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Evolution of Parkinson's Disease Trial Characteristics: 2005 - 2017

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Introduction

In the past 20 years phenomenal progress has been made helping researchers understand the chain of events that leads to the damage and loss of dopamine-producing brain cells in Parkinson's disease. Treatment for PD includes pharmacotherapy, functional stereotaxic neurosurgery (deep brain stimulation), and supportive therapy such as physiotherapy, speech therapy, and dietary measures. There, however, are still no approved neuroprotective/interventional drug treatments for Parkinson's disease that have been shown to slow, halt, or reverse progression. A longitudinal analysis of PD study characteristics may provide a deeper understanding of clinical trials dynamics and demonstrate how research paradigms have been changing across the years. This poster aims to fill this knowledge gap by providing unique insight into PD clinical trials methodology by analyzing research activity in terms of study phase prevalence and selected internal aspects of study complexity.

Methods

The data analyzed in this study was extracted from www.clinicaltrials.gov on 10Jul2018. The selection criteria that were applied when the data was extracted are listed in Table 1.

Table 1. Selection Criteria

Criterion	Selection
Indication	Parkinson's disease
Recruitment status	Recruiting, not yet recruiting, active – not recruiting, completed, enrolling by invitation, suspended, terminated, withdrawn, unknown status
Sex	Males and females
Age	All age groups
Study type	Interventional clinical trial
Phase	Early Phase 1, Phase 1, Phase 2, and Phase 3
Funder type	Industry

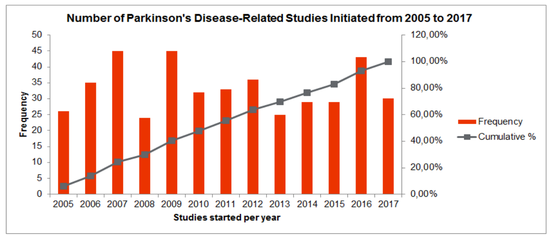
The result of the selection criteria yielded a total of 453 studies from 2005 to 2018. After excluding 20 trials from the analysis due to incomplete data, a total of 433 clinical trials were analyzed in this study. The decision to limit the scope of the analysis was driven by the scarcity of the information concerning the studies initiated prior to 2005. It was in 2004 that the FDA mandated for industry-sponsored AD clinical trials to be registered on the website; thus, there are fewer data on these trials prior to 2005. It also is noteworthy to mention that trials of non-pharmacologic therapeutic approaches such as devices and procedures were included in the analysis, although they constituted a marginal number of studies and did not affect the analysis results significantly.

The studies were divided into four arbitrarily-chosen time intervals: 2005 – 2007 (3 years, 106 studies), 2008 – 2010 (3 years, 102 studies), 2011 – 2013 (3 years, 94 studies) and 2014 – 2017 (4 years, 134 studies). In terms of study phases, 135 Phase 1, 125 Phase 2, 116 Phase 3, and 57 Phase 4 studies were reviewed. All statistical analyses (chi square metric; $\chi 2$) were undertaken in exploratory fashion, without a priori hypotheses; alpha was set at 0.05. Descriptive statistics were utilized to characterize the data by: number of trials, year of study initiation, trial indication, use of biomarkers, intervention model type, masking type, and use of outcome measures (i.e., cognitive, functional, neuropsychiatric, and global scales).

Results

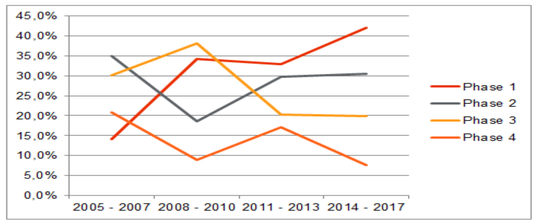
Results: Number of PD-Related Clinical Trials From 2005 to 2017

Graph 1. Number of Parkinson's Disease-Related Studies Initiated from 2005 to 2017



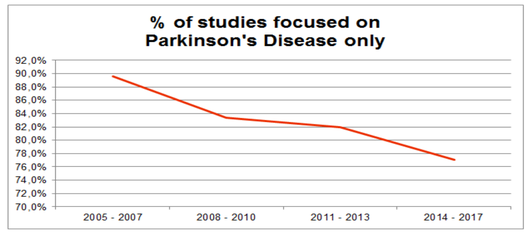
The number of PD-related trials fluctuated over time. The highest number of registered PD-related trials fell in 2007, 2009 (both N = 45) and 2016 (N = 43). In the last three years ~~in~~ an increased number of Phase 1 studies was observed ($\chi 2$= 39.82 (9), p<0.005):

Graph 2. Changes in numbers of studies initiated between 2005 and 2017 by Phase



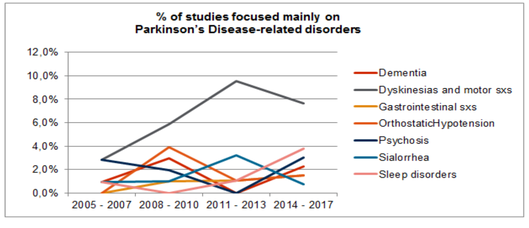
Throughout the years the majority of the studies were focused on Parkinson's disease (total 82.7%), although other PD-related indications became gradually more popular ($\chi 2$= 47.13 (30), p< 0.05):

Graph 3. Percentage of studies focused mainly on Parkinson's Disease.



Other PD-related disorders became more frequent topics of research, especially dyskinesias and other motor symptoms (total 6.5%), psychosis (total 2.1%), dementia, sleep problems, and orthostatic hypotension (each total 1.6% of the studies). Clinical trials concerning other PD-related disorders, such as dementia, depression, gastrointestinal symptom, and sialorrhea constituted total 2.6% of the studies.

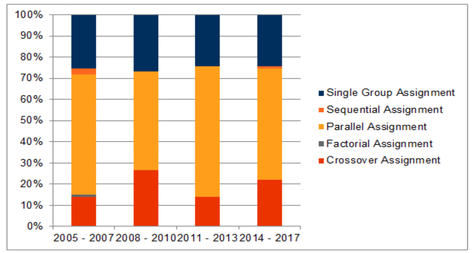
Graph 4. Percentage of studies focused mainly on Parkinson's Disease-related disorders.



Results: Study Design – Intervention Models

The three most popular intervention models in PD studies were: Parallel Assignment (232 studies), Single Group Assignment (108 studies), and Crossover Assignment (83 studies). Other models, such as Factorial Assignment and Sequential Assignment were used very rarely (in 1 and 4 studies, respectively). There were no statistically significant changes over time in preferences of a specific study design ($\chi 2$= 24.24 (15), p= 0.061).

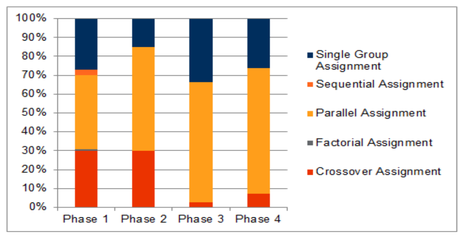
Graph 5. Type of Intervention Models from 2005 -2017



An analysis of data across study phases indicated significant differences in the frequency of study designs used at each phase ($\chi 2$ = 68.1, (15), p< 0.005):

1. Parallel assignment – the most frequently used in Phase 3 and 4 studies (respectively, 66.8% and 66.7% of the studies). Less frequently used in Phase 1 and Phase 2 studies (39% and 54% of studies).
2. Single Group assignment - less frequently used in Phase 2 studies (14.5% of the studies) compared with other phases (Ph. 1 = 26.5%, Ph. 3 = 33.6%, Ph. 4 = 26.3% of the studies).
3. Crossover assignment – more frequently used in Phase 1 and 2 (29.4% and 29.0%) than in Phase 3 and 4 (respectively, 2.6% and 7.0% studies).

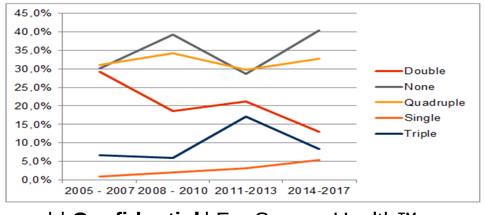
Graph 6. Type of Intervention Models by study phase



Results: Study Design – Blinding/Masking

Preferred blinding/masking type changed from 2005 through 2017 ($\chi 2$ = 30.38 (15), p<0.05). Over time Double Masking become less popular (change from 29.2% to 13%), whereas No Masking and Single Masking grew more popular (change from 30.2% to 40.5% and from 0.9% to 5.3%). Frequency of the other masking types did not change significantly.

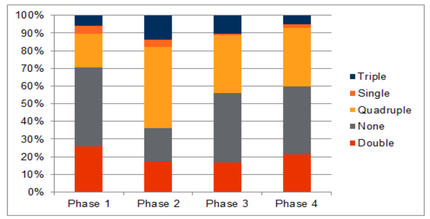
Graph 7. Changes in frequency of blinding/masking type use across years



Statistically significant differences in terms of a preferred blinding/masking model between study phases were observed ($\chi 2$ = 45.621 (15), p< 0.005):

1. No masking was frequently used in Phase 1 (44.9%), phase 3 (38.8%) and phase 4 (38.6%) studies. The high rater of No Masking in the Phase 3 studies can be explained by Open Label Extension studies.
2. The quadruple masking model was especially popular in Phase 2 (46%), Phase 3 (31.9%) and Phase 4 (33.3%) studies compared to Phase 1 (19.1%) studies.

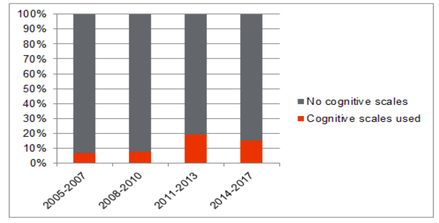
Graph 8. Type of masking by study phase



Results: Outcome Measures – Cognitive Assessment Scales

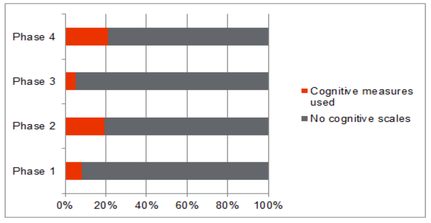
Cognitive assessments were rarely implemented in study protocols, although a positive trend has been noticed in the past few years (an increase from 6.6% to 15.3% between 2005 and 2017; $\chi 2$ = 10.27 (3), p<0.05).

Graph 9. Use of cognitive measures across time.



In terms of the study phases, cognitive scales were most frequently used in Phase 2 (19.4%) and Phase 4 (21.1%) studies, compared with Phase 1 and Phase 3 studies (8.1% and 5.2% of the studies; $\chi 2$ = 17.54 (3), p<0.005).

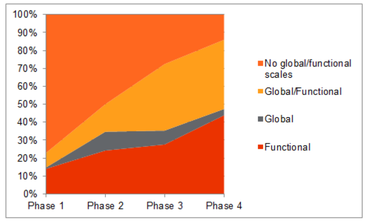
Graph 10. Use of cognitive measures by study phase



Results: Outcome Measures – Global/Functional Assessment Scales

Global/Functional scales (e.g., UPDRS, PDQ-39, MHYS) were more frequently used in all study phases compared with the cognitive tools. The higher the study phase, the greater likelihood global/functional scales were used ($\chi 2$ = 109.3 (6), p<0.005).

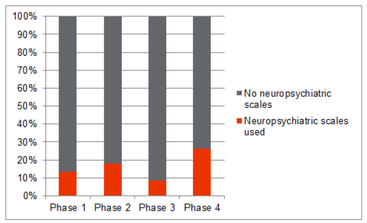
Graph 11. Use of global/functional measures by study phase



Results: Outcome Measures – Neuropsychiatric Assessment Scales

Frequency of use of neuropsychiatric scales was stable across time (around 15% of the studies employed such measures; $\chi 2$ = 7.68 (3), p=0.053). They were most frequently used in Phase 2 and Phase 4 studies (17.7% and 26.3% of the studies; $\chi 2$ = 10.48 (3), p<0.05).

Graph 12. Use of neuropsychiatric measures by study phase



Conclusions

In general, the clinical trials methodology applied between 2005 and 2017 has undergone some evolution over time.

1. **Indications:** The number of PD-related trials fluctuated over time. Recently PD-related symptoms and disorders have gained more attention as potential targets of pharmacological interventions.
2. **Increase of Phase 1 studies after 2014:** This suggests new compounds entering the development pipeline.
3. **Cognitive measures** were rarely used in PD clinical trials, although they started being employed more frequently recently. More popular are global/functional assessment scales. There have been no major changes in the psychometric assessment methodology.
4. **Single Group Assignment, Parallel Group Assignment and Cross – Over Assignment** are the most popular intervention models. This is consistent with clinical trials methodology and similar to research in other neurodegenerative disorders, such as Alzheimer's Disease.
5. **Masking model** use changed over time – no masking and single masking became more popular. This is due to the increased number of the Phase 1 studies, in which these masking models are often used (when controlled for Study Phase, only Phase 1-related over time changes were significant, $\chi 2$ = 22.93 (12), p<0.05).

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