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Early Clinical Predictors of Treatment-Resistant and Functional Outcomes in Parkinson's Disease

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Abstract: **Background:** The aim of this work was to identify early clinical predictors of important outcomes in Parkinson's disease (PD). In PD, treatment-resistant (e.g., dementia, falling) and other important functional outcomes (e.g., declines in quality of life [QOL] and activities of daily living [ADL]) emerge and become increasingly disabling.

Methods: We analyzed longitudinal data from 491 early, untreated PD subjects who enrolled in the PreCEPT trial, had baseline SPECT dopamine transporter deficit, and have continued in the PostCEPT observational cohort. After PreCEPT, antiparkinsonian medications were added if needed. Baseline clinical precursors were examined as potential predictors of selected outcomes. Separate and multivariate logistic regressions, adjusted for certain baseline factors, were performed for dichotomized outcomes evaluated at the last PostCEPT visit.

Results: On enrollment, subjects had average disease duration of 0.8 years and were followed for an average of 5.5 years. Some baseline precursors were found to be predictive: disease stage, cognitive, and ADL scores for dementia; disease stage, ADL, and motor and freezing scores for hallucinations; disease stage, depression, ADL, and freezing and walking scores for falling; and ADL, depression, and motor and walking scores and disease stage for QOL decline. No baseline clinical feature predicted decline in ADL. Being on levodopa was not a significant predictor of any outcome, but subjects on a dopamine agonist were significantly *less* impaired with respect to falling, abnormal Mini–Mental State Examination, and QOL.

Conclusions: Although there are limitations, results support the value of longitudinal follow-up of clinical trial populations to identify early clinical precursors of important outcomes and thereby identify high-risk patients early on.

Parkinson's disease (PD) is the second-most common neurodegenerative disease. Involvement of dopamine-releasing nigral neurons leads to the characteristic features of PD, namely, bradykinesia, resting tremor, rigidity, and postural instability. In recent years, attention has focused on the more widespread distribution of neurodegeneration[1] and the importance of so-called nonmotor aspects of PD.[2] Studies suggest that as the disease advances, it is these nonmotor features, which tend to be poorly or unresponsive to dopaminergic therapy, that often dominate in producing disability and reducing quality of life (QOL).[3]

Whereas most research efforts to identify disease-modifying, neuroprotective therapies in PD have been directed toward

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nigral degeneration and motor decline, it is just as worthwhile to consider experimental therapies aimed at delaying or preventing the appearance of nonmotor, treatment-resistant features or in slowing declines in activities of daily living (ADL) and QOL. Clinical trials can be more efficient and less costly when a high-risk subject cohort can be identified and studied. With these principles in mind, we analyzed data from a large cohort of PD patients that has been systematically assessed longitudinally since early disease (PostCEPT cohort[4]) in order to determine the frequency of onset of key treatment-resistant nonmotor (dementia, hallucinations) and motor (falling) outcomes and measured declines in ADL and QOL and those baseline clinical features that best predicted these outcomes. Our focus on falling, psychosis, and cognitive impairment is particularly important given that, when present in early PD, these features are associated with increased mortality.[5] It is also possible that the presence of these particular outcomes early on could indicate a more appropriate diagnosis of dementia with Lewy bodies.

Patients and Methods

The PostCEPT cohort consists of 537 patients originally enrolled with early, untreated PD as part of a controlled clinical trial of a mixed-lineage kinase inhibitor (PreCEPT trial)[6] and is part of a longitudinal clinical assessment program for biomarker development that has been previously described.[4] After completing PreCEPT, subjects were treated with symptomatic antiparkinsonian medications as dictated by emerging disability. The study was approved by the authorized institutional review board at each participating site.

Treatment-resistant outcomes were operationally defined as follows: dementia (Mini–Mental State Examination [MMSE][7] score <24 or Montreal Cognitive Assessment [MoCA][8] score <26), hallucinations (UPDRS[9] thought disorder item score ≥2), and falling (UPDRS falling item scored ≥1 or UPDRS postural stability item scored ≥2). The functional outcomes were operationally defined as: ADL decline (Schwab and England Activities of Daily Living Scale [S/E ADL][10] score decline by ≥15 from baseline) and QOL decline (Parkinson's Disease Quality of Life [PDQ-39][11] summary score in the highest quartile).

Baseline clinical features assessed as possible predictors for the outcomes included scores on the MMSE, S/E ADL, UPDRS walking, falling, and freezing items and total motor component, and Beck Depression Inventory (BDI][12]) and Modified H & Y stage.[13] Subjects having baseline beta-CIT ((^{123}I) beta-carboxymethyoxy-3-beta-(4-iodophenyl) tropane) single-photon emission computed tomography (SPECT) scans[14] without evidence of dopamine deficiency (SWEDD subjects) were identified and eliminated from the analyses. Related to these baseline features, subjects were excluded from the PreCEPT trial if they had H & Y >2.5, UPDRS resting tremor score ≥3 in any body part, dementia (MMSE ≤26), or BDI score ≥15.

Subjects meeting the criteria for each outcome at the most recent clinical assessment were identified. Baseline clinical features that were represented by continuous variables or that had multiple categories were dichotomized and coded 0 or 1, with 1 indicating more impaired status. For each baseline feature and outcome, logistic regression was used to compare subjects reaching the outcome and those who did not, adjusting for baseline age, sex, duration of PD, and treatment assignment in the PreCEPT trial. Analyses of decline in the S/E ADL score were also adjusted for the baseline score. Subjects already experiencing an outcome at baseline were excluded from the analyses of that outcome. Analyses were repeated adjusting for use of levodopa and/or a dopamine agonist at the outcome visit. For each outcome, those variables that were significant in the univariate analyses were entered into a single multivariate model.

Results

At the PreCEPT baseline visit, 407 (75.8%) of the 537 subjects who later enrolled in PostCEPT were randomized to study medication (CEP-1357), and 130 (24.2%) were assigned to placebo. At baseline, 491 (91.4%) of these subjects showed evidence of dopamine transporter (DAT) deficit in striatal uptake as assessed by beta-CIT SPECT; 43 (8.0%) of the subjects showed no significant deficit and were therefore classified as SWEDD subjects (and eliminated from our data analyses); and 3 subjects did not have a baseline scan.

Baseline clinical characteristics at the time of enrollment into the PreCEPT trial for the 491 DAT deficit subjects included in the analyses are shown in Table 1.

At the time of last assessment in PostCEPT, average duration of illness since diagnosis for these 491 subjects was 6.3 years, and they had been prospectively followed for an average of 5.5 years; 21% were taking L-dopa alone, 32% were taking a dopamine agonist alone, 20% were taking L-dopa and a dopamine agonist, and 27% were taking neither L-dopa nor a dopamine agonist.

Table 2 summarizes the results of our analyses of PreCEPT baseline clinical predictors for subsequent PostCEPT nonmotor and treatment-resistant outcomes among DAT deficit subjects. The number (%) of subjects experiencing each outcome, the odds ratios, and their 95% confidence intervals are shown. Results shown in Table 2 were substantially unchanged when adjusted for the use of L-dopa/dopamine agonist. For each outcome, those variables that were significant in the univariate

TABLE 1 PreCEPT baseline characteristics, DAT deficit subjects (N = 491)

	Mean (SD)	Range
Age	59.6 (9.4)	32.0–83.6
Years since diagnosis	0.8 (0.8)	0.1–5.0
Total UPDRS	25.2 (10.1)	3.0–59.5
UPDRS Motor Score	18.3 (8.0)	2.0–43.5
UPDRS Mental Score	0.7 (1.1)	0–6
UPDRS ADL Score	6.2 (3.2)	1–20
H & Y	1.7 (0.5)	1–3
S/E ADL Rater	92.8 (5.0)	70–100
MMSE	29.3 (1.0)	20–30
Beck Depression Score	2.4 (2.6)	0–14
Sex male, N (%)	325 (66)	

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TABLE 2 Odds ratios, PreCEPT predictors of PostCEPT outcomes, DAT deficit subjects

	Abnormal MMSE	Abnormal MoCA	Falling	Hallucinations	QOL Decline	S/E ADL Decline
Outcome definition	MMSE <24	MoCA <26	UPDRS 13 ≥ 1 or UPDRS 30 ≥ 2	UPDRS 2 ≥ 2	PDQ39 in highest quartile	Decline ≥15
No. of subjects	490	489	475	491	489	490
Outcome frequency (%)	19 (3.9)	137(28.0)	79 (16.6)	34 (6.9)	128 (26.2)	67 (13.7)
BL MMSE <30	2.9[a] (1.0, 8.6)	1.9[b] (1.2, 2.9)	0.9[b](0.5, 1.5)	1.4 (0.7, 2.9)	1.1[b](0.8, 1.7)	1.5 (0.9, 2.7)
BL Beck DI >1	1.3 (0.5, 3.4)	1.3 (0.9, 2.0)	3.8[b] (2.1, 6.8)	1.6[b](0.8, 3.4)	3.1[a](2.0,4.9)	1.1 (0.6, 1.9)
BL H & Y > 2	1.3[b](0.3, 5.4)	2.4[a] (1.1, 5.2)	3.9[b] (1.7, 8.6)	4.3[b] (1.7, 11.3)	2.2[b](1.1, 4.6)	2.1 (0.8, 5.2)
BL S/E ADL <95	4.6[b](1.5, 14.6)	2.3[b] (1.5, 3.6)	2.3[b] (1.4, 3.8)	4.4[b] (1.9, 10.0)	2.0[a](1.3,3.1)	0.6 (0.3, 1.0)
BL UPDRS Motor Score >17	3.2[a] (1.0, 10.4)	1.4 (0.9, 2.2)	1.5 (0.9, 2.5)	2.6[a] (1.2, 5.7)	1.6[a](1.1, 2.5)	1.3 (0.7, 2.3)
BL Falling (UPDRS 13 ≥ 1)	—	0.8 (0.2, 2.5)	—	2.2[b](0.5, 10.4)	1.1 (0.4, 3.7)	0.6 (0.1, 4.6)
BL Freezing (UPDRS14 ≥ 1)	3.3 (0.9, 11.8)	1.8 (0.8, 4.1)	4.4[b] (1.9, 10.2)	4.8[b](1.8, 12.7)	2.0[b](0.9, 4.4)	2.3 (0.8, 6.3)
BL Walking (UPDRS 15 ≥ 1)	0.8 (0.3, 2.0)	0.9 (0.6, 1.4)	2.0[b] (1.2, 3.5)	1.9 (0.9, 4.1)	1.9[b](1.2, 2.9)	1.6 (0.9, 2.8)

[a]Statistically significant ($P < 0.05$).
[b]Statistically significant ($P < 0.01$).
BL, baseline; Beck DI, Beck Depression Inventory.

analyses were entered into a single multivariate model and the results are shown in Table 3. A number of significant predictive relationships between baseline features and later outcomes were identified. For abnormal MMSE (<24), baseline MMSE, S/E ADL, and UPDRS total motor score were predictive. For abnormal MoCA (<26), baseline MMSE, S/E ADL, and disease stage were predictive. S/E ADL was the stongest predictor of abnormal MMSE, and both S/E ADL and baseline MMSE were the strongest predictors of abnormal MoCA after multivariate analyses. (Results were similar when these two outcomes were combined into a single "dementia" outcome.) For falling, baseline BDI, disease stage, S/E ADL, freezing, and walking scores were predictive. After multivariate analyses, BDI and freezing score remained significant predictors. For psychosis (hallucinations), baseline disease stage, S/E ADL (significant after multivariate analysis), motor scores, and freezing were predictive. For QOL decline, baseline BDI (significant after multivariate analyses), disease stage, S/E ADL, motor, and walking scores were predictive. None of the baseline clinical features were able to predict decline in ADL. Being on L-dopa was not a significant predictor of any of these outcomes. Subjects on a dopamine agonist, however, were significantly *less* likely to fall, experience a decline in QOL, or an abnormal MMSE.

Discussion

A potential shortcoming of our study was that we were likely dealing with a biased sample in that it included subjects attending tertiary care centers for PD and those who had been willing to take part in a placebo-controlled drug trial, and so the results may not be representative of a general PD population. Another potential bias was the medication choices made by the tertiary care physicians, and it is unclear how these choices influenced the impact of the medications on our outcomes. Another potential shortcoming was the limited number of baseline clinical measures that were included as part of the PreCEPT clinical trial and the limited number of outcome measures that were part of the PostCEPT longitudinal assessment protocol. Furthermore, the breadth and depth of a particular outcome may not have been satisfactorily captured with the existing measures. For example, task forces have published recommended diagnostic criteria for dementia[15] and psychosis[16] in the setting of PD, and these involve more extensive information than gathered in our study and considered in our analyses. Another limitation is that the predictors assessed are not determinants per se, but rather measured risk factors of the outcomes of interest. Our study is also limited in that we assessed outcomes only in the approximately first 5–6 years of illness.

One longitudinal study suggested that dementia is an almost inevitable consequence of PD, present in 83% of patients after 20 years of illness.[17] It is clear that dementia is a key factor in the overall disability that emerges as the disease progresses; its presence is associated with a 2-fold increase in mortality in PD patients[18] and neuropsychiatric aspects of dementia are major determinants of caregiver distress,[19] making dementia a critical target for experimental therapies aimed at preventing or fore-

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TABLE 3 Odds ratios for PostCEPT outcomes from multivariate models including significant PreCEPT predictors from univariate analyses, DAT deficit subjects

	Abnormal MMSE	Abnormal MoCA	Falling	Hallucinations	QOL Decline	S/E ADL Decline
Outcome definition	MMSE <24	MoCA <26	UPDRS 13 ≥ 1 or UPDRS 30 ≥ 2	UPDRS 2 ≥ 2	PDQ-39 in highest quartile	Decline ≥15
BL MMSE <30	2.7 (0.9, 8.1)	1.8** (1.2, 2.8)	—[b]	—	—[b]	—
BL Beck DI >1	—	—	3.1[b] (1.7, 5.6)	—	2.8[b] (1.8,4.4)	—
BL H & Y >2	—[b]	1.8[b](0.8, 4.0)	2.1 (0.9, 5.1)	2.1(0.7, 6.1)	1.2 (0.5, 2.6)	—
BL S/E ADL <95	3.7[b] (1.1, 12.0)	2.1[b](1.3, 3.3)	1.4 (0.8, 2.5)	3.1[a](1.3, 7.4)	1.4 (0.9, 2.3)	—
BL UPDRS Motor Score >17	2.3 (0.7, 7.6)	—	—	1.6 (0.7, 3.7)	1.3 (0.9, 2.1)	—
BL Falling (UPDRS 13 ≥ 1)	—	—	—[a]	—	—	—
BL Freezing (UPDRS14 ≥ 1)	—	—	2.7[a] (1.1, 6.8)	2.7 (0.9, 7.5)	—	—
BL Walking (UPDRS 15 ≥ 1)	—	—	1.3 (0.7, 2.3)	—	1.4 (0.8, 2.2)	—

[a]Statistically significant ($P < 0.05$).
[b]Statistically significant ($P < 0.01$).

stalling its occurrence. We found that cognitive function as assessed at baseline with the MMSE was predictive of the emergence of dementia, suggesting that cognitive decline in patients destined for dementia has already started early in the illness. This finding is in keeping with other studies that utilized more extensive neurocognitive testing and identified measureable cognitive impairments, most prominent in the areas of memory and executive function, in newly diagnosed PD patients.[20,21] The fact that motor and ADL function at baseline were also predictive of dementia suggests that some patients have more advanced illness, probably also including cognitive aspects, near the time of diagnosis. It also suggests that subtle cognitive deficits might contribute to difficulties in motor and daily functions early on so that these features serve as predictors of eventual dementia. A novel finding was that patients taking a dopamine agonist drug were less likely to develop dementia (as well as declines in QOL), an interesting observation that deserves further study. It is possible that patients treated with a dopamine agonist had lower severity of illness at the time treatment was initiated than those treated with L-dopa, or that dopamine agonists were avoided by the treating clinicians in subjects with some evidence of impaired cognition.

Hallucinations and other manifestations of psychosis in PD are generally viewed as consequences of dopaminergic drug therapy. Patients with dementia are probably more susceptible to drug-induced psychosis. It may not be surprising then that baseline measures of disease stage (H & Y, S/E ADL) and motor dysfunction (UPDRS total motor score, freezing) predicted the development of psychosis given that these features may have identified individuals who would require higher doses of dopaminergic drugs. The recorded use of L-dopa or a dopamine agonist did not, however, predict the development of psychosis.

Baseline walking, freezing, and ADL scores and H&Y stage, which are closely dependent on the presence or absence of imbalance in the earlier stages, are logical predictors of later falls. It is uncertain why baseline depression is predictive of falling, and this relationship deserves further study. It is possible, for example, that disturbances in serotonin and noradrenergic pathways that have been linked to depression might contribute to the mechanisms of falling in PD patients. Dementia, hallucinations, and falling are characteristic features of dementia with Lewy bodies, and it is possible that, for at least some of the patients found to have these problems early on, dementia with Lewy bodies may be the more accurate diagnosis.

Depression, daily functional impairment, overall motor dysfunction, and gait problems are all known important contributors to decline of QOL in PD, so their identification as predictors is logical. Depression and degree of functional independence were similarly found to be good predictors of deterioration of health-related QOL in the DATATOP trial cohort.[22] The failure of any of the baseline precursors to significantly predict later decline in ADLs is unexplained, but may be owing to the possibility that deterioration of daily functioning in PD has heterogeneous causes across patients and that early individual deficits cannot accurately predict this outcome.

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Overall, our results have generally confirmed the results of several other studies. Our approach is, however, unique in that it involves a very large sample size, patients very early in the course of PD, and uses instruments commonly employed in clinical trials. In addition, our analyses eliminated subjects with SWEDD. Our findings suggest that we can identify baseline clinical precursors of treatment-resistant and functional outcomes, ultimately allowing us to identify high-risk (enriched) patient samples for experimental therapeutic studies aimed at delaying or preventing the appearance of these outcomes. In this way, smaller sample sizes with selected higher-risk subjects can be used, resulting in substantial cost savings in such future studies. Some of the identified baseline predictors are unexpected and may suggest new lines of investigation into the neurobiological mechanisms of these outcomes. It will be of interest to determine whether biological measurements at baseline, such as neuroimaging or metabolic analyses, add to the predictive value of the clinical variables.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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B.R.: 1A, 1B, 1C, 3B
J.E.: 2B, 3B
A.E.L.: 1A, 1B, 1C, 3B
K. Marek: 1B, 1C, 3B
K. Marder: 1A, 1B, 3B
J.B.: 1A, 3B
R.E.: 1A, 3B
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I.S.: 1A, 1B, 1C, 3B

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References

1. Braak H, Del Tredici K, Rub U, et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197–211.
2. Langston JW. The Parkinson's complex: parkinsonism is the tip of the iceberg. *Ann Neurol* 2006;59:591–596.
3. Lim S-Y, Fox SH, Lang AE. Overview of extranigral aspects of Parkinson disease. *Arch Neurol* 2009;66:167–172.
4. Ravina B, Tanner C, DiEuliis D, et al. A longitudinal program for biomarker development in Parkinson's disease: a feasibility study. *Mov Disord* 2009;24:2081–2090.
5. Lo RY, Tanner CM, Albers KB, et al. Clinical features in early Parkinson disease and survival. *Arch Neurol* 2009;66:1153–1158.
6. The Parkinson Study Group PRECEPT Investigators. Mixed lineage kinase inhibitor CEP-1347 fails to delay disability in early Parkinson disease. *Neurology* 2007;69:1480–1490.
7. Folstein MF, Folstein SE, McHugh PR, et al. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
8. Gill DJ, Freshman A, Blender JA, et al. The Montreal Cognitive Assessment as a screening tool for cognitive impairment in Parkinson's disease. *Mov Disord* 2008;23:1043–1046.
9. Fahn S, Elton RL; Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Goldstein M, Calne CD, eds. *Recent Developments in Parkinson's Disease*. Volume II. Florham Park, NJ: MacMillan; 1987:153–163.
10. Schwab RS, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson IML, eds. *Third Symposium on Parkinson's Disease*. Edinburgh: Livingstone; 1969:152–157.
11. Peto V, Jenkinson C, Fitzpatrick R. PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. *J Neurol* 1998;245(Suppl 1): S10–S14.
12. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:53–63.
13. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967;17:422–427.

doi:10.1002/mdc3.12273

14. Neumeyer JL, Wang SY, Milius RA, et al. 123I-2B-carbomethoxy-(4-iodophenyl) tropane: high affinity SPECT radiotracer of monoamine reuptake sites in brain. *J Med Chem* 1991;34:3144–3146.

15. Dubois B, Burn D, Goetz C, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the Movement Disorders Society Task Force. *Mov Disord* 2007;22:2314–2324.

16. Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. *Mov Disord* 2007;22:1061–1068.

17. Hely MA, Reid WGJ, Adena MA, et al. The Sydney Multicenter Study of Parkinson's Disease: the inevitability of dementia. *Mov Disord* 2008;23:837–844.

18. Louis ED, Marder K, Cote L, Tang M, Mayeux R. Mortality from Parkinson's disease. *Arch Neurol* 1997;54:260–264.

19. Leiknes I, Tysnes OB, Aarsland D, Larsen JP. Caregiver distress associated with neuropsychiatric problems in patients with early Parkinson's disease: the Norwegian Park West Study. *Acta Neurol Scand* 2010;122:418–424.

20. Muslimovic' D, Post B, Speelman JD, et al. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology* 2005;65:1239–1245.

21. Pedersen KF, Larsen JP, Tysnes OB, Alves G. Prognosis of mild cognitive impairment in early Parkinson's disease. The Norwegian ParkWest Study. *JAMA Neurol* 2013;70:580–586.

22. Marras C, McDermott MP, Rochon PA, Tanner CM, Naglie G, Lang AE. Predictors of deterioration in health-related quality of life in Parkinson's disease: results from the DATATOP trial. *Mov Disord* 2008;23:653–659.

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