Model Innovation in Parkinson's Disease Drug Development: Linking Quantitative Systems Pharmacology to the Patient Voice

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Objective:

There is a growing sense of urgency to integrate the voice of the patient in drug development in Parkinson's disease (PD). Public private partnerships are uniquely poised to align stakeholders and enable innovative patient-focused drug development paradigms. Strategy and initial progress will be presented on the development of a unique Quantitative Systems Pharmacology (QSP) model for PD therapeutics.

Background:

QSP uses mathematical models to characterize pathophysiology and drug pharmacology in the development of new pharmaceuticals. The heterogeneous nature of PD pathophysiology, however, can lead to unanticipated side effects, off-target effects, pharmacodynamic drug interactions, and poor patient response in general. A fully validated QSP model for will require PD patient engagement in designing the model and identifying the appropriate targets.

FIGURE 1

Distinct time regions for various common sampled data sources in past attempts to understand Parkinson's Disease progression and heterogeneity. Only through merging and integrating these data sources can we develop credible PD patient phenotypes and meaningful disease progression trajectories.

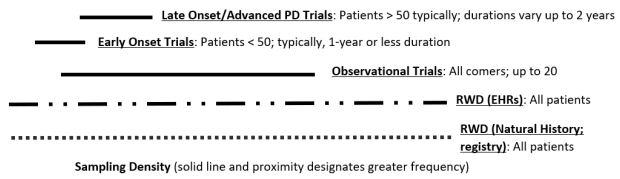

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TABLE 1

Recently FDA-approved drugs for Parkinson's Disease illustrating the known versus unknown elements of Mechanism of Action (MOA) in support of the need for a holistic Quantitative Systems Pharmacology for the myriad of etiologies currently classified as PD

Year Approved	Drug Name (Class)	Indication	Presumed MOA	Evidence (POC established?)
1999	Entacapone (COMT inhibitor)	Adjunct to levodopa/carbidopa in patients with idiopathic Parkinson's Disease who experiences signs and symptoms of end-of-dose "wearing-off"	Believed to be through its ability to inhibit COMT and alter the plasma pharmacokinetics of levodopa.	Characterized by documented periods of "on" (periods of good functioning) and "off" (periods of relatively poor functioning), despite optimum levodopa therapy; not systematically evaluated in patients who do not experience fluctuations
2004	Apomorphine (multi-modal actions: aporphine alkaloid; alpha-adrenergic, serotonergic, anti-dyskinesia agent, and dopamine agonist	Indicated for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) in patients with advanced Parkinson's disease.	The precise mechanism of action as a treatment for Parkinson's disease is unknown, although it is believed to be due to stimulation of post-synaptic dopamine D2-type receptors within the caudate putamen in the brain.	Based on UPDRS scores in 3 clinical trials: many side effects and narrow therapeutic window
2007	Rotigotine (Neupro)	Indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.	The precise mechanism of action of rotigotine as a treatment for Parkinson's disease is unknown, although it is thought to be related to its ability to stimulate dopamine receptors within the caudate putamen in the brain	Effectiveness demonstrated in randomized, controlled trials in patients with early-stage Parkinson's disease not receiving concomitant levodopa therapy as well as in patients with advanced-stage Parkinson's disease on concomitant levodopa.
2007	Rivastigmine (Exelon)	Indicated for the treatment of mild-to-moderate dementia associated with Parkinson's disease (PD)	Precise mechanism of rivastigmine's action is unknown; postulated to exert its therapeutic effect by enhancing cholinergic function (accomplished by increasing the concentration of acetylcholine by reversible inhibition of its hydrolysis by cholinesterase).	The effect of rivastigmine may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process.
2014	Droxidopa (Nothera)	Indicated for symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and nondiabetic autonomic neuropathy	NORTHERA is directly metabolized to NE and is believed to exert its pharmacological effects through NE; The exact mechanism of action of NORTHERA is unknown	Primary efficacy endpoint was mean change from randomization to the end of study in the Orthostatic Hypotension Questionnaire (OHQ) composite score, a patient-reported outcome that measures symptoms of nOH and impact on patient's ability to perform daily activities that require standing and walking
2015	Carbidopa / levodopa extended release (Rytary)	Indicated for the treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.	Mechanism of action presumed the same as IR carbidopa/levodopa – still poorly understood.	Improved symptoms in patients with both early and advanced PD and offered significantly improved Unified Parkinson Disease Rating Scale scores and "on" times, without worsening troublesome dyskinesias when compared to other levodopa formulations.
2015	Carbidopa / levodopa intestinal form (Duopa)	Indicated for Parkinson disease, postencephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication	Mechanism of action presumed the same as IR carbidopa/levodopa – still poorly understood.	Significant improvements in 'off' time and 'on' time without troublesome dyskinesia, and QoL measures maintained in the longer term.
2016	Pimivanserin (Nuplazid)	Indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis	Presumed related to antagonist/inverse agonist at serotonin 5HT2A receptors; less potent antagonist/inverse agonist actions at 5HT2C receptors.	Ongoing - primary clinical endpoint is reduction in the Positive and Negative Syndrome Scale (PANSS) positive score. Secondary clinical endpoints comprise multiple clinical ratings (positive and negative symptoms, depressive-, obsessive-compulsive symptoms, quality of life, social functioning, sexual functioning, and side-effects)
2017	Safinamide (Xadago)	Adjunctive treatment to carbidopa/levodopa in patients with Parkinson disease experiencing "off" episodes; has not been shown to be effective as monotherapy for the treatment of Parkinson disease.	Presumed reversible inhibition of selective MAO-B, as a mesylate salt, thus reducing the degradation of dopamine; inhibits glutamate release and dopamine reuptake in the brain.	Meta-analysis confirmed benefit as add-on therapy for Parkinson's disease patients suffering from motor fluctuations.
2017	Amantadine (Gocovri)	Indicated in the treatment of parkinsonism and drug-induced extrapyramidal reactions.	Not completely understood; weak, non-competitive antagonist of the NMDA receptor, which increases dopamine release and prevents dopamine reuptake.	POC based on reduction in L-DOPA-induced dyskinesia in PD patients; notable that Phase III studies were not required to switch from an anti-parkinsonian to an antidyskinetic indication, and amantadine became the first drug widely used to suppress treatment-related dyskinesia in PD
2018	Levodopa inhalation (Inbrija)	Indicated for intermittent treatment of Off episodes in patients with PD treated with carbidopa/levodopa.	Presumed based on conversion to dopamine in the brain - thought to be the mechanism whereby levodopa relieves the symptoms of PD.	Based on primary endpoint of change in UPDRS Part III motor score from pre-dose Off state to 30 minutes post-dose, measured at Week 12

Methods:

An initial QSP model framework will be generated using the LIFE approach developed by Rutgers' QSP group and in collaboration with the QSP Steering Committee. An extensive literature review will be harmonized using artificial intelligence/machine learning querying to form the base for the QSP model. Software tools for the simulation of the QSP model will also be developed. A platform (QTIPS) will be created that will serve as a conduit for PD patients' real-world experiences in the development of the model.

Results:

Identification of the target literature for the initial QSP model development has been initiated. An R/Shiny-based prototype QTIPS platform has been developed (https://kylebarrett.shinyapps.io/QSP_Builder) as a proof-of-concept tool to facilitate patient engagement. Input from people living with PD has been ongoing to assure that the QSP model reflects concepts and potential new targets that are aligned with patient needs..

Conclusions:

The development of a QSP model for PD drug development complements important principles of the Critical Path for Parkinson's Consortium by engaging the PD patient's voice, both on the developmental side and as a contributor of real-world data. This will allow to perform virtual trials informed by the final, validated QSP model, to generate patients (clinical avatars) that better resemble real-life patients. QTIPS may have tremendous impact for drug development and provide a tool for PD patients to make more informed individualized drug choices.

Next Steps:

CPP in partnership with Rutgers University has initiated a project to conduct a landscape analysis of QSP in PD and develop a proof-of-concept model over the next two years. Through a consortium approach, CPP will be able to solicit input from people with Parkinson's and technical advice from PD experts across industry, academia, non-profits organizations, and regulators.

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