Parkinson's Disease

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Introduction

Parkinson's disease is a disorder that affects nerve cells, or neurons, in a part of the brain that controls muscle movement. In Parkinson's, neurons that make a chemical called dopamine die or do not work properly. Dopamine normally sends signals that help coordinate your movements. No one knows what damages these cells.

Symptoms of Parkinson's disease may include:

- Trembling of hands, arms, legs, jaw and face
- Stiffness of the arms, legs and trunk
- Slowness of movement
- Poor balance and coordination

As symptoms get worse, people with the disease may have trouble walking, talking or doing simple tasks. They may also have problems such as depression, sleep problems or trouble chewing, swallowing or speaking.

Disease Description

Parkinson's disease (PD) belongs to a group of conditions called motor system disorders**,** which are the result of the loss of dopamine-producing brain cells. The four primary symptoms of PD are tremor, or trembling in hands, arms, legs, jaw, and face; rigidity, or stiffness of the limbs and trunk; bradykinesia, or slowness of movement; and postural instability, or impaired balance and coordination. As these symptoms become more pronounced, patients may have difficulty walking, talking, or completing other simple tasks.

PD usually affects people over the age of 50. Early symptoms of PD are subtle and occur gradually. In some people the disease progresses more quickly than in others. As the disease progresses, the shaking, or tremor, which affects the majority of PD patients may begin to interfere with daily activities. Other symptoms may include depression and other emotional changes; difficulty in swallowing, chewing, and speaking; urinary problems or constipation; skin problems; and sleep disruptions. There are currently no blood or laboratory tests that have been proven to help in diagnosing sporadic PD. Therefore the diagnosis is based on medical history and a neurological examination. The disease can be difficult to diagnose accurately. Doctors may sometimes request brain scans or laboratory tests in order to rule out other diseases.

Agency Guidelines

There is no special FDA guideline for drug approvals for Parkinson's Disease.

In September 2008 the EMA published a guideline Guideline on Clinical Investigations of Medicinal Products in the Treatment of Parkinson's Disease which became into effect in February 2009.

Clinical Trial Endpoints

from National Parkinson Foundation

Parkinson's Disease Rating Scales.

Several rating scales have been developed to measure the impact of PD on a patient and family. These scales are used in research to determine eligibility to participate in a research trial or to assess severity and disease progression. Scales may also be used in clinical practice to identify and monitor problems or gauge clinical function and degree of progression.

PD Evaluation Scales

- Unified Parkinson Disease Rating Scale (UPDRS): monitor PD disability and impairment. The above mentioned EMA guideline mentions the UPDRS II and III scales as **accepted scales to measure the efficacy** of a drug for Parkinson's Disease.
- Modified Hoehn and Yahr Scale: global assessment of severity in PD based on clinical findings and functional disability.

Quality of Life Assessment in PD

- Disease-specific measure of subjective health status that is completed by patients.

Cognitive Assessment in PD

- Mini Mental Status Exam (MMSE): Standardised and validated scale used as a screening instrument for cognitive impairment.
- Montreal Cognitive Assessment (MoCA): Developed to detect mild cognitive impairment.
- Dementia Rating Scale: Used to assess dementia in a wide range of neuropsychological conditions.
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Sleep Assessment in PD

- Epworth Sleep Scale: Validated self-report measure of daytime sleepiness covering any designated time period.
- PD Sleep Scale (PDSS): Uses a visual analogue score for each of 15 features commonly associated with sleep disturbance in PD.

Mood and Behaviour

- Geriatric Depression Scale: Designed to assess depressive symptoms in the elderly, self-report measure.
- Beck Depression Inventory (BDI): Used to measure the severity of depression, self-rated.
- Hamilton Depression Scale: Most utilised rating scale for patients with primary depression.
- Parkinson Disease Fatigue Scale (PFS): Surveys the physical aspects of fatigue and their impact on the patient's daily function, self-report instrument.
- Neuropsychiatric Inventory (NPI): Evaluates behavioural abnormalities that occur in demented patients.
- Brief Psychiatric Rating Scale:Designed for schizophrenia patients, but one of the most widely used scales in Parkinson trials concerning drugs for PD psychosis.

Other

- Patient Diaries: Developed as a tool to measure a person's motor state when the person is at home or is not being observed by a health care provider. Completed by patient or by caregiver.

Clinical Trial Design

- *Describe common clinical trial designs here...*
- *Uptitration, Down-titration, optimal dose scheme, fixed dose scheme*
- *Special Clinical trials to be conducted for PD*

Data Challenges

Prior and Concomitant Medication

One of the data challenges in the PD indication are prior- and concomitant medication.

Since patients who suffer from PD are mostly elderly patients who either suffer from other diseases or have to take combinations of several other treatments for PD (e.g. Levodopa) some data challenges occur with Prior- and Concomitant medication.

Especially the use of Levodopa is part of the protocol criteria in patients with advanced PD. In clinical trials patients need to be on a stable dose within a defined time interval prior to the first study treatment. One of the challenges is to well define this stability criteria. The following issues can occur and it has to be defined what stability means:

1. patients switch their Levodopa dosing scheme, but not their total dose. E.g. they have to take Levodopa 2 times daily with a total dose, but due to change of symptoms they have to switch to a 4 times daily dose with an unchanged total dose. This is often misinterpreted as a change of dosing.
2. Due to the side effects of Levodopa, Levodopa is mostly administered as a combinational therapy. Common practice is to co-administer L-Dopa with a peripheral DOPA decarboxylase inhibitor such as carbidopa or with a benserazide to prevent the peripheral synthesis of dopamine from L-DOPA. These combinational therapies potentially lead to challenges in terms of L-DOPA stability definitions. E.g. cases where L-DOPA is co-administered with cardidopa and the cardidopa dosage is unstable are often misjudged as unstable L-DOPA doses.

Exposure

Based on the disease severeness patients who suffer from PD need to follow a dosing schedule which requires multiple tablet intakes. Often patients also have to take dosages during the night. Due to these facts the collection, cleaning and analysis of exposure data is more challenging than in indications which require once or twice daily doses.

There are also treatments like once daily patches which require special attention. Since patches can detach the collection of the actual adhesiveness can be challenging as well.

Patient Reported Outcomes

Data Collection

Recently the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institutes of Health (NIH) founded an external working group of about 70 experts to develop Common Data Elements (PD CDEs). These are now ready for feedback from the lager PD clinical research community, see Common data Elements Parkinson's Disease for more details.

Like projects for other diseases like Epilepsy the CDE project strives to create content related standards for the data collection. The PD CDE is focussed on the most important elements to collect data, share it and analyze it through collaboration of the PD research community.

SDTM Data

Right now there is no special SDTM Domain for the indication PD.

Since most of the measured efficacy data is based on findings the data should be stored in the Findings About (FA) SDTM domain.

ADaM Data

Most of the measured efficacy data for PD is collected in questionnaires which are stored in SDTM.QS. The combination of all CRF data from SDTM.QS with derivations for analysis in the corresponding ADaM datasets can easily lead to extremely huge datasets. It is reasonable to split the single efficacy measurements in single ADaM datasets.

References

1. National Institutes of Health (National Institute of Neurological Disorders and Stroke)
2. National Parkinson Foundation
3. Movement Disorder Society