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PERSPECTIVE

A modeling informed quantitative approach to salvage clinical trials interrupted due to COVID-19

Hugo Geerts | **Piet van der Graaf**

Certara-SimCyp, Berwyn, Pennsylvania, USA

Correspondence
Hugo Geerts, Head Neuroscience QSP, Certara-SimCyp, 686 Westwind Dr, Berwyn, PA 19312, USA.
Email: hugo.geerts@certara.com

Abstract

Many ongoing Alzheimer's disease central nervous system clinical trials are being disrupted and halted due to the COVID-19 pandemic. They are often of a long duration' are very complex; and involve many stakeholders, not only the scientists and regulators but also the patients and their family members. It is mandatory for us as a community to explore all possibilities to avoid losing all the knowledge we have gained from these ongoing trials. Some of these trials will need to completely restart, but a substantial number can restart after a hiatus with the proper protocol amendments. To salvage the information gathered so far, we need out-of-the-box thinking for addressing these missingness problems and to combine information from the completers with those subjects undergoing complex protocols deviations and amendments after restart in a rational, scientific way. Physiology-based pharmacokinetic (PBPK) modeling has been a cornerstone of model-informed drug development with regard to drug exposure at the site of action, taking into account individual patient characteristics. Quantitative systems pharmacology (QSP), based on biology-informed and mechanistic modeling of the interaction between a drug and neuronal circuits, is an emerging technology to simulate the pharmacodynamic effects of a drug in combination with patient-specific comedications, genotypes, and disease states on functional clinical scales. We propose to combine these two approaches into the concept of computer modeling-based virtual twin patients as a possible solution to harmonize the readouts from these complex clinical datasets in a biologically and therapeutically relevant way.

KEYWORDS
physiology-based pharmacokinetic modeling, protocol deviations, quantitative systems pharmacology

1 | INTRODUCTION

A large majority of ongoing trials have been affected by the COVID-19 pandemic and trials in Alzheimer's disease (AD) are particularly affected, because of the long duration and the specific risks of the patient population. The U.S. Food and Drug Administration (FDA) has recently published guidance stating, "FDA recognizes that protocol modifications may be required, and that there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures. The necessity for, and impact of, COVID-19 control measures on trials will vary depending on many factors, including the nature of disease under study, the trial design, and in what region(s)

the study is being conducted" (FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards March 2020, updated on April 2, 2020).

We expect that these events will lead to unprecedented issues of "missingness" in the datasets, probably far beyond the number of missing data usually encountered in clinical trials. At the time of trial pause, there will be patients who have completed the trial, those who started and were at different time points in the trial when it was interrupted, and those who enrolled but have not yet started. We expect a substantial amount of protocol amendments for the patients currently in the trial such as involuntary drug holiday (especially with intravenous [IV] formulations), change in medications (anxiolytics, antidepressants) for addressing mental health issues, and missing site visits that can be partially mitigated by remote monitoring. The involuntary drug holidays are of particular concern as the underlying pathological mechanism that was targeted with the drug is no longer affected and the patient faces a completely new pathological environment when the drug trial is restarted. In addition, because each patient starts at a unique time, they are at different points in their pathological trajectory at the time of interruption. In addition, there will be subjects from the last two groups that will not return to the trial once it restarts because AD patients face an additional burden due to their age, fragility, comorbidity, comedication, and other factors.

The number of patients that have completed the trial is likely to be insufficient to achieve the power for detecting a clinically relevant improvement. In the worst-case scenario the whole trial needs to start over again, delaying any possible successful treatment for a number of years and at an enormous cost for sponsors, patients, and their caregivers.

We cannot afford to lose all the information collected so far from these interrupted trials; therefore, we must explore all possible avenues to recover as much knowledge as possible. Traditional statistical methods such as last observation carried forward for accounting for missing data will be a first step to address this issue. However, because many of the disease-modifying studies follow the patients over 1 to 2 years, the number of missing subjects with protocol amendments can be considerable. For example, consider a regular 18-month phase III study enrolling about 600 patients/year (50/month) with an anticipated enrollment of 1800 patients. In this case when the trials are halted at any point between 18 and 32 months after start of enrollment, up to 60% of subjects in the trial can face substantial disruptions.

One novel analytical method to address this "missingness" is a virtual twin patient approach, based on mechanistic modeling, including physiologically based pharmacokinetics (PBPK) and quantitative systems pharmacology (QSP). PBPK modeling uses virtual populations to predict drug performance across all human organs, based on in vitro and in vivo data. PBPK can predict drug exposure levels in the tissue of interest (here the brain) based on patient, drug characteristics, concomitant medications, and genotypes of metabolizing enzymes and is encouraged by regulators. QSP then builds on PBPK by integrating quantitative drug data with knowledge of its mechanism of action. For complex, heterogeneous diseases such as AD, QSP predicts how drugs modify key cellular and neuronal networks involved in cognition in space and time and how functional readouts are impacted by human pathophysiology and the drug's pharmacology.

To model the pharmacodynamic and efficacy effects, a virtual twin QSP model of trial subjects, using the same comedications, genotypes, biomarkers, amyloid beta (Aβ) and tau load as in the real trial can be created. Because the pharmacology and target exposure of central nervous system (CNS) active comedications in current AD clinical practice is well documented, and the pharmacodynamical effect of certain common genotype variants can be derived from imaging studies,[9,25] we can create virtual twin patients with the same characteristics. Modeling the pharmacology and the pharmacokinetic profile of the investigative drug together will allow researchers to simulate the cognitive trajectory of these individual virtual patients. Introducing information from imaging and biofluid biomarkers could further help define both levels of target engagement for the investigative drug and disease state.

This mechanism-based QSP approach has been successfully applied in blindly predicting an unexpected clinical phase I scopolamine challenge study in healthy volunteers with a drug affecting a new yet-untested target (Nicholas et al.[20]). The modeling platform also was able to generate a testable hypothesis on the cognitive worsening of β-site amyloid precursor protein cleaving enzyme (BACE) inhibitors[13] and the different outcomes for the two phase III trials with aducanumab in AD.[12] In a different indication and with regard to pharmacodynamical drug–drug interactions, the model has documented the interaction between acetylcholinesterase inhibitors, memantine, smoking, and antipsychotics on cognitive outcome in a schizophrenia population.[11] In this particular case, the model was able to reconcile discordant findings in the literature.

Examples in other neurodegenerative diseases include an Unified Parkinson's Disease Rating Scale (UPDRS)-calibrated QSP model for motor symptoms in Parkinson's disease.[22] This model blindly predicted the complex pharmacodynamical interactions on extrapyramidal motor symptoms in a real-world clinical practice dataset of schizophrenia patients while on two antipsychotics.[16]

2 | DETAILED DESCRIPTION Of THE VIRTUAL TWIN APPROACH IN AD

2.1 | Pharmacokinetic central profile of active compound in the human brain

A computer simulation model of each patient focusing on drug levels, replicates the patient's various individual attributes that affect a drug's fate in their body and hence its effects. These attributes include the patient's age, weight, height, sex, ethnicity, and genetics of drug metabolizing enzymes and drug transporters. The simulation outcome takes into account the patient's current drug dosage, fed or fasted state,

comorbid conditions and comedications that affect the activity of certain metabolic enzymes and transporters, and level of organ function. As an example this platform was used to accurately predict olanzapine exposure in individual patients for model-informed precision dosing.[21]

Another computer model[10] simulates the interaction of pharmacological agents with transporters at the blood-brain barrier (BBB) to derive an estimate of brain or cerebrospinal fluid (CSF) penetration. This model can be adapted to the BBB in demented patients using the documented protein composition and distribution.[1] In addition, PBPK models have been developed for the uptake of monoclonal antibodies.[3] Taken together, integration of these models can inform the central drug levels at an individual patient basis.

2.2 | Calibrated ADAS-Cog model using a QSP model

The calibrated QSP model for cognition in AD has been extensively described before (Roberts et al.[23] and Nicholas et al.[20]). Basically, the model consists of a biophysically realistic network of 80 prefrontal cortex pyramidal glutamatergic and 40 GABAergic interneurons, with the effects of dopaminergic, serotonergic, noradrenergic, and cholinergic modulation (see also section S2 in supporting information) and is based on the stability of a memory trace within a working memory paradigm. The model takes into account a progressive AD neuropathology using a time-dependent elimination of synapses and neurons together with cholinergic deficit. Furthermore, this QSP model has been calibrated using 28 different drug-dose-duration interventions with acetylcholinesterase inhibitors and 5-HT_6 antagonists.[23]

For other patient populations, such as mild cognitive impairment (MCI), the cholinergic deficit is replaced by a cholinergic hyperactivity likely as a consequence of compensatory upregulation of the choline acetyl transferase enzyme.[15] Here the progressive neuronal loss over time is also reduced eight-fold to take into account the different timescales.

Current implementation of the QSP platform includes the physiology associated with the G-protein coupled receptors D_1, D_2, D_3, D_4; 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_3, 5-HT_4, 5-HT_6; M_1 and M_2 mACHR, α_7, and $\alpha_4\beta_2$ nACHR, adrenerge α_1 and α_2; the ligand-gated glutamate subtypes NR2A, NR2B, NR2C, NR2D, AMPA, GABA-A α_1, GABA-A α_2, the neurotransmitter transporters GlyT1, DAT, SERT, and NRT; the enzymes AChE, COMT, and PDE9. This will cover most of the approved CNS active medications.

2.3 | Implementation of the pharmacodynamic effect of comedications

The receptor model has been described in detail in other works[27,28] (see section S1 in supporting information). Basically, this module simulates the competition between neurotransmitters, active moiety of drugs, and positron emission tomography (PET) tracer molecules (if present) at the postsynaptic receptor, for example a dopamine synapse under natural in vivo firing conditions. The model can be extended to other neurotransmitter systems such as serotonin, norepinephrine, and cholinergic systems and can also be used to determine the impact of common gene variants on neurotransmitter dynamics (see below).

Target engagement of donepezil, an AChE-inhibitor with a K_i of 20 nM[30] is derived from imaging studies with ^{11}C-PMP.[11] This corresponds to brain AChE-inhibition levels of 35% at 10 mg[6,24] and leads to ACh half-lives of 6.9 and 7.7 milliseconds for donepezil at 5 and 10 mg and to half-lives of 5.9, 6.8, and 7.7 milliseconds for galantamine at 8, 16, and 24 mg with similar outcomes for rivastigmine. The subsequent changes in ACh half-life affects activation levels of muscarinic and nicotinic receptors, leading to corresponding modifications in glutamate and GABA (see Table S2 in supporting information for biological references).

In addition, the small allosteric potentiating effect of galantamine on nAChR[30] is implemented as a 10% or 15% (respectively, for 16 and 24 mg) relative increase in both α_7 nAChR and $\alpha_4\beta_2$ nAChR activation levels.

Memantine is a relatively weak NMDA-R inhibitor that has a larger affinity for the NMDA-NR2C/2D subunit[18] in physiological conditions. Based upon the observation that the NR2C/2D subunits are preferentially located on inhibitory interneurons,[19] memantine's pharmacology is implemented using a two-fold greater inhibition on interneurons as compared to pyramidal cells. Data further suggest that the functional memantine concentration in the human brain is relatively small in the range of a 1% decrease in gNMDA on interneurons.[23]

First-generation benzodiazepines (such as lorazepam) are implemented as agonists at the GABA-A α1 and GABA-A α2 receptor. The α1 receptor is localized both on inhibitory-excitatory and on inhibitory-inhibitory GABAergic synapses, while α2 is predominantly located at the inhibitory-excitatory synapses. Second-generation benzodiazepines such as midazolam more preferentially affecting the α2R, are implemented by reducing the effect at the α1 inhibitory-inhibitory synapses by 50% compared to the effect at α2 inhibitory-excitatory synapses. Different doses can be implemented ranging from 2.5% to 10% reduction at α1R.

Anti-depressants are implemented by increasing the half-life of serotonin dose-dependently between 6.25% and 25% increase with corresponding effects on all the 5-HTR implemented in the model (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5HT_3, 5HT_4, and 5HT_6).

The pharmacodynamic effect of active moiety (including the pharmacology of metabolites) of antipsychotics such as risperidone, paliperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole is implemented at a low dose, corresponding to one third of the dose taken by schizophrenia patients.[11] The affinity parameters for each individual drug and neurotransmitter for all the human receptors were derived from the standardized Psychoactive Drug Screening Program (PDSP) database (http://pdsp.med.unc.edu/indexR.html).[2] Functional intrasynaptic concentration of the various antipsychotics were derived using the receptor competition model, described above with published ^{11}C-raclopride displacements.

2.4 | Implementation of the pharmacodynamic effect of some common genotype variants

The same receptor competition model can be used to determine the pharmacodynamic effect of genotypes. To reproduce experimental findings that the COMTVal158Met genotype affects the displacement of the D_1R PET radiotracer NNC-112 in healthy unmedicated volunteers,[25] the synaptic half-life of dopamine in the COMTVV case was adjusted to 100 milliseconds, 130 milliseconds in the COMTMV, and 160 millisecond in the COMTMM case. Similarly, the displacement of the 5-HT_4 PET tracer [11C]SB207145 is dependent upon the 5-HTTLPR s/l isoform,[9] resulting in a half-life of 55 milliseconds for the LL case, 75 milliseconds for the Ls case, and 100 milliseconds for the ss case.

Apolipoprotein E (APOE) genotypes can be implemented using different synapse densities with APOE4 homozygotes a 20% lower and non-APOE4 carriers had a 20% higher synapse density compared to APOE4 heterozygote genotype.[4,8,17]

2.5 | Implementation of amyloid pathology

The effect of amyloid load on cognitive outcome has been described in detail in other works.[12,13] Basically, the differential dose-dependent effect of short (Aβ40) and long (Aβ42) forms on glutamatergic[29] and nicotinic neurotransmission[5] is implemented for the amyloid trajectory of individual patients and translated into an anticipated Alzheimer's Disease Cognitive Assessment Scale-Cognitive Subscale (ADAS-Cog) readout. In this implementation, Aβ is not assumed to enhance the toxicity of neurons; neurotoxicity is likely driven by other factors, such as tau pathology and oxidative stress. As discussed above, with forced drug holidays for amyloid reducing agents, the model can simulate the cognitive outcome for an individual patient amyloid trajectory while taking into account the specific interruption in treatment and reversal to the natural progression history.

2.6 | Implementation of tau pathology

The effect of tau pathology on neuronal firing dynamics and brain region activity can be simulated based on preclinical data illustrating the effect of tau oligomers on action potential characteristics, most notably the widening of the action potential profile.[14] This can be basically reproduced by reducing Na-conductance at the axon initial segment (AIS) and K+ conductance in other compartments of the neuronal cells. This is in line with electrophysiology measurements in an FTD V337M hIPSC cell line.[26] Widening the action potential can affect neuronal synchronization and affect emerging properties in networks that are related to cognitive outcome.

For tau modulating agents affecting spatio-temporal progression of tau pathology, an extensive QSP model has been developed that includes tau secretion, extracellular processes such as capture by antibodies, diffusion along the axonal sheet, and binding to acceptor molecules; internalization, axonal transport along microtubule, oligomerization with endogenous tau, and degradation of misfolded tau protein to secretion into the next synapse.[7] This model has been extensively validated with preclinical and clinical data.

2.7 | Validation strategy

A particularly interesting aspect of this approach is the de-risking of the model's predictability by introducing a number of validation steps. This can take place in three steps (see Figure 1).

1. A virtual twin population from the completers database will be generated with exactly the same properties as the real population in terms of comedications, genotypes, amyloid and tau status, and the baseline cognitive readout taht is related to disease state. There is no need to know final outcome data from this cohort of subjects that have completed the full trial. The QSP model will then generate a fully blinded set of expected clinical outcomes at the individual patient level, which can be compared to the real outcomes. In the worst-case scenario where there is no alignment between predicted and actual functional data, a sensitivity analysis can help to identify key shortcomings and ultimately iteratively improve the QSP model.
2. A second similar validation strategy can also be applied to partial completers if they have intermediate functional readouts (for instance half-way through the trial), again based on baseline conditions as outlined above. The QSP model will then derive predictions for the intermediate functional readouts at the individual patient level.
3. A third validation step is based on the predictions of clinical outcomes for those patients that have re-started the trial, based on the baseline conditions when they started the trial but now when including the many protocol amendments (drug holiday, change of medication, etc.). For the patients who are re-starting, the model would generate the anticipated functional trajectory for the new modified protocol which will be compared to the actual functional readout at the end of the study.

Once these validations are performed satisfactorily with a predefined similarity criterion, this method can then be applied prospectively to predict clinical progression of the original protocol design for those patients that had their trial interrupted (see Figure 1). The Virtual Twin platform could simulate the outcome of the non-interrupted virtual twin by "projecting" the anticipated clinical trajectory according to the unchanged trial protocol. In addition, for some dropout patients, final simulated outcome at the end of the full original trial could be generated. In principle, this "stitching or bridging together" would allow researchers to "pool" these new data with the data from the completer cohort and hopefully generate larger patient cohorts to mitigate the

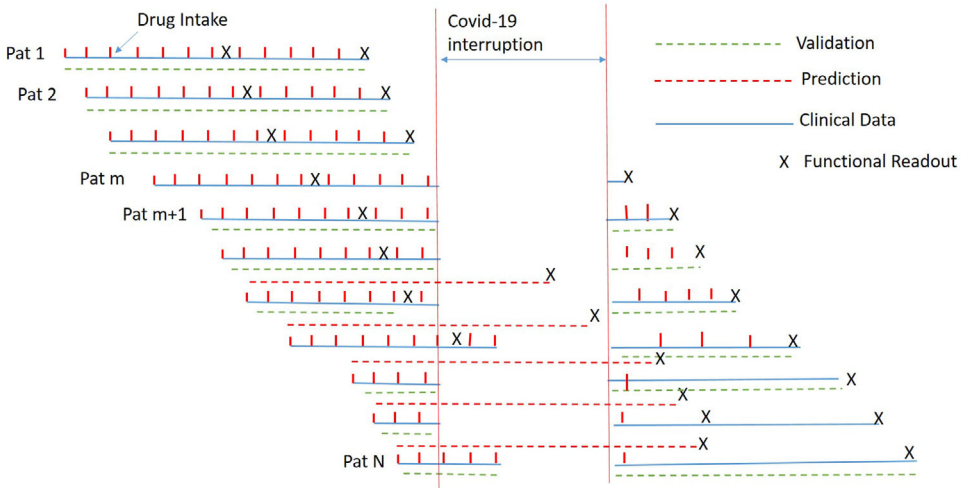

FIGURE 1 Detailed description of the quantitative systems pharmacology virtual twin approach. A number of patients have already completed the trial (top rows), while others who have started but not yet finished (bottom rows) will have different type of interruptions. Drug intakes (for instance biweekly antibody injections) are represented by red marks whereas X stands for a clinical visit and readout. The green stippled lines are predictions based on baseline characteristics for the actual duration of the trial for each individual patient. The patients that have not yet finished have either intermediate functional readouts or readouts after protocol amendments and trial resumption and the virtual twin predictions can be compared to these actual outcomes. The red stippled lines are then predicted outcomes from the virtual twin platform for the patients with interrupted trials and subjects that have dropped out, but according to their original uninterrupted functional trajectory. In this way the virtual twin approach can "stitch" the outcomes together and allow the real completers (patients 1.M-1) and the virtual completers (patients M..N) to be "pooled," allowing for an analysis by the original statistical plan

intrinsic variability. In this way the original power calculations and statistical analysis plan can be used.

3 | DISCUSSION

This report described a new potential approach to address the many protocol amendments and drop-outs happening in the middle of ongoing AD trials as a consequence of the COVID-19 pandemic. The approach is based on the concept of the virtual twin in which each individual patient is replaced with a computer model of multiple tissues for brain exposure and neuronal brain circuits, relevant for cognitive readout and where specific properties such as comedications, certain genotypes, and individual amyloid and tau status can be explicitly introduced, based on biophysical principles on how they interact with the investigative drug or placebo. Because this approach works at the individual patient level, it can deal with large amounts of missing data and account for many different possibilities, including unforced drug holiday and change of medications. The approach needs also much less information compared to other statistical or bioinformatics approaches.

The current version of this model allows researchers to run virtual patient trials in AD and tauopathies on amyloid and tau modulating agents, in addition to symptomatic treatments affecting a wide range of dopaminergic, serotonergic, cholinergic, glutamatergic, GABAergic, and norepinephrine neurotransmitters. Other therapeutic approaches such as neuroprotection, neuroinflammation, and mitochondrial stabilization are currently out of range but can in principle be integrated in later versions.

A particularly interesting aspect of this approach is the emphasis on validation. Because the model is already calibrated on group average data from publicly available sources, the relevant parameters for the additional pharmacodynamic interactions with comedications and genotypes can be reasonably constrained with even a small number of completers. In the situation where there are no completers (for instance when trials were interrupted before the first completers read out), data from other completed trials with similar or slightly different therapeutic interventions could be used for validation. Even if these trials were negative, there is probably a distribution of good responders, non-responders, and subjects worsening over time. Ideally, pooling data from different sponsors might be another solution to cover a large range of targets and conditions. It has to be emphasized that this validation will be performed by prospectively predicting the functional outcome solely based on the baseline characteristics without knowledge of the outcome.

There are a number of limitations in this approach. As mentioned above the current version of the platform does not cover all therapeutic interventions, therefore a number of targets currently being tested in the clinic are beyond the scope of the model. There might be other genotypes that drive the clinical outcome beyond the three implemented here, for instance the BDNFVal66Met genotype. Although baseline biomarkers of amyloid, tau load status, and brain atrophy can provide a fairly good estimate of the pathology, only in those cases in which we have intermediate sequential biomarker readouts do we have an estimate for the individual rate of pathology accumulation and subsequent cognitive trajectory.

This model uses ADAS-Cog as the primary readout. Many ongoing trials use different clinical scales such as AD Composite Score

(ADCOMS) and Clinical Dementia Rating-Sum of Boxes (CDR-SOB). It might be possible to derive relationships between these scales, as they are all functional. An alternative possibility is to normalize all readouts back to the ADAS-Cog outcome, generated by the predictive platform, and compare that outcome between the treatment arms. Finally, another major limitation of this approach is the unknown central effects of the SARS CoV-2 virus for those patients who become infected; these might interfere with the AD pathology or at least impact the functional cognitive readout. Importantly, the validation steps (especially step 3) outlined above can address this possibility in more detail.

In summary, a virtual twin approach using QSP with the extensive validation as outlined in this paper, can enable the extrapolation of the clinical trajectory for the many patients unable to complete the trial, thereby helping to salvage the information gathered at substantial human and investment cost for the research participants, their family members, health-care professionals, and sponsors. When the trial restarts (likely with a new protocol), the platform in principle can bridge the before and after to hopefully salvage the investment and communicate continuity of information with scientists and regulators.

CONFLICTS OF INTEREST

The authors are employees of Certara-SimCyp.

REFERENCES

1. Al-Majdoub ZM, Feteisi Al, Achour H, et al. Proteomic quantification of human blood-brain barrier slc and abc transporters in healthy individuals and dementia patients. *Mol Pharm*. 2019;16(3):1220-1233.
2. Besnard J, Ruda GF, Setola V, et al. Automated design of ligands to polypharmacological profiles. *Nature*. 2012;492(7428):215-220.
3. Chang HY, Wu S, Meno-Tetang G, Shah DK. A translational platform PBPK model for antibody disposition in the brain. *J Pharmacokinetics Pharmacodynamics*. 2019;46(4):319-338.
4. Chung WS, Verghese PB, Chakraborty C, et al. Novel allele-dependent role for APOE in controlling the rate of synapse pruning by astrocytes. *Proc Natl Acad Sci USA*. 2016;113(36):10186-10191.
5. D'Andrea MR, Nagele RG. Targeting the alpha 7 nicotinic acetylcholine receptor to reduce amyloid accumulation in Alzheimer's disease pyramidal neurons. *Curr Pharm Des*. 2006;12(6):677-684.
6. Darreh-Shori T, Kadir A, Almkvist O, et al. Inhibition of acetylcholinesterase in CSF versus brain assessed by 11C-PMP PET in AD patients treated with galantamine. *Neurobiol Aging*. 2008;29(2):168-184.
7. Diaz K, Jeromin SA, Haas M, Geerts H. A computer model simulating the effect of Tau antibodies on the inter-cellular spread of Tau. *Alzheimer's Dementia*. 2019;15(75):24.
8. Dumanis SB, Tesoriero JA, Babus LW, et al. ApoE4 decreases spine density and dendritic complexity in cortical neurons in vivo. *J Neurosci*. 2009;29(48):15317-15322.
9. Fisher PM, Holst KK, Mahon Mc, et al. 5-HTTLPR status predictive of neocortical 5-HT4 binding assessed with [(11)C]SB207145 PET in humans. *NeuroImage*. 2012;62(1):130-136.
10. Gaohua L, Neuhoff S, Johnson TN, Rostami-Hodjegan A, Jamei M. Development of a permeability-limited model of the human brain and cerebrospinal fluid (CSF) to integrate known physiological and biological knowledge: estimating time varying CSF drug concentrations and their variability using in vitro data. *Drug Metab Pharmacokinet*. 2016;31(3):224-233.
11. Geerts H, Roberts P, Spiros A. Assessing the synergy between cholinomimetics and memantine as augmentation therapy in cognitive impairment in schizophrenia. A virtual human patient trial using quantitative systems pharmacology. *Front Pharmacol*. 2015;6:198.
12. Geerts H, Spiros A. Learning from amyloid trials in Alzheimer's disease. A virtual patient analysis using a quantitative systems pharmacology approach. *Alzheimer's Dementia*. 2020;16(6):862-872.
13. Geerts H, Spiros A, Roberts P. Impact of amyloid-beta changes on cognitive outcomes in Alzheimer's disease: analysis of clinical trials using a quantitative systems pharmacology model. *Alzheimer's Res Ther*. 2018;10(1):14.
14. Hill E, Karikari TK, Moffat KG, Richardson MJE, Wall MJ. Introduction of tau oligomers into cortical neurons alters action potential dynamics and disrupts synaptic transmission and plasticity. *eNeuro*. 2019;6(5).
15. Ikonomovic MD, Mufson EJ, Wuu J, Cochran EJ, Bennett DA, DeKosky ST. Cholinergic plasticity in hippocampus of individuals with mild cognitive impairment: correlation with Alzheimer's neuropathology. *J Alzheimer's Dis*. 2003;5(1):39-48.
16. Kadra G, Spiros A, Shetty H, et al. Predicting parkinsonism side-effects of antipsychotic polypharmacy prescribed in secondary mental healthcare. *J Psychopharmacol*. 2018:269881118796809.
17. Kim J, Yoon H, Basak J. Apolipoprotein E in synaptic plasticity and Alzheimer's disease: potential cellular and molecular mechanisms. *Mol Cells*. 2014;37(11):767-776.
18. Kotermanski SE, Johnson J. Mg2+ imparts NMDA receptor subtype selectivity to the Alzheimer's drug memantine. *J Neurosci*. 2009;29(9):2774-2779.
19. Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg PH. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. *Neuron*. 1994;12(3):529-540.
20. Nicholas T, Duvvuri Sridhar, Leurent Claire, Raunig David, et al. Systems Pharmacology Modeling in Neuroscience: Prediction and Outcome of PF-04995274, a 5HT4 Partial Agonist, in a Clinical Scopolamine Impairment Trial. *Advances Alzheimer's Dis*. 2013;2(3):83-98.
21. Polasek TM, Tucker GT, Sorich MJ, et al. Prediction of olanzapine exposure in individual patients using physiologically based pharmacokinetic modelling and simulation. *Br J Clin Pharmacol*. 2018;84(3):462-476.
22. Roberts P, Spiros A, Geerts H. A Humanized Clinically Calibrated Quantitative Systems Pharmacology Model for Hypokinetic Motor Symptoms in Parkinson's Disease. *Front Pharmacol*. 2016;7:6.
23. Roberts PD, Spiros A, Geerts H. (A) Simulations of symptomatic treatments for Alzheimer's disease: computational analysis of pathology and mechanisms of drug action. *Alzheimers Res Ther*. 2012;4(6):50.
24. Shinotoh H, Aotsuka A, Fukushi K, et al. Effect of donepezil on brain acetylcholinesterase activity in patients with AD measured by PET. *Neurology*. 2001;56(3):408-410.
25. Slifstein M, Kolachana B, Simpson EH, et al. COMT genotype predicts cortical-limbic D1 receptor availability measured with [11C]NNC112 and PET. *Mol Psychiatry*. 2008;13(8):821-827.
26. Sohn PD, Huang CT, Yan R, et al. Pathogenic tau impairs axon initial segment plasticity and excitability homeostasis. *Neuron*. 2019;104(3):458-470.
27. Spiros A, Carr R, Geerts H. Not all partial dopamine D(2) receptor agonists are the same in treating schizophrenia. exploring the effects of bifeprunox and aripiprazole using a computer model of a primate striatal dopaminergic synapse. *Neuropsychiatr Dis Treat*. 2010;6:589-603.
28. Spiros A, Geerts H. A quantitative way to estimate clinical off-target effects for human membrane brain targets in CNS research and development. *J Exp Pharmacol*. 2012;4:53-61.
29. Wang Y, Zhou TH, Zhi Z, Barakat A, Hlatky L, Querfurth H. Multiple effects of beta-amyloid on single excitatory synaptic connections in the PFC. *Front Cell Neurosci*. 2013;7:129.

30. Woodruff-Pak DS, Lander C, Geerts H. Nicotinic cholinergic modulation: galantamine as a prototype. *CNS Drug Rev*. 2002;8(4):405-426.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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