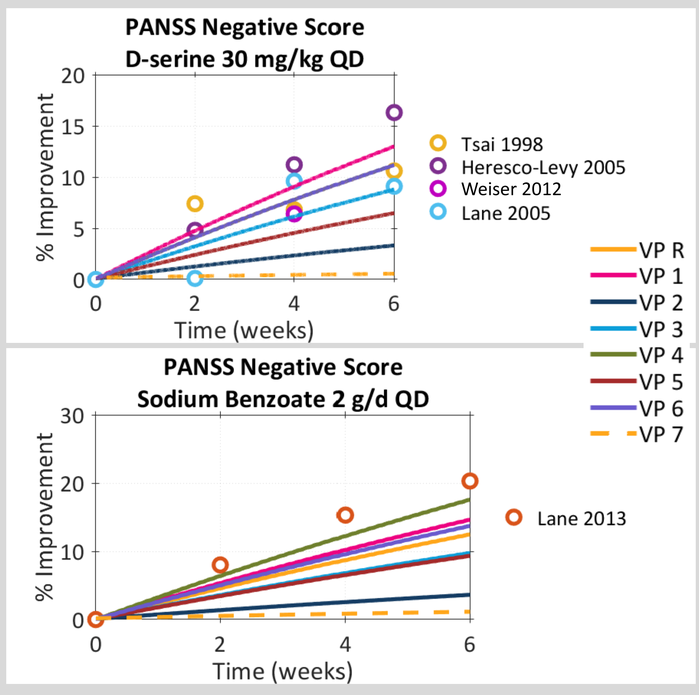

Figure 3. Comparative improvement in PANSS Negative Score in VPs over 6 weeks of simulated treatment with D-serine (top) or sodium benzoate (bottom) compared to literature data (open circles on figure)[2 - 6]

Results: DAAO Inhibitor Properties

Compound properties can be explored via Platform Sensitivity Analysis

- A sensitivity analysis was performed to investigate the impact of varying DAAO inhibitor IC50 compound properties on PANSS-negative score (Figure 4)
- Decreasing the IC50 of the inhibitor to the low μM range would have an impact on the compound efficacy, exceeding that of comparator therapies that are engaging the same NMDA-mediated mechanism
- While the empirical relationship between D-serine binding to NMDAR and symptom scores is not constrained by data beyond ~30% (See whole system behavior), results suggest synaptic mechanisms are not saturated and therefore still have room to improve

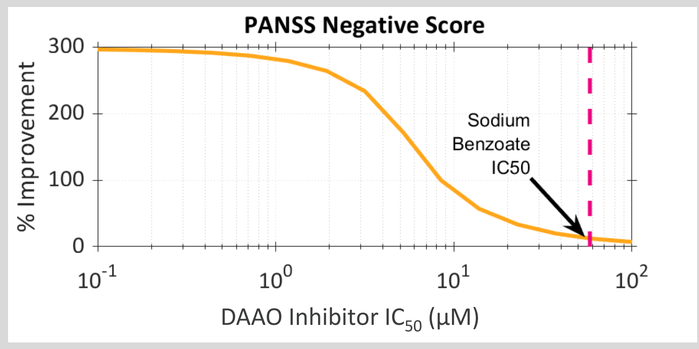

Figure 4: PANSS Negative score for a range of DAAO inhibitor IC50s after 6 weeks of treatment

Results: Mechanisms

Diffusion of D-serine from plasma to synapse contributes to DAAO inhibitor efficacy

- Given the modest improvements under oral D-serine administration, it was expected that D-serine diffusion to brain would contribute little to DAAO inhibitor efficacy
- To test this assumption, VP5 was created, with ~50% as much contribution from plasma D-serine than VP R
- Contrary to expectations, simulations show weaker efficacy for VP5 compared to VP R, illustrating that peripheral D-serine diffusion into brain may be a significant contributor to DAAO inhibitor efficacy (Fig. 5)

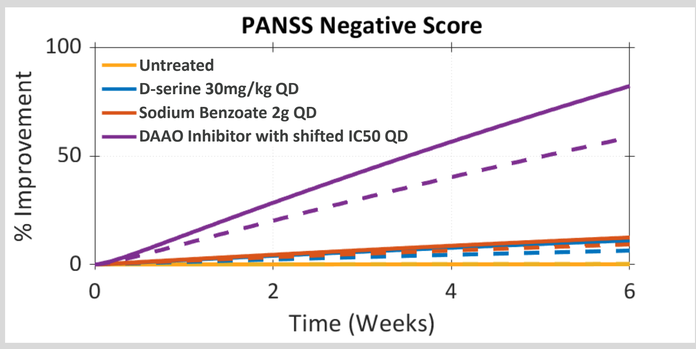

Figure 5. PANSS Negative scores in Reference VP (solid lines) versus VP 5 (dashed lines)

Conclusions

- Mechanistic modeling clarifies and quantifies biological mechanisms that connect DAAO inhibition to improvement in negative symptom scores
- Explorations using multiple Virtual Patients demonstrate that the prediction of superior efficacy due to better compound properties does not change under different assumptions
- Use of this model is expected to reduce risk for clinical development of DAAO inhibitors

References

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