On-off related fluctuations of non-motor symptoms in patients with Parkinson's disease

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Summary

The first part of this thesis is a general theoretical overview of Parkinson's disease, its symptoms, and fluctuations in those symptoms. The second part comprises a description of the study of existing literature and the pilot study that were conducted as components of the thesis.

The primary aim of this thesis is to investigate the relationship between levodopa-dependent motor fluctuations and non-motor fluctuations in Parkinson's disease patients. The obvious symptoms - bradykinesia, tremors, reduced swing of arms, rigidity, altered posture, and imbalance - are well known and were already addressed by James Parkinson in 1817. However, Parkinson's disease also results in other, non-motor symptoms. These 'hidden' symptoms nevertheless trouble patients, and may even have an equal or more severe negative impact on the quality of life that the patients experience.

The pilot study of this thesis is a component of a larger research project taking place at Ahus. It is conducted by assessing patients using the validated screening tools, the Visual Analogue Scale (VAS) and the Unified Parkinson's Disease Rating Scale (UPDRS). Statistical analyses are performed with SPSS 25 statistical analysis software. Due to a small size of the cohort, the pilot study does not provide statistically significant data. However, the results correlate well with previous studies with larger cohorts.

The thesis emphasises the need for increased scientific attention to the relationship between fluctuations in non-motor symptoms, and in motor symptoms. Several earlier studies have demonstrated the significant impact of non-motor symptoms on patients' quality of life.

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Abbreviations used in the thesis

P	Parkinsonism
PD	Parkinson's disease
MS	Motor symptoms
NMS	Non-motor symptoms
MF	Motor symptoms fluctuations
NMF	Non-motor symptoms fluctuations
MAO	Mono Amine Carboxylase
QoL	Quality of Life
PP	Parkinson Plus
SN	Substantia Nigra
SNpc	Pars compacta of Substantia Nigra
$Motor_{off}$	Off state in terms of MS control
$Motor_{on}$	On state in terms of MS control

Introduction

Motivation

With a prevalence of more than 1% in the elderly population (3), Parkinson's disease (PD) is a common illness. It is the second most common neurodegenerative disease in the world. With a disease like PD, which holds obvious symptoms that may disturb the communication between patients and their caregivers, it is easy for the latter to forget the less obvious symptoms of the disease. Nonetheless, non-motor symptoms of PD are of significant importance for patients' quality of life (QoL) (4). It is therefore of the greatest importance that patients' caregivers are aware of these aspects of the disease. It is also important that patients are aware of, and well educated about, these symptoms in order to lessen their feelings of guilt and shame. In addition, recent research has shown that, with proper treatment, significant relief may be obtained from many of these symptoms (5). I hope that this thesis will contribute to making the non-motor symptoms of PD less of an unknown factor for patients and their caregivers.

Background

A historical glance at the understanding of Parkinson's disease

Most people have an idea of what Parkinsonism looks like. Several celebrities are ambassadors for this life-changing disease: its victims range from Muhammad Ali and Johnny Cash to the former pope, John Paul II.

James Parkinson's description of the 'shaking palsy' came as early as 1817, and is recognised as the first description of Parkinsonism. About the clinical signs, he wrote: 'Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured' (6). During the late 1800s, the French physician Charcot made an effort in provide a more precise description of the 'shaking palsy', and distinguished it from other 'shaking' states by proposing the name of Parkinson's disease (7). During the 1920s, much work was done to investigate the pathophysiology of the disease, and the substantia nigra (SN) was proposed as the anatomical site of damage (8). Hoehn and Yahr further studied the onset, mortality, and progression of PD. Their staging system was introduced in an article published in 1967 (9). Much scientific work has been conducted since then, and scientists have identified the pathology of the disease. The work of Braak and his group, published in an article in 2003, explains in detail the microscopic development of the stages of the disease (10). A short summary of Braak et al. conclusions are discussed later in this thesis.


FIG. 165.—Paralysis agitans. (After St. Leger.)

Figure 1 Parkinsonism as presented in 1886

Definition of Parkinsonism and Parkinson's disease

What is called as 'Parkinson's' by most people is referred to as 'Parkinsonism' (P) by physicians. The cardinal symptoms of Parkinsonism are rest-tremors, bradykinesia, muscular rigidity, and postural and gait impairment (11). The most common cause of Parkinsonism is PD, which is classified based on pathophysiological changes in the brain of the patient. Several clinical tools have been developed to differentiate between PD and P, but the gold standard for a diagnosis of PD is degeneration of the

SN and Lewy-pathology, observed in post-mortem pathological examinations (11). Parkinson plus (PP) is a term used for a group of movement disorders with Parkinsonism, in addition to other symptoms that make it possible to diagnose the disorder. Besides PD, other common causes for Parkinsonism are drug-induced Parkinsonism, progressive supranuclear palsy, Lewy-body dementia, vascular Parkinsonism and multiple system atrophy (13).

Step 1. Diagnosis of Parkinsonism	Step 2. Exclusion criteria for PD	Step 3. Supportive criteria for PD (≥3 required for definite diagnosis)
Bradykinesia[a] and ≥1 of the following: Muscular rigidity; 4–6 Hz rest tremor; Postural instability[b].	Repeated strokes with stepwise progression Repeated head injury Definite encephalitis Oculogyric crises Use of neuroleptic or dopamine-depleting agents at onset of symptoms >1 affected relative Sustained remission Strictly unilateral features after 3 y Supranuclear gaze palsy Cerebellar signs Early severe disautonomy Early severe dementia with disturbances of memory, language or praxis Babinski sign Cerebral tumor or communicating hydrocephalus on neuroimaging Negative response to large doses of levodopa (malabsortion excluded) Exposure to known neurotoxin (e.g. MPTP)	Unilateral onset Rest tremor Progressive disorder Persistent asymmetry affecting side of onset most Excellent response (70–100%) to levodopa Severe levodopa-induced chorea Levodopa response for ≥5 y Clinical course of ≥10 y

PD: Parkinson's disease; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; y: years; [a]Delayed onset of voluntary movement with increasing reduction of amplitude and speed of repetitive movements; [b]Unrelated to primary visual, cerebellar, vestibular or proprioceptive dysfunction.

Figure 2. The United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria for PD. Copied from Utiumi, 2014 (12)

Epidemiology of Parkinson's disease

The overall incidence of Parkinson's disease ranges from 10 to 18 per 100,000 person-years (13). The principal risk factors for PD are advanced age and male sex: for males over 80 years of age, the incidence rises to 143-237 per 100,000 person-years (13). Several other risk factors have been identified, in particular, a family history of PD or tremors, a history of constipation, and a history of an absence of smoking history (14). Even though advanced age is one of the major risk factors for PD, there is are significant numbers of younger people who have the disease (13).

Pathophysiology of Parkinson's disease

The brain consists of an extensive network of neurons and synapses that stretches far beyond the understanding of human beings, and certainly beyond the scope of this thesis. As stated above, systematic research on the brain as concerns PD started in the early 1920s (8). A great deal of scientific work has been done since then, and even though much uncertainty remains, a considerable amount of knowledge is now available. The histopathophysiological hallmark of PD is aggregation of α-synuclein protein, leading to degeneration of neurons, called respectively Lewy bodies and Lewy neurites, in the SN (11), the region of the brain that is the main site of dopamine production. The subsequent decline in the functioning of this area of the brain is believed to cause the symptoms observed in Parkinson's disease.

In 2003, a scientific group led by the German Heiko Braak published an article that revealed considerable information that aids the understanding of PD. By performing post-mortem pathological examination of the brains of 110 PD patients, Braak and his group found that the pattern of neuronal damage was predictable. The group utilised the visualisation of α-synuclein

aggregates and interpreted these as markers of degradation. They later compared the distribution of degeneration to the patients' clinical stages (10).

The title of the main article by Braak and his group is 'Staging of brain pathology related to sporadic Parkinson's disease'. What follows is a summary of the findings of what now is called the 'Braak theory'.

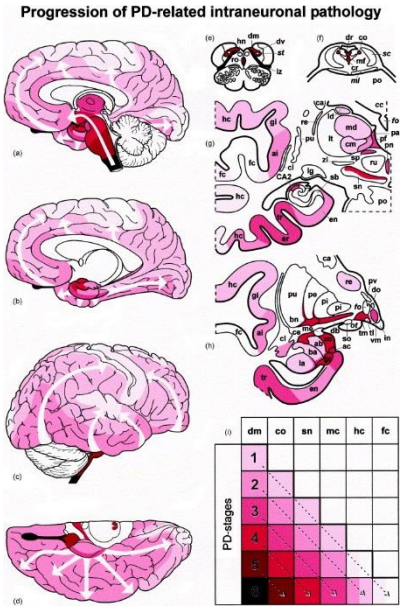


Figure 3. The Braak theory explained visually. Copied from Braak, 2002 (9)

Parkinson's disease is can be divided into six stages that are based on the extent of the pathophysiological severity and the distribution of lesions (i.e. degeneration and aggregation of Lewy bodies) within the brain. Stages 1 and 2 are generally confined to the medulla oblongata. Braak et al. found lesions in the dorsal motor bodies of cranial nerves IX and X (n. glossopharyngeus and n. vagus), the intermediate reticular zone, the caudal raphe nuclei, the gigantocellular reticular nucleus, and the coereleus-subcoereleus complex. Stage 3 is defined as the pathology of stage 2 with the addition of midbrain lesions, particularly in the pars compacta of the SN. In stage 4, the lesions extend to the temporal mesocortex and allocortex without the neocortex being affected, in addition to the pathology of stage 3. Stage 5 comprises the lesions from stage 4, as well as lesions in higher-order sensory association areas of the neocortex and prefrontal neocortex. Stage 6 defines a state that includes all the preceding stages with the addition of lesions in the first-order sensory association areas of the neocortex and premotor areas, occasionally with mild changes in the primary sensory areas and the primary motor field. (10)

Motor-symptoms of Parkinsonism and Parkinson's disease

Motor symptoms are the hallmark of Parkinsonism and Parkinson's disease. The cardinal symptoms of Parkinsonism are rest tremors, bradykinesia, muscular rigidity, and postural and gait impairment (11).

Resting tremor are often the first motor symptom of PD. They have a frequency of 3-5 Hz, are usually asymmetric and worsen with contralateral motor activity and anxiety. Bradykinesia refers to problems in rapid alteration of movement. Rigidity is increased resistance to movement in the joints. Rigidity may be felt on examination of a patient's wrist or ankle. It often gives the examiner the impression of rotating a cogwheel. Postural instability refers to reduced balance and is one of the parameters tested in the UPDRS – the test is performed by pulling a standing patient backwards. Reduced balance is of multifactorial aetiology, though it remains an important clue to the progression and diagnosis of Parkinsonism.

Even though these motor symptoms might seem obvious and easy to assess, an objective assessment is of great importance for P and PD patients. The UPDRS is a well-known, widely tested and widely used test for the measurement of symptom control in Parkinsonistic patients (15). Part III of the UPDRS is concerned with motor symptoms, and is well-acknowledged among PD specialists.

Non-motor symptoms of Parkinson's disease

Unfortunately, PD involves symptoms other than the obvious motor symptoms (MS). The non-motor symptoms (NMS) are known to impact on patients' independence, and they have a significant impact on patients' loss of health-related QoL (16).

The NMS are not a new discovery. They had already been described by Parkinson in 1817, when he noticed sleep disorders, pain, and bowel symptoms in patients (6). It is beyond doubt that the motor symptoms have received the most attention from both scientists and caregivers over the decades; however, in the late 1960s, scientists began to pay attention to NMS (17). These have received much attention in recent years, though a comprehensive understanding of them is still a long way off in terms of both scientific research and clinical work. Much knowledge has been gained between the time of Parkinson's essay and Braak's report. The latter finally provided a pathophysiological link between MS and NMS.

Neuropsychiatric symptoms
Depression, apathy, anhedonia, anxiety
Dementia
Impulse control disorders
Hallucinations, delusions (usually medications induced)
Sleep dysfunction
Disorders of sleep initiation and maintenance
Insomnia, poor sleep efficiency
Primary sleep disorders
Restless legs syndrome, periodic legs movement disorder
Sleep apnea (obstructive and central)
Parasomnias
REM sleep disorder (REM behavior disorder)
Non-REM sleep–related movement disorders
Vivid dreaming
Excessive daytime sleepiness
Autonomic dysfunction
Bladder dysfunction
Orthostatic hypotension
Hyperhydrosis
Sexual dysfunction
Gastrointestinal symptoms
Constipation
Hypersalivation
Dysphagia
Sensory symptoms
Pain
Olfactory dysfunction
Visual symptoms (diplopia, vision blurring)
Other symptoms
Fatigue
Weight loss
Weight gain (can be medication induced)

Figure 4: List of different NMS. Copied from Simuni, 2008 (2)

As stated by Martinez-Fernandes et al., different studies reports NMS in PD to occur in 60% to 97% of PD patients (1). These NMS are categorised as neuropsychiatric, autonomic, and sensory symptoms. The three NMS that this thesis is concerned with are depression (neuropsychiatric), anxiety (neuropsychiatric), and pain (sensory). The other symptoms are briefly explained.

Neuropsychiatric NMS

Conditions such as fatigue, apathy, attention problems, and forgetfulness are common and important neuropsychiatric NMS, but are outside the scope of this thesis.

Depression affects approximately 40% of PD patients (18). One study reports that depression affects health status in PD twice as much as do motor symptoms (19). It has been suggested that depression arises as a result of damage to systems of serotonergic, limbic, noradrenergic, and dopaminergic transmission (20). According to the Braak-theory (10), the brain-stem nuclei are affected at an earlier stage of the disease than is the SN; it is therefore possible to explain that depression may precede the motor symptoms of PD, as reported in studies (21).

Anxiety might be a preclinical risk factor for PD (22). The prevalence of anxiety in PD is highly uncertain, though one large study reported it as being 45% (18). Anxiety is reported to have a greater impact on QoL than motor severity has (19). The most common anxiety disorders are social phobia, panic disorder, and generalised anxiety disorder (23). In further discussions in this thesis, we will not distinguish between the different kinds of anxiety.

Sensory NMS

Sensory NMS account for diverse symptoms. These range from the loss of the sense of smell and visual symptoms to different types of pain. Only the latter is discussed further in this thesis. Pain is

one of the most common complaints in PD patients. Diffuse pain, musculoskeletal pain, neuralgic pain, and burning sensations are all frequent symptoms of PD. According to a systematic review article, the prevalence of musculoskeletal pain – the most common type of pain in PD – is reported to range from 44% to 70% (24). A recent German study reported the presence of pain in PD patients to be as high as 91% (25).

Musculoskeletal pain is a very common complaint, not only in PD patients. However, a recent cohort study from Taiwan showed that PD patients are more likely to develop musculoskeletal pain than a control group (26). The rise in prevalence in musculoskeletal pain is believed to be because of destructions of neuropathways (27). For further discussions on pain in this thesis, we will not differentiate the different kinds of pain.

Autonomic NMS
Light-headedness, GI-symptoms, drenching sweats, flushing, bladder dysfunction, trouble swallowing, and many more are autonomic NMS of PD (1). These are important NMS of P and PD, though they are beyond the scope of this thesis.

Impulse-control disorders in Parkinson's disease
Impulse-control disorders (ICDs) are defined as the presence of pathological gambling, compulsive shopping, hyper sexuality and/or binge eating. A systematic review conducted in 2013 indicated that these kinds of actions affect 6% to 15% of PD patients. The same study also demonstrated that these actions often appeared or worsened following the initiation of dopaminergic therapy or a dosage increase (28). Gambling is the most discussed ICD. An Italian research report from 2006 showed that pathological gambling is significantly higher in PD patients than in control subjects. This study indicated a prevalence of pathological gambling in 6.1% in a PD population versus 0.25% in a control group (29). It is not clear whether it is PD itself or the dopamine treatment that causes these problems.

Fluctuations in Parkinsonism and Parkinson's disease
In PD, fluctuations refer to the alternation between periods with good symptom control (i.e. on-periods) and periods with reduced symptom control (i.e. off-periods). These fluctuations arise in a proportion of patients after several years of levodopa treatment. Fluctuations are categorised as motor fluctuations (MFs) and non-motor fluctuations (NMFs).

There are several patterns of fluctuations: 'End-of-dose-wearing off' is when patients experience symptoms before their next medication dose. 'Unpredictable offs' are when patients suddenly experience akinesia or freezing of the gait. 'Delayed on' or 'dose-failure' is when a patient experiences delayed or poor symptom relief from the dose. (30)

Motor fluctuations
Motor fluctuations refer to changes in the control of motor symptoms. In a literature review from 2001, MFs are estimated to affect 40% to 50% of levodopa-treated PD patients after 4–6 years of treatment (31). Dyskinesia, that is, hyperkinetic involuntary movements, arise along with alterations in symptom control.

Non-motor fluctuations

One of the earliest descriptions of NMFs came in 1976, when Marsden noted that patients' akinesia was often associated with sweating, fear, and flushing (32). In 1986, Nissenbaum conducted a study to explore mood changes in relation to MFs; however, at that time, it was believed that motor status could account for mood changes (33). Some years later, in 1995, Maricle conducted a study with the title 'Dose-response relationship of levodopa with mood and anxiety in fluctuating Parkinson's disease: a double-blind, placebo-controlled study'. He and his group concluded that fluctuations in mood and anxiety were a pharmacological effect, and not a placebo as had previously been believed (34).

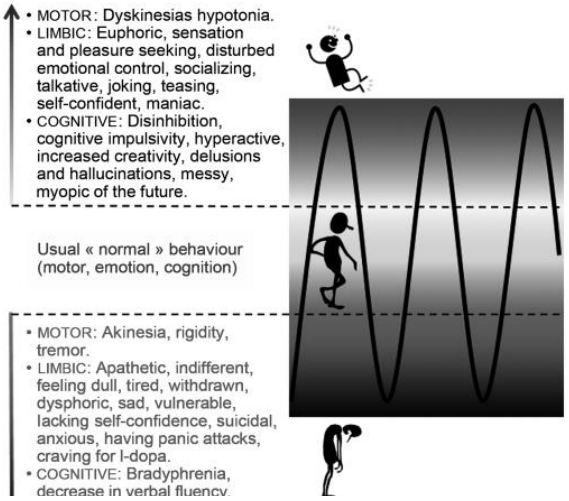


Figure 5 Copied from Martinez-Fernendez 2016 (1)

NMF frequently effects patients' QoL to a greater extent than does MF (35, 36). There is a great degree of heterogeneity among studies on the prevalence of NMF in PD, with results ranging from 17% to 100%, as reported by Martinez-Fernandez et al. (1). Neuropsychiatric symptoms are most common in NMF. NMF has also been shown to be present in the absence of MF in 7% PD patients in one study (37).

Treatment of Parkinsonism and Parkinson's disease

The first documented treatments for PD were recorded in the famous 1817 essay. At the time, the recommendation was venesection in order to divert blood and inflammatory pressure away from the brain and spinal cord (6). Fortunately, progress has occurred since then. In the late 1800s, treatment with belladonna was attempted by one of Charcot's pupils (38). Several anticholinergic agents were used in the years that followed (8). In London, George Barger and James Ewens first synthesised dopamine in 1910. It took more than 50 years before the discovery of the power that dopamine had on the relief of the symptoms of Parkinson's disease. In 1961, the neurologist Walther Birkmeyer injected L-dopa into a Parkinsonistic patient and observed what he described as a 'spectacular effect' (39). Treatment with L-dopa remains the cornerstone of PD treatment, though it gives nothing but symptomatic relief.

Dopamine replacement therapy

While there remains no cure for Parkinson's disease, several drugs – principally levodopa, dopamine agonists, and monoamine oxidase B (MAO-B) inhibitors – are licensed for use for the treatment of PD patients. It is possible to obtain a significant and clinically relevant improvement in symptoms with the use of these drugs.

Levodopa is the first line of treatment in PD/P. It is a prodrug that is converted to dopamine after being administered. The drug is well-absorbed in the small intestine, but a significant portion of the drug is degraded by monoamine oxidase (MAO) already in the intestine. Levodopa is a short-lived drug with Cmax=1/2 hour and Half-life=2 h. Following absorption in the small intestine, Levodopa is quickly converted to dopamine in the peripheral parts of the body (i.e. parts of the body other than the brain), and this results in several troublesome side effects, in addition to the fact that the brain

receives less of the active medication. Therefore, levodopa is, as a general rule, administered together with a decarboxylase inhibitor (often carbidopa) that inhibits the conversion of levodopa to dopamine (i.e. it inhibits MAO) in the peripheral regions, in order to ensure that levodopa acts where it is supposed to act – in the brain. About 80% of patients show initial improvement in motor-symptoms and about 20% of patients experience nearly full regression of motor-symptoms. Unfortunately, there are several problems with levodopa treatment. In addition to the side effects of levodopa, one major problem is that the effect of the medication is reduced over the first few years; after 5 years, approximately 66% of patients experience worse symptoms than when they were diagnosed. The side effects of levodopa are also significant for dyskinesia, fluctuations in the clinical state, nausea and anorexia, postural hypotension, and psychological effects (i.e. disorientation, insomnia, nightmares, delusions or hallucinations). (40) (p. 493)

Dopamine agonists are more effective than Levodopa in the symptomatic relief of the motor-symptoms. The newer agents are D2/D3 selective and show lower levels of troublesome fluctuations, which are a big problem with Levodopa. These agents are also short acting and requires administration three times a day. The side effects are significant for somnolence, hallucinations and impulse control problems. (40) p. 494-495)

MAO-B-inhibitors are selective inhibitors and they do therefore not cause the well-known side effects experienced with MAO inhibitors (which are often used to treat depression). They work by decreasing the breakdown of dopamine. There are different types of MAO-B inhibitors and the side effects they produce differ. It has been postulated that they are neuroprotective (because of the role of MAO-B in neurotoxicology), though there is no clear evidence to support this hypothesis. Studies have shown that Rasagiline might delay progression of PD. Rasagiline also has fewer side effects than the older Selegiline. Safinamide is a new drug that is undergoing clinical trials. It inhibits both MAO-B and dopamine reuptake. (40) (p. 495)

Advanced treatments

Advanced treatments compromise for deep brain stimulation (DBS) and intraduodenal and -jejunal levodopa pump. Indications for these procedures are more or less the same. They are reserved for patients with QoL-reducing fluctuations. DBS is an established and effective method of symptom relief in PD. Several different areas of the brain can be stimulated; high-quality evidence is available for the stimulation of the subthalamic nucleus and globus pallidus internus (41). DBS is an option when fluctuations and dyskinesias are troublesome and the MS responds to levodopa. Non-motor symptoms can improve with DBS; however, further research is required to understand the underlying mechanisms for this effect (11). The invasiveness of the procedure involved in inserting a DBS is an obvious disadvantage.

Continuous duodenal levodopa administration is performed by inserting a transabdominal tube, linked to a pump that delivers levodopa to the duodenum in an almost continually matter. Due to the drug's short half-life and the complex motor fluctuations that often occur after years of oral levodopa administration, this is a better treatment than the latter (42). One recent study claims that patients might choose duodenal administration over DBS (43).

Objective

In recent years, non-motor symptoms and fluctuations have received increased attention from the patients suffering from Parkinson's disease and their caregivers. However, there remains a significant mismatch between this level of attention and the impact on these patients' quality of life. As levels of attention have increased, more studies on the topic have been published; however, considerable research is still required before we have sufficient knowledge in this field.

This thesis aims to compare the severity of the non-motor symptoms of depression, anxiety, and pain in motor 'on' phases and in motor 'off' phases in Parkinson's disease patients.

Method

Overview

The thesis aims to contribute to an ongoing scientific project at Akershus University Hospital. The project has the title 'Levodopa-sensitive non-motor symptoms in Parkinson's disease in early and late phase'. The major objective of the project is to compare non-motor symptoms in motor 'on' and motor 'off' phases for patients with Parkinson's disease. To be able to evaluate and compare these symptoms in 'on' and 'off' phases, we need to examine patients in order to assess the level of their symptoms. These patient assessments have been structured as a pilot study. As a basis for understanding and interpreting the results of the pilot study, it was deemed wise to obtain an overview of recent studies and reports on this area of knowledge. Therefore, most of the following chapters of the thesis' are presented in two parts. The first consider the *pilot study*, and the second the search for and interpretation of existing literature, in the *literature review*.

Description of the method

Method for the pilot study

The patients for this study were recruited from the existing patient lists at Akershus University Hospital ('Ahus'). Ahus is a regional hospital close to the capital of Norway and is the primary hospital for about 500,000 people. The patient population from which participants were drawn either showed signs of Parkinsonism, were diagnosed with Parkinson's disease, or came to the hospital for levodopa testing. All the assessments were done during a trial of levodopa. The patients were asked to participate, either on the day of arrival or several days before they arrived at the hospital. The patients signed an informed consent and the method of and background to the study were briefly explained to them. The number of participants totalled six, evenly distributed between males and females. The mean age was 64.5 years. Patients with severe depression, dementia, or psychosis were excluded from the study. Two of the six patients did not complete the questionnaires, both of them due to a lack of motivation during an off-phase.

Age	Gender	Year of diagnosis	Level of education	Inpatient or outpatient	Self-reported fluctuating symptoms	Finished the study
73*	Male	2005	Higher education	Inpatient	Yes	No
67	Female	1991	Higher education	Outpatient	Yes	No
49	Male	2013	Upper secondary	Outpatient	No	Yes
48	Female	2016	Upper secondary	Outpatient	No	Yes
78	Female	2006	Higher education	Inpatient	Yes	Yes
72*	Male	2005	Higher education	Outpatient	Yes	Yes

*Table 1. Demographic data of the cohhort. *The same patient included at two different times.*

All the patients went through two evaluations. The first evaluation was conducted when the patients arrived at the hospital (outpatients) or early the next morning (inpatients), before they had taken their levodopa dosage. In the first evaluation, they were UPDRS-assessed by either a neurologist or a trained medical student, and, without extensive instructions, they marked the VAS for depression, anxiety and pain. None of the patients had taken any PD related medication for at least the last XXX hours before the first evaluation, and they were thus expected to be in their off-phase. Following the first evaluation, the patients were given a dose of levodopa. Between 90 and 150 minutes following the administration of levodopa, the same operator (for most cases, but not all) repeated the UDPRS and the VAS-schemes in a second evaluation. The examiner read the forms to the patients who were unable to read. The patients were also asked to complete the HADS, BIS-11, BIS/BAS, NMMS, and QUIP at some point during their stay at the hospital.

Method for the literature review

PubMed was selected as the search engine for the literature review. The searches were undertaken between the 5th of January 2018 and the 9th of January 2018. All the searches were filtered to present articles from 2016 and 2017 only. The first step in filtering of the results was to read the article's title. When the title of the article appeared to be relevant, the abstract was read. Based on the abstract, some articles were read in full. Some of the articles provided highly interesting references to other articles, which were read even though they did not fulfil the criterion of being published in 2016 or 2017. To avoid the threatening pitfall of not retrieving the latest articles, one last search for all the keywords, including results from 2018, was conducted on the 9th of January 2018; however, no relevant articles were found with this particular search.

Depression [title] AND Parkinson [title] generated 12 results. Two concerned depression of the heart rate in Wolf-Parkinson and were immediately excluded. and were immediately excluded. Seven abstracts were read, and three articles were read in full. None of these articles pertained to fluctuations.

Anxiety [title] AND Parkinson [title] generated four results. Two concerned the process of diagnosing anxiety in PD patients; the abstracts of these two were read. The two others cross-matched with the depression search and were read in full.

Pain [title] AND Parkinson [title] generated 11 results. One of these concerned Wolf-Parkinson, one was a case report, and one did not have an abstract; these three were not read at all. Four of the articles concerned the pathophysiology of pain in PD; the abstracts of these were read. One cohort study appeared interesting; however, it did not concern fluctuations and therefore only the abstract was read. One epidemiological and two management articles were read full.

Fluctuations [title] AND Parkinson [title] generated two results. Both were RCT of newer medications. Both abstracts were read, and interestingly, two novel medications (Opicapone and Safinamide) appeared to be promising for our patients. Though interesting, these articles were not especially relevant for this thesis and therefore they were not read beyond the abstracts.

Nonmotor [title] AND Parkinson [title] generated 10 results. Two of these did not have an abstract. Eight of the abstracts were read. None of the articles was primarily concerned with NMF.

Nonmotor [title] AND Parkinson AND fluctuations generated nine results. All abstracts were read. Five of the articles appeared to contain significant information about NMFs and were printed and read in full.

In summary, the searches generated a total of 46 unique results. Seven of these were obviously not relevant to this thesis or lacked an abstract. Thirty-nine abstracts were read, of which 11 appeared to be relevant for the thesis and thus the articles were read in full. Of the 11 articles read in full, four appeared to be relevant (1, 44-46). Of these four, two were reviews (1, 46) and two research reports. During the PubMed searches and the reading of the findings, one substantial research report from 2013 was found (47). Though this report did not fit the chronological inclusion criteria, it is highly relevant and of high quality – therefore it is included in the pool of articles that form the literature review.

Inclusion and exclusion criteria

For the pilot study

The inclusion criterion for the study was that the patients were already undergoing treatment or investigation for PD or Parkinsonism at Ahus. In addition, all the patients had a planned trial of levodopa treatment at the time of the examinations. The exclusion criterion was the presence of severe depression, severe dementia, or psychosis. Due to the limited resources available for this thesis, the availability of examiners also influenced whether patients were included.

For the literature review

The articles were included or excluded based on a subjective assessment of their relevance to the thesis. No articles were excluded due to poor quality.

Ethics of the pilot study

This study is exempted from ethics approval, by the Regional Committee for Medical and Health Research Ethics, section Southeast in Norway. This decision is based on the following statement: *All the patients in this study will follow the same line of treatment as they would have done without participating in the study, and there are none significant disadvantageous consequences for the participants*.

Description of the questionnaires and scales used in the pilot study

Motor-UPDRS is a component of the well-known UPDRS. The UPDRS is one of the most widely used and widely tested scale (15) for following the longitudinal course of PD and Parkinsonism. Some of the main weaknesses of this scale are the absence of an NMS rating and inadequate instructions for raters (48). Only part 3, UPDRS-III, was used.

The VAS-100mm is used to measure three variables in this study. This test is performed by asking the patient to draw a cross on a 100mm-long line with 'no pain/depression/anxiety' at one extreme (point 0) and 'worst possible pain/depression/anxiety' at the other (point 100). The VAS is a simple tool, although it may not be particularly accurate. Nonetheless, it is a simple, sensitive, fast, and quite reliable tool to assess these variables.

For bodily pain, the VAS-100mm was the only quantitation tool of choice for this study. This scale is easy to understand for the patient and quick to conduct. The VAS has been widely used for a long time to measure bodily pain of different sorts (49). It is also easy to implement in the results of this study. The following thresholds for interpretation of the results have been suggested: 0-4 mm: no pain, 5-44 mm: moderate pain, 45-74 mm: moderate pain and 75-100 mm: severe pain. Eleven millimetres is suggested as the minimal clinically significant change (50). The scale has been criticised as not being precise (51); however, we found it to be the most manageable scale for this study.

The VAS-100mm for subjective measures of depression is reported to correlate quite well with HADS scores (52). The same study highlighted that VAS is less precise in demented patients; however, we

believe that this problem is minimised due to the exclusion of severely demented patients in our patient group.

The VAS-100mm for anxiety is reported to have a relatively good correlation with other anxiety-measurement tools (53).

The Non-Motor Symptoms Scale (NMSS) is a novel tool for assessing the progress or potential response to treatment of NMS (54). It consists of nine main areas with 30 subsequent items. The NMSS has been revised, and is held to be 'an acceptable, reproducible, valid, and precise assessment instrument for non-motor symptoms in Parkinson disease' (55). The Norwegian version was used.

Tha Modified Hoehn and Yahr Staging is a tool for the quick classification of Parkinsonism patient's. The original staging tool was introduced in an article already in 1967 (9), but is still helpful in assessment of PD/P patients. It is widely used and calculates a score of between 0 and 5 based on the impact of the disease. While the original scale only includes whole-point increments, the modified scale includes 0.5 increments. According to the Movement Disorder Society's 2004 report, the strengths of the Hoehn & Yahr scale are its wide utilisation and acceptance. Weaknesses are its mixing of impairment and disability and that it is non-linear (56).

Criticism of the study

Of the pilot study

The low number of subjects is critical for the study's ability to present statistically significant data. A greater number of subjects was desirable at the point at which work with this thesis began, but limited resources made that impossible. All the data in this study is based on subjective assessments, which represents a possible source for several types of biases. As depression, anxiety, and pain all are multifactorial symptoms, it would be impossible to definitively eradicate this source of bias; however, some blinding of the operators could reduce the level of uncertainty. The inclusion criteria for the patients might lead to a selection of patients, that is, towards those with less well-controlled Parkinsonism. This could possibly result in a selection bias towards patients with more severe symptoms. On the other hand, we experienced that patients with more severe symptoms were less motivated to participate in the study.

Of the literature review

PubMed was the only search tool used, and the results were filtered to 2016 and 2017. Therefore, many relevant publications were not included. A broader search would have been extremely time consuming and would have exceeded the resources available for the thesis. In addition, two high-quality reviews were included in the study. It is the author's belief that these reviews include the most relevant articles that could possibly have been included in the thesis.

Results

Results of the literature review

The prevalence of NMF varies across different studies. In the various studies, the prevalence of NMF in PD patients is reported to range from 17% to 100% (1). One study with a large cohort of 300 PD patients found the total prevalence of NMF in PD to be 20%, and the prevalence of NMF in motor-fluctuating PD patients to be 33% (46, 57).

				Rate of specific NMS in %			
Author/ Year	Type of sample	Rate of MF %	Rate of NMF %	Neuro-psychiatric	Auto-nomic	Sensory	Rating tool
Hillen and Sage 1996	Patients presenting MF n=130	100	17	32	44	24	Open questionnaire
Raudino 2001	Consecutive patients n=47	80.8	60	20.3	62.9	16.6	Open questionnaire
Witjas et al. 2002	Patients presenting MF n=50	100	100	100	94	90	Structured questionnaire
Gunal et al. 2002	Consecutive patients n=85	84.7	NA	15.3	29.2	38.3	Open questionnaire
Storch et al. 2013	Patients presenting MF n=100	100	NA	NA	None	NA	NMSQuest, WOQ9
Seki et al. 2013	Consecutive patients n=464	69	40	49	32	45	WOQ19
Brun et al. 2014	Consecutive patients n=303	NA	19	44	49	44	Open questionnaire
Storch et al. 2015	Patients presenting MF N=73	100	100	NA	NA	NA	NMMS
Picillo et al. 2016	De novo drug naïve patients (prospective 4-year follow-up) n=47	38.3	55.3	NA	NA	NA	WOQ19

a Differences in prevalence are partially attributed to methodological issues. Hillen and Sage and Raudino calculated the prevalence for each category (neuropsychiatric, autonomic, and sensory) of symptoms among all reported NMS. Witjas and colleagues reported the proportion of patients with fluctuating NMS among a sample of motor-fluctuating patients. Gunal and colleagues and Seki and colleagues reported the number of patients in whom presentation or change in NMS were associated to motor fluctuations. Brun and colleagues detailed the percentage of patients with each type of NMS among those patients with NMF. Storch reported the presence or absence of each NMS in the respective ON or OFF motor state. Finally, Picillo and colleagues asked patients to answer whether NMS where present and whether they improved after dopaminergic treatment.

NA, not available.

Table 2. Modified from Martinez-Fernandez, 2016 (1)

The prevalence of neuropsychiatric fluctuations varies from 15% to 100% for all PD patients (1) and from 32% to 100% in patients with manifest MFs (46). According to a study published in 2013, fluctuations in anxiety (28%) and depression (47%) are two of the most prevalent NMF-symptoms in PD patients with or without MF (47). The two review articles state that sensory symptoms and pain fluctuate from 39% to 45% (1) and from 30% to 90% (46), respectively.

There is no clear relationship between MF and NMF for most of the non-motor symptoms; however, depression, anxiety, and pain are reported to fluctuate in conjunction with motor fluctuations. Anxiety and depression are repeatedly reported as appearing in a clear correlation, both temporally and in terms of severity, in an MS_{off} state (44, 45, 47). According to the review from 2017, pain also clearly fluctuates in conjunction with motor fluctuations (46). Storch and colleagues found a statistically and clinically significant relationship between MF and depression (p-value <0.001 and ΔVAS MS_{on}-MS_{off} >10%), anxiety (p-value <0.001 and ΔVAS MS_{on}-MS_{off} >10%) and pain (p-value 0.001 and ΔVAS MS_{on}- MS_{off} >10%) (46).

		ON state			***OFF state***			
Symptom	***No. Of patients***	***Mean +/- SD***	***Median***	***10th/90th percentile***	***Mean +/- SD***	***Median***	***10th/90th percentile***	***p-value***
Anxiety	Clinical Examination (n =99/99)	4.1 ± 14.7	0	0/70	16 ± 27.2	0	0/60	<0.001
	Self-rating at home (n=75/72)	7.4 ± 16.9	0	0/25	17.4 ± 22.3	8	0/48	<0.001
Depression	Clinical Examination (n =98/98)	10.1 ± 20.8	0	0/40	29.9 ± 31.7	20	0/70	<0.001
	Self-rating at home (n=75/72)	8.0 ± 16.0	0	0/28	24.5 ± 25.4	13	0/65	<0.001
Pain	Clinical Examination (n =99/99)	14.3± 22.8	0	0/50	24.4 ± 30.8	10	0/80	0.001
	Self-rating at home (n=75/71)	17 ± 22.9	4	0/54	27.4 ± 26.6	20	0/64	<0.001

Numbers in mm on VAS-100 mm scale. For the self-ratings, the mean number of ratings per patient (max = 5 per motor state) ranged from 2.9-3.1 rating for on state, and 2.8-3.0 rating for off state. The p-values represent data from Wilcoxon rank test comparing severity in on state with severity in off state.

Table 3 Modified from Storch, 2013 (47). The study included 100 PD patients and was published in Neurology in 2013

Results of the pilot study

Demographic and clinical data for the cohort are presented in table 1. Two (50%) of the subjects reported fluctuations during direct questioning and three (75%) showed NMS during the NMSS evaluation (mean value = 46), with the greatest frequency and severity in area 2, 7, and 9.

All the subjects showed a decrease in UPDRS-III between the first and the second evaluation (meanΔ -18.5), and most of the subjects self-reported as MS_{off} at the first evaluation and MS_{on} at the second evaluation.

						VAS-anxiety		VAS-depression				
			Year of	UPDRS-III						VAS-pain		
Pat.no	Age	Gender	diagnosis	Off	On	Off	On	Off	On	Off	On	HADS
1100*	73	Male	2005	-	34	-	9,7	-	5,8	-	2,9	7
1003*		Female	1991	-	-	-	-	-	-	-	-	9
1005	49	Male	2013	23	9	15,2	2,0	0	0	0	0	2
1004	78	Female	2006	28	16	24,0	2,9	0	3,4	35,3	3,9	7
1006	48	Female	2016	33	23	68,6	48,0	14,7	5,9	3,9	1,9	14
1000	72	Male	2005	49	11	1,9	0,5	38,6	2,0	31,7	0,0	3

*Table 4 Overview of the pilot study cohort, combined with some of the results. VAS-scores are given in %. *Same subject as 1000 at a different date. *Did not complete all parts of the study, and are therefore not included in the results.*

VAS-depression was present in 50% of the subjects in MS_{off}, and in 75% in MS_{on} (mean MS_{off} 13±18, mean MS_{on} 3±2). All the subjects who completed the study reported VAS-anxiety in both off and on phases (mean MS_{off} 27 ±29, mean MS_{on} 13 ± 23). VAS-pain was present in 75% in MS_{off} and 50% in MS_{on} patients (mean MS_{off} 18±18, mean MS_{on} 2±2). For anxiety and pain, all the subjects reported equal (n=1) or lower (n=3) VAS-scores in MS_{on} than in the MS_{off}. For depression, three patients reported lower values in MS_{on}, and one patient reported slightly higher VAS (Δ3.4 %) in MS_{on}. None of the differences between MS_{off} and MS_{on} is statistically significant.

		On	Off	Difference between On and Off		
Symptom	N	Mean ± SD	Mean ± SD	Mean value	95% konf.int	p-value
UDPRS-III	4	14,7 ± 6,2	33,3 ± 11,3	18,5	-2,3 - 39,3	0.067
Anxiety	4	13,3 ± 23,1	27,42 ± 28,9	14,1	4,6- (-0,5)	0.055
Pain	4	1,5 ± 1,9	17,7 ± 18,3	16,3	8,8- (-11)	0.162
Depression	4	2,8 ± 2,5	13,3 ± 18,2	10,5	9- (-18,3)	0.331

Table 5 Presentation of the mean values with standard derivation and confidence interval. Only subjects that completed all stages are included in this table.

Fig. 7 UPDRS-levels in Motor-off and Motor-on. Y-axis representing UPDRS-score

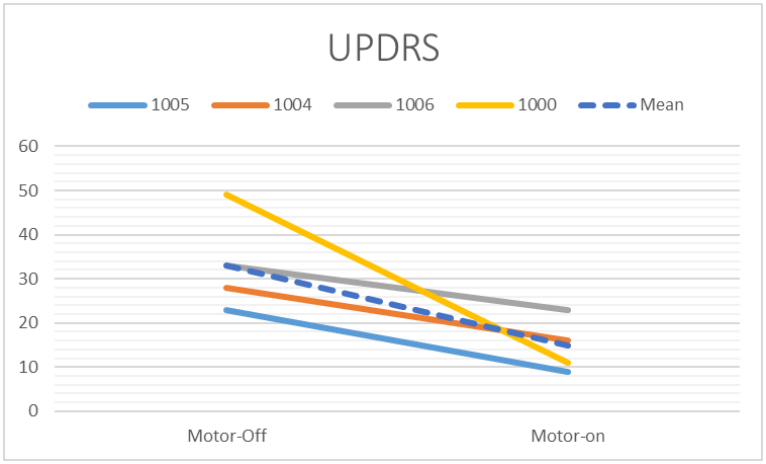


Fig. 8 VAS-Anxiety in Motor-off and Motor-on. Y-axis representing VAS-score

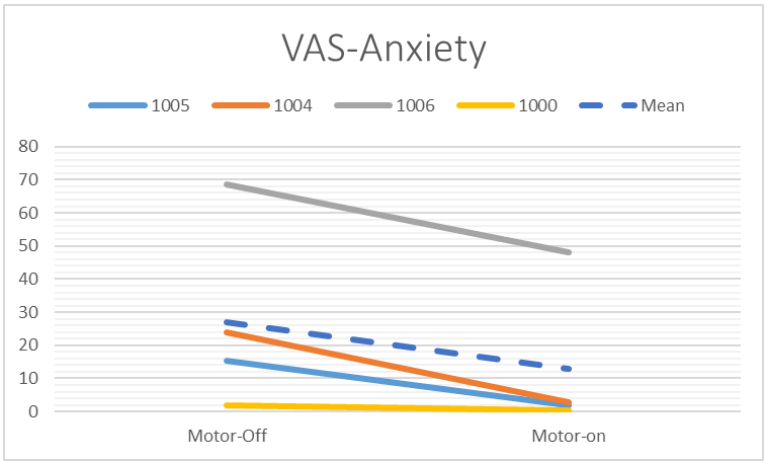


Fig. 9 VAS-depression in Motor-off and Motor-on. Y-axis representing VAS-score

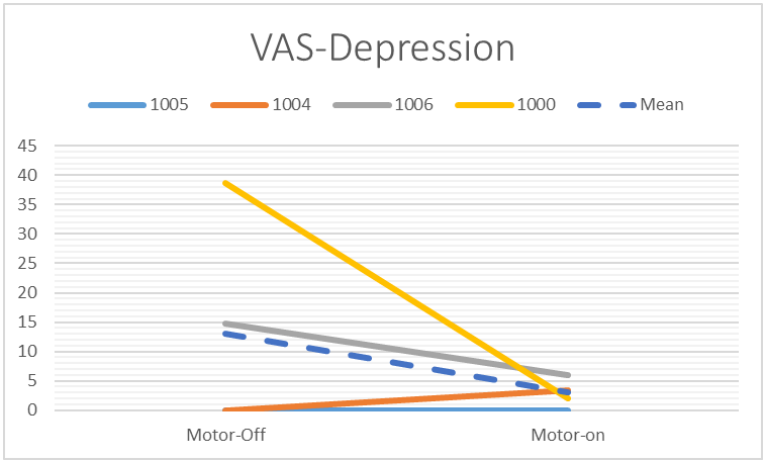
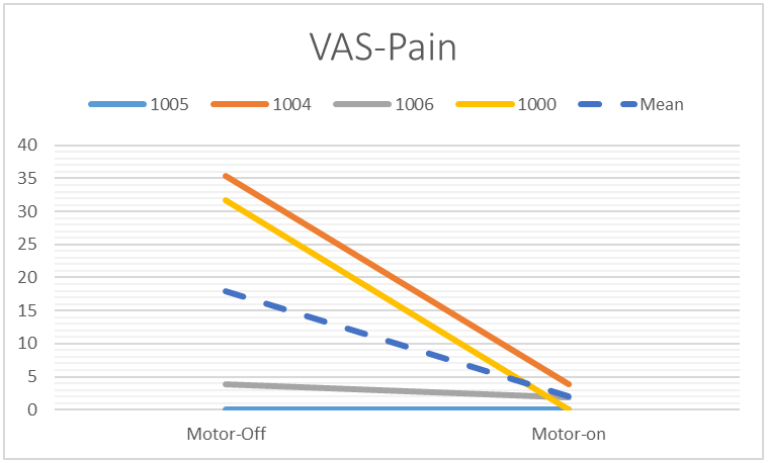


Fig. 10 VAS-pain in Motor-off and Motor-on. Y-axis representing VAS-score



Summary of data for all the subjects included in the pilot study																
Subject no	**Age**	**Gender**	**Year of diagnosis**	**Level of education**	**Clinical setting for assessment**	**Self-reported fluctuations**	**Finished The study**	**UPDRS off**	**UPDRS on**	**VAS-Anxiety in Motor$_{off}$**	**VAS-Anxiety in Motor$_{on}$**	**VAS-Depression in Motor$_{off}$**	**VAS-Depression in Motor$_{on}$**	**VAS-Pain in Motor$_{off}$**	**VAS-Pain in Motor$_{on}$**	**HADS**
1100†*	73	Male	2005	Higher education	Inpatient	Yes	No	-	*34*	-	*9,7*	-	*5,8*	-	*2,9*	*7*
1003†	??	Female	1991	Higher education	Outpatient	Yes	No	-		-		-		-		*9*
1005	49	Male	2013	Upper secondary	Outpatient	No	Yes	*23*	*9*	*15,2*	*2,0*	*0*	*0*	*0*	*0*	*2*
1006	48	Female	2016	Upper secondary	Outpatient	No	Yes	*28*	*16*	*24,0*	*2,9*	*0*	*3,4*	*35,3*	*3,9*	*7*
1004	78	Female	2006	Higher education	Inpatient	Yes	Yes	*33*	*23*	*68,6*	*48,0*	*14,7*	*5,9*	*3,9*	*1,9*	*14*
1000*	72	Male	2005	Higher education	Outpatient	Yes	Yes	*49*	*11*	*1,9*	*0,5*	*38,6*	*2,0*	*31,7*	*0,0*	*3*
Mean		-	-	-	-	-	-	33.25	18.6	27.4	12.6	13.3	3.4	17.7	1.7	**7**

*Table 6 Summary of data from all the subjects, including those who did not finish the study. *The same patient participated at two different times, but only finished the study once. †Did not finish the study.*

ICD-scores for all the subjects included in the pilot study				
Subject no	**BIS-11**	**BISBAS**	**QUIP**	**NMMS**
1100*	57	75	0	55
1103*	62	49	4	19
1005	62	45	0	0
1004	59	71	2	66
1006	66	58	0	39
1000	55	69	0	79
MEAN	60.5	61	1	43

*Table 7 ICD-score for all the subjects included in the pilot study. *Did not finish the study.*

Discussion

Literature review

The studies indicate that NMF are highly prevalent and are an important determinant of the QoL of PD patients. The studies make it clear that pain, anxiety, and depression differ from other NMS in the manner in which they are clearly correlated with fluctuations in motor symptoms.

Pilot study

The results of this study demonstrate a clear tendency towards lower levels of VAS-depression, VAS-anxiety and VAS-pain in the MS_{on} than in the MS_{off}. However, because of the small number of subjects, the study do not provide any statistically significant data.

VAS-depression was reported by two of the subjects in their MS_{off} phase, and both experienced a relative reduction in VAS-depression of more than 40% in their MS_{on} phase. No consensus is reached regarding a significance level for VAS-depression; however, it seems appropriate to claim that two of the subjects in this study attained a significant relief from MS_{off} to MS_{on}. The two subjects without significant relief did not suffer from significant VAS-depression in MS_{off}.

VAS-anxiety was reported by all the subjects in MS_{off}. However, one of these reported only 1.9mm on the VAS. Williams and colleagues concludes that a change of 10mm to 15mm can be regarded as an 'important difference' (58). With Williams' definition taken into account, three of the subjects experienced an 'important difference' in anxiety, with the difference ranging from 13.2mm to 21.1mm, while one experienced virtually no difference.

VAS-pain in the significant range(more than 10mm on the VAS) (59) was reported by two of the subjects in the MS_{off} phase. Both of these experienced a reduction in pain from the MS_{off} to the MS_{on}. Importantly, according to Birds' definition of significant VAS-pain (59), both of the subjects presenting pain in this study had a clinically significant reduction in pain from the MS_{off} to the MS_{on}.

Some studies have suggested that a VAS-change of 10-15 mm is a plausible definition of a 'clinical significant' change (58, 59). By interpreting this definition of a clinically significant change in VAS as being 10mm, one can see that 6 of the total 12 VAS-ratings in this study show a lower value in MS_{on} than in MS_{off}. The mean VAS for all the parameters was also reduced of more than 10mm.

As explained above, none of the results of this pilot study is statistically significant. However, they show a clear tendency and correlate well with similar studies with larger cohorts. In addition, the results correlate well with the patients' own experiences.

Conclusion

Conclusion the literature review

Over the last decades, non-motor symptoms and non-motor fluctuations have been subject to increased attention; however, there is still a significant mismatch in the knowledge about NMF, and NMFs and their influence on PD patients' QoL. Hoping for further research in the years to come appears to be well-justified.

Conclusion of the pilot study

No conclusions can be drawn from the pilot study due to the small number of subjects. However, there is a clear tendency towards a reduction in the NMS studied from the $Motor_{off}$ phase to the $Motor_{on}$ phase. The results from this study correlate with recent research. It is expected that a greater number of subjects would be a sufficient adjustment to the study, in order to obtain statistically significant data.

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