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What Is the Role of Dopamine Transporter Imaging in Parkinson Prevention Clinical Trials?

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Recent advances in the understanding of the natural course of brain pathophysiology in the major neurodegenerative disorders including Alzheimer disease and Parkinson disease (PD) have led to therapeutic approaches targeting abnormal brain protein deposition. In PD in particular, there is a need for reliable biomarkers to assess and quantify the clinical consequences of this pathology and support clinical evaluation of the efficacy of new therapeutic strategies. Some clinical measures tracked longitudinally can provide evidence for the efficacy of the therapeutic intervention. These include both motor and non-motor assessments like the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDSUPDRS), quality of life measures, and attaining clinical milestones (e.g., need for medication, onset of falling). Unfortunately, these measures were not developed for tracking the slow rate of clinical change and its high variability between PD patients, nor the resulting difficulty in measuring a reduction in the rate of change of these outcomes. Furthermore, many current trials seek eligibility determinations for trial enrollment in early disease, especially in identifying premotor PD and at-risk individuals for whom, theoretically, the treatment may delay or even prevent the onset of some clinical manifestations of early PD.[1,2] In this context, CSF, blood and tissue biomarkers, genomics, and imaging have all been proposed as potential tools to aid in clinical trial eligibility determinations, as well as monitoring the natural course of illness and measuring the efficacy of treatment on slowing disease progression.[3,4] Imaging is of value in providing a phenotypic snapshot in living human brain of specific pathologic processes that would otherwise only be obtainable at postmortem.[5,6]

In considering these research applications of biomarkers, 123-I ioflupane SPECT has the longest track record among imaging biomarkers used in this context with potentially high sensitivity for detecting subtle changes in brain many years before the manifestation of motor symptoms. Review of the potential roles of dopamine transporter (DaT) SPECT imaging serves as a case study for consideration of the issues that apply to all biomarkers for these challenging studies. Is the biomarker reliable across clinical sites, logistically feasible, quantitative, and with adequate reproducibility and signal to noise to track longitudinal changes? Can the biomarker be used in any of the following scenarios: in screening at-risk individuals or enhancing the diagnostic accuracy of the cohort, tracking serial changes over time, or providing objective evidence of drug-target engagement or treatment efficacy in slowing, halting, or reversing the expected trajectory of change?

What Do We Want to Measure?

Ideally, we want to measure the change of some outcomes over time, which reflects the disease pathology as it manifests in the meaningful change in clinical and/or functional outcome measures in early disease. When comparing the onset and progression of clinical outcomes such as MDS-UPDRS motor scores with biomarkers of brain pathology, the latter shows changes well before clinical motor symptoms arise, meaning much is happening in brain without any discernible clinical effects. As a result, by the time diagnosis is made, there may be a 50%

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Glossary

BPnd = binding potential; **DaT** = dopamine transporter; **GBA** = glucocerebrosidase A; **LRRK2** = leucine-rich repeat kinase 2; **MDS-UPDRS** = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; **PD** = Parkinson disease; **RBD** = REM sleep behavior disorder; **SBR** = specific binding ratio.

reduction in a measure such as dopamine transporter density in patients manifesting with very early motor symptoms.[7,8] This suggests that there is a long period of change during which individuals remain clinically silent. It is possible there may be strategies using multiple, staged biomarker assessments to render an accurate prediction or probability that an individual is at risk for phenotype conversion to PD within an expected time frame. The goal is to catch high-risk persons early in the neurodegenerative process to prolong the time to motor symptom onset.

Optimally we would like to measure objective pathophysiologic changes occurring in the brain separate from the downstream processing that occurs in motor networks and nonmotor pathways. Currently, we can target the nigrostriatal dopaminergic network integrity with DaT imaging agents such as 123-I ioflupane with SPECT or vesicular transporter tracers (e.g., ^{18}F AV-133) and dopamine metabolism by ^{18}F-FDOPA with PET. Ideally, a better target might be alpha-synuclein deposition, a primary etiologic event involved in the formation and spread of Lewy bodies and more directly related to the symptom expression, as suggested in pathologic studies by Braack and others.[9,10] The relative advantages and drawbacks of the various options for quantitative scintigraphic biomarkers in PD clinical also need consideration of logistical factors such as availability to multiple sites. This discussion is beyond the scope of this article. Rather we focus here on 123-I ioflupane SPECT, arguably the most widely used imaging tool in PD research. For more than 2 decades in Europe and 1 decade in the United States, it has been possible to use the commercially available agent to assess the density and pattern of dopamine transporters as an adjunct in clinical diagnosis by characterizing the integrity of the synaptic terminals arising from nigral projections to the striatum. The agent has been used in research for even longer than that resulting in a body of knowledge supporting a role in PD clinical trials, but is it useful in disease prevention trials?

What We Know

From a technical standpoint, while the primary clinical assessment of 123-I ioflupane SPECT is a qualitative, binary read for positivity, the needs of multicenter PD treatment trials require a quantitative outcome for assessing relatively small changes over time. In this regard, the pharmacokinetics of 123-I ioflupane provide a route to a semiquantitative measure, the specific binding ratio (SBR) that is theoretically linearly related to the density of the target site. The striatal count density measured from the image and dividing by a background region (occipital lobe or cerebellum) minus 1 gives the SBR obtained when scanning occurs during equilibrium or secular equilibrium of tracer specific binding to its target. This condition is met 3–4 hours after injection when 123-I ioflupane achieves secular equilibrium, meaning the rates of washout from the target bound and background region are equal, resulting in an unchanging ratio measure. This is an estimate of the binding potential (BPnd) which is equal to Bmax/Kd, the density of transporters divided by the inverse of the affinity to the receptor/transporter.[11] SBR is not an absolute measure of DaT such as BPnd and can overestimate or underestimate BPnd depending on pharmacokinetics, image reconstruction, region of interest sampling method, etc.

Although the outcome measure SBR is well-understood from pharmacokinetic modeling theory, the implementation of this outcome in a PD treatment trial requires multiple imaging sites with different cameras and site practices and procedures, all of which conspire against the robust intersite comparability for a poolable quantitative dataset. Image standardization was a critical initial priority of the Parkinson Progression Marker Initiative study, an international naturalistic study of PD biomarkers for evaluating progression, which developed standardization practices currently in use.[12]

Relevant to PD prevention trials where confirmation of a DaT deficit in at-risk individuals, disease monitoring, or other use of DaT imaging might be considered, there is much information about the performance of 123-I ioflupane known, but also much that we still need to understand. Focusing first on what we know, 4 observations regarding DaT-SPECT may be germane to PD preventive trials.

Observation 1

There is about a 50% reduction of age-expected SBR in early patients at the cusp of their clinical PD diagnosis.

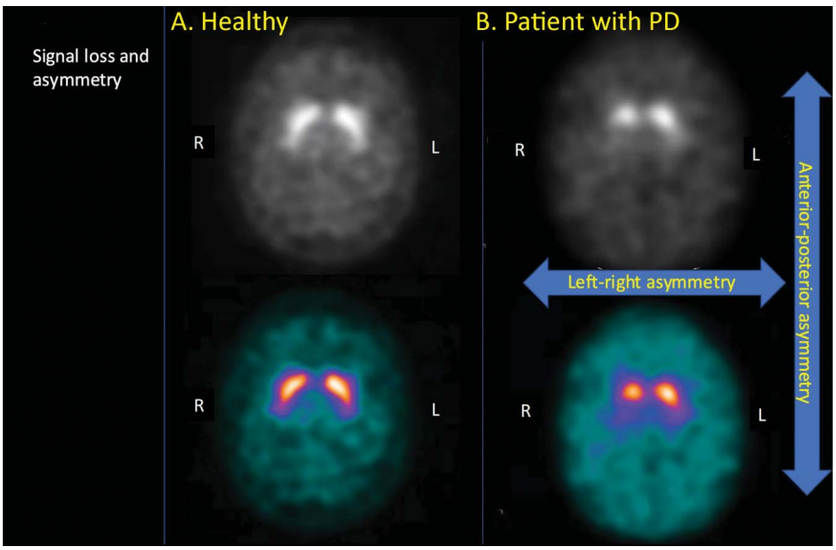
This is good in the sense it may be possible to find these individuals to try to slow down or even stave off the onset of motor symptoms. However, it is very hard to find these individuals in a way that is efficient and meets cost requirements for a clinical trial.

Observation 2

DaT imaging demonstrates striatal uptake and SBR with left/right striatal asymmetry and within each striata, anterior–posterior asymmetry (Figure 1).

The topographical consequence of these asymmetries are striatal subregional SBRs which follow an orderly pattern of

Figure 1 Signal Loss and Asymmetry



123-I ioflupane SPECT in a healthy volunteer (A) and de novo Parkinson research participant (B) show characteristic left-right and anterior-posterior asymmetry seen in PD. This pattern of loss has bearing on the optimized uses of DaT imaging in clinical trials. DaT = dopamine transporter; PD = Parkinson disease.

diminution that is maintained on serial scans over 4 years or more.

The difference in the density of transporters moving from caudate (anterior) to putamen (posterior) creates striatal subregions that individually may be best suited to different clinical research roles (Figure 2). For example, the contralateral posterior putamen shows the greatest reduction in SBR, making it the most sensitive region for detecting DaT loss, for example, in an at-risk cohort. At the same time, it may not be best for tracking longitudinal changes, as the low count rates make the variance of the change measure higher than in other regions.[13] The exception to this might be in cellular implantation scenarios, for example, where stem cells placed in putamen would theoretically be more easily visualized than caudate when assessing transplant viability.

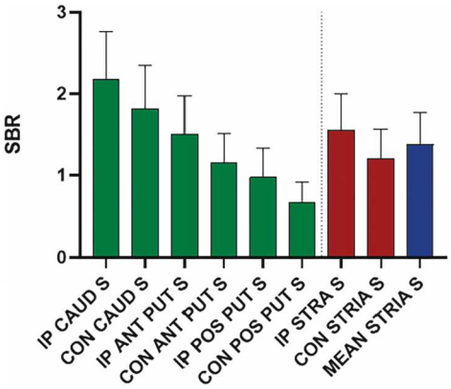
The fact that the subregional pattern of reduction is maintained over the disease course suggests a model of progression with similar rates of change for the striatal subregions, but different onset times (or a phase shift) from one subregion to another. This is essential, within a single scan, 6 different snapshots of the stage of pathologic change within that individual.

Observation 3

The SBR signal changes over time, about 11% in the first year and 17%–20% after 2 years.

However, the variance in the percent change in SBR is high with a coefficient of variation of about 100%. Hence, it is feasible to measure changes in a cohort population consistent with progressing disease, but it cannot be reliably used as a single scan to provide information about whether a 10% change is

Figure 2 Baseline Regional Striatal SBR Analysis



Ipsilateral > contralateral
Caudate > ant putamen > after putamen

N = 333
Patients with PD
Original PPMI study cohort

Regional striatal subregion mean SBRs (green bars) demonstrate the topographic pattern consequent of the left-right and anterior-posterior differential asymmetry noted in Figure 1. SBR = specific binding ratio.

Table 1 Factors Influencing the Specific Binding Ratio

Biological factors
Dopamine transporter density
Age, sex
Pharmacokinetic factors—rate of uptake, metabolism and elimination of tracer
Drugs competing with DaT scan for DaT binding
Patient ability to remain motionless in the camera
Genetic: allelic variants of DaT
Technical factors
Equipment: resolution and sensitivity of selected camera, collimators
Performance drifts over time
Photon flux counts in image
Reconstruction/attenuation correction/filtration
Size and placement of regions of interest

Abbreviation: DaT = dopamine transporter.

different from a 20% in that person.[12,14–16] Those factors which affect SBR, unrelated to DaT density, require close attention (Table 1) to control as many sources of variance, both biological and technical, when using 123ioflupane to measure progressive change. To put it in context, the variance characterizing all serial measures in PD clinical trials is high. Among the various putative progression biomarkers, DaT imaging provides the best power for detecting a signal change in progressing Parkinson patient cohort; however, it is not ideal.

Observation 4

The correlation of SBR with motor and clinical scores is highly significant, but with very modest r values.

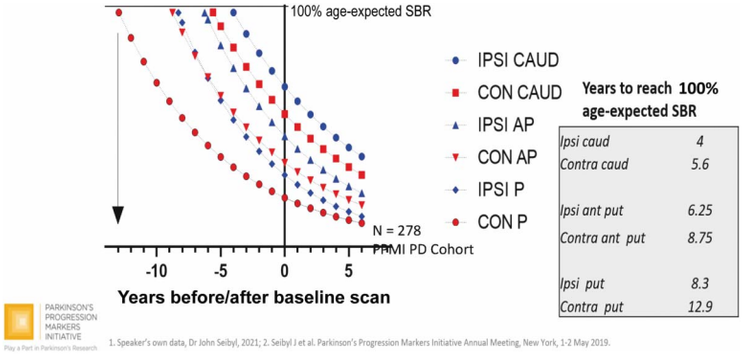
This is because the correlation depends on *when* in the disease course the correlations are assessed. Brain imaging biomarkers provide information about a very specific component of the CNS, while clinical outcomes get filtered and processed through a number of steps downstream from striatal DaT density measures. The imaging and clinical measures are complementary, providing data about different parts of the system. We expect that biomarker assessments are not going to march in stride because they have different time windows of onset, change, and quiescence. For example, patients with early Parkinson disease often have unilateral symptoms (H-Y 1), but SBR changes are noted on both sides of the brain with the contralateral side showing more profound deficits.[17] In this case, there is no correlation between the presence of 25%–30% deficit and motor symptoms because there is no motor sequela. In a short period, the ipsilateral side will manifest symptoms and now there is a correlation with the SBR, which grows stronger with time. Rather than focusing on the lack of correlation, it is useful to consider what additional information is available in the differences between biomarkers and clinical and functional outcomes in a more integrative fashion as applied to clinical trials.

What We Would Like to Know

What Does the SBR Actually Measure?

Does SBR measure the density of transporters, neuronal loss, the integrity of the synaptic terminal, all/some/none of these? The loss of signal on DaT-SPECT has been looked at in some nonclinical studies assessing in vivo DaT-SPECT and ex vivo or in vitro substantia nigra pars compacta neuron density, DaT density, or other related measures.[18–20] For example, Bäck et al.[20] demonstrated in a rat lesion model that in vivo DaT-SPECT signals correlated with ex vivo estimates of striatal DaT density and the number of nigral neurons. Human postmortem correlation with DaT-SPECT reflects the challenges in acquiring these data, especially the long intervals between the scan and pathologic assessment of the brain,[21] low participant numbers, different scan analyses, different neuropathologic outcomes, and moderate inter-rater agreement among neuropathologists hamper clarification of the question of the translational meaning of the SBR.

Figure 3 Years to 100% Age-Expected SBR by Subregion



Estimate in years of duration of premotor pathologic progression for striatal subregions based on modeling of the exponential curve fit to Ioflupane SPECT SBRs determined a baseline, year 1, 2 and 4 scans. The most affected region, the contralateral putamen, suggests a nearly 13-year period of change where motor function remains intact. SBR = specific binding ratio.

Table 2 Power Calculations for PD Clinical Trials

Endpoint	N	Signal change: Baseline–year 1 Mean (SD)	Sample sizes: Necessary to detect 1 y differences: Reduce by 50%: 80% Power	Reduce by 50%: 90% Power	Reduce by 25%: 80% Power	Reduce by 25%: 90% Power
Alpha-synuclein	360	−11.33 (605.6)	358,902	480,468	1,435,598	1,921,860
Tau	360	−0.17 (7.17)	226,352	303,020	905,184	1,211,786
Aβ	360	18.43 (71.91)	1,914	2,562	7,650	10,240
P-tau	360	4.38 (12.85)	1,082	1,448	4,322	5,784
MDS-UPDRS Part III	334	4.51 (8.17)	416	556	1,654	2,212
Total MDS-UPDRS	334	7.45 (11.56)	306	408	1,212	1,622
DaT-SPECT: mean striatum SBR	360	−0.175 (0.205)	176	234	696	930

Abbreviations: DaT = dopamine transporter; MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PD = Parkinson disease; SBR = specific binding ratio.

It is also important to remember other factors unrelated to transporter density influence SBR, both biological and technical; age and sex; pharmacokinetic factors; rate of uptake; metabolism; genetic variants of the DaT allele; drugs that compete for DaT; and technical factors such as the equipment, resolution, the photon density in the image, data reconstruction and filtering, how regions of interest are placed, etc. Given the various ways noise and variance can infiltrate the data, much effort is placed on image acquisition, processing, and analyses standardization.

How Wide Is the Time Window to Make a Preventative Intervention in PD?

As noted above, there is a significant amount of pathologic change occurring in the brain without clinical manifestations. This window of opportunity for optimal intervention is before motor symptoms when more function may be salvaged. The duration of this interval may be estimated from longitudinal DaT-SPECT imaging in progressing patients with PD over time. Figure 3 shows the longitudinal SBRs expressed as a percent of age-expected uptake for all 6 regional striatal subregions in 278 patients with PD. Each region was fit to a monoexponential curve from which the theoretical SBRs were calculated and back extrapolated to 100% age-expected uptake and the years of premotor symptom change estimate are along the x-axis. There is a pattern of nonoverlapping curves generated from the SBRs. The contralateral putamen has the lowest uptake curve and hence the longest time to reach 100% of age-expected binding. This corresponds to about 13 years over which DaT loss occurs, assuming that the exponential fit is a robust model for DaT signal loss at these early time points.

With this time frame in mind, the critical task is to now identify a clinical assessment algorithm that maximizes the yield of scan-positive patients without motor symptoms and determine, if possible, the expected time before motor symptoms evidence.

How Do We Use At-Risk Cohorts to Help Us in Progression Trials?

At-risk cohorts are particularly attractive for preventative clinical trials because of the possibility of developing Parkinson's motor symptoms within the time window of a clinical study. Two genotypes, glucocerebrosidase A (GBA) and leucine-rich repeat kinase 2 (LRRK2), have been evaluated with Ioflupane SPECT imaging at baseline in nonmanifest carriers and manifest patients with PD,[22] the latter with some longitudinal DaT imaging. Both GBA and LRRK2, carriers not manifesting typical idiopathic PD motor symptoms, have subtlety elevated motor ratings and lower Montreal Cognitive Assessment scores relative to healthy volunteers. However, there were no differences on the baseline DaT imaging, in fact the GBA carriers showed slightly higher mean striatal SBR. The motor manifesting LRRK2 group had somewhat milder motor symptoms compared with the idiopathic PD group, but for GBA, there was no difference in motor scores among patients with PD . There was slightly less reduction in the mean striatal SBR for both genotypes compared with the PD group. Moreover, when considering the longitudinal DaT-SPECT in GBA and LRRK2, there are roughly equivalent annualized rates of percent change in striatal SBR for both at-risk genotypes compared with spontaneous PD. These are interesting but preliminary findings in an ongoing study that needs additional data to sort out the relevance of these cohorts to preventative trial designs in PD.[23]

Other at-risk cohorts are patients with REM sleep behavior disorder (RBD) or olfactory loss.[24] Both of these measures enhance the likelihood of finding an abnormal DaT-SPECT scan in the absence of motor symptoms. The overall positivity rate of SPECT scans in these at-risk groups taken together is about 34%, with slightly higher net positive scans in the RBD patients at about 40%. Baseline scans for these at-risk patients follow a similar topographic

pattern to patients with idiopathic PD yet are just slightly higher SBRs.

How Can Imaging Be Used in Clinical Trial Design?

Critical to assessing the feasibility of clinical trial design is the determination of how many patients are needed to demonstrate a significant effect of treatment for a specific study design. Sample sizes are indicated for clinical motor ratings, imaging, and CSF data (Table 2) for a hypothetical study, a 2-arm, placebo-controlled trial where there is 50% or 25% slowing of rate of change of the progression marker (power = 0.8 or 0.9, $p < 0.05$, 2-tailed). The most power is achieved with DaT imaging because, although noisy, there is less variability in these data than in some of the other measures. This also underscores how difficult it is to measure slow change and in particular a slowing of that slow change. Such measurements are highly susceptible to even small differences in the variance.

How Can We Do Better?

There are a number of ways we can improve and optimize Ioflupane SPECT or other imaging biomarkers in support of PD clinical trials. We first need to optimize the algorithms for identifying imminent at-risk converters and fast progressors and do this more efficiently than currently. We can also be more thoughtful in how we apply SPECT measures to take advantage of the regional heterogeneity of DaT binding. Novel voxel-wise analytic strategies and PET versions of dopaminergic or other targets (α-synuclein) might improve the noise characteristics of the imaging outcome measure.[25] More sophisticated integration of biomarkers to take advantage of the complementary information they provide should be leveraged to improve study design and implementation. Finally, the correlation of neurohistopathology with imaging measures will help clarify what imaging is measuring and bring improvements in characterizing PD progression using scintigraphic imaging measures.

Final Comments

Notwithstanding the difficulties described in performing at-risk and preventative trials for PD, a good deal of foundational work has been done developing the toolbox for use in these studies. Imaging and nonimaging biomarkers could be important tools supporting the design and conductance of these trials. Dopamine transporter imaging, in particular, has various potential roles, including as a means to identify at-risk patients who are likely to phenoconvert over the course of the trial, to monitor changes or lack of changes as a result of therapy, and to power and provide fundamental information about the natural course of idiopathic PD and its early and complex clinical manifestations.

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Appendix Authors

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John Peter Seibyl, MD	Institute for Neurodegenerative Disorders, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Phillip Kuo, MD, PhD	Department of Radiology, University of Arizona, Tucson; Invicro, LLC, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data

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