

On-off related fluctuations of non-motor symptoms in patients with advanced parkinson's disease treated with intraduodenal levodopa (Duodopa®)

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Abstract

Background: Parkinson's disease (PD) patients with advanced disease experience motor symptoms, motor complications and multitude of nonmotor symptoms (NMS). These NMS are common, and have a negative impact on the quality of life (QOL). Although known, the frequency and severity of NMS fluctuations are not thoroughly investigated.

Objectives: This study aimed to test the use of VAS and HADS to rate short term NMS-fluctuations in patients with advanced and complicated PD, and the correlation to motor fluctuations.

Method: HADS and VAS was used on three inpatients to rate pain, depression and anxiety, once in the "off" state and once in "on". Motor function was evaluated with UPDRS, and daily function with a custom questionnaire.

Results: All patients had a lower HADS score in "on" than they did in "off". Two patients showed less anxiety and depression in "on" compared to "off". Pain appeared to be more individual, as two experienced little change and the third had half the pain in "on" compared to "off".

Discussion: Whether fluctuations of pain, anxiety and depression occur or not, and the severity of these, seems to be highly individual. The findings seem consistent with what is known on this topic. Although little statistics can be gained from the results, patients appeared to be able to reflect their short term fluctuations in depression, pain and anxiety through HADS and VAS. Recall bias did not appear to be a problem. A larger scale study using these tools in this setting could be possible.

Table of Contents

INTRODUCTION	4
PARKINSON'S DISEASE	4
PATHOLOGY IN PD	4
EFFECT OF LEVODOPA TREATMENT	5
DOPAMINE AGONISTS.....	5
CONTINUOUS DOPAMINERGIC STIMULATION.....	5
MOTOR COMPLICATIONS	5
MOTOR FLUCTUATIONS	6
DYSKENISIAS.....	6
NONMOTOR SYMPTOMS.....	6
NEUROPSYCHIATRIC SYMPTOMS	7
ANXIETY	7
DEPRESSION	7
MOOD FLUCTUATIONS	8
DOPAMINERGIC TREATMENT OF DEPRESSION	8
ANTIDEPRESSANT TREATMENT	8
PAIN	8
LATE STAGE PD.....	9
STAGING.....	9
OBJECTIVES	9
METHODS	10
PATIENTS/SELECTION	10
INSTRUMENTS	10
ANALYSIS.....	11
RESULTS	11
DISCUSSION	14
ACKNOWLEDGMENTS	15
APPENDIX 1:	22
SPØRRESKJEMA:	22

Introduction

Parkinson's disease

The average age of onset of Parkinson's disease (PD) is 65 years, and more than 1% of the elderly population is affected by PD(1). It is the second most common age-related neurodegenerative disease, and the prevalence increases with age (1;2). PD is a progressive disease, caused primarily by neuronal loss in substantia nigra. PD is traditionally regarded as a movement disorder characterized by motor features. These motor features are the cardinal symptoms of the disease and are bradykinesia, rigidity, rest tremor and postural instability(3). Each case of PD is different, but the disease often starts with prodromal symptoms. After a while asymmetrical and unilateral symptoms emerge, followed by bilateral motor symptoms (4;5). As the disease progresses patients experience increasing symptoms and may have trouble completing simple tasks, walking and talking. The progression of the disease is non-linear, and the motor function declines faster in early stages compared to later(6;7). In the later stages the patients get motor complications, balance and gait impairments, and some experience psychosis and dementia.

The aim of treatment in PD is to reduce motor and nonmotor symptoms in order to improve the patient's quality of life (QOL) and to reduce mortality and complications. The main treatment focus for neurologists has been the reduction of the motor symptoms of the disease, and these symptoms definitely have a negative influence on the patients QOL. Among the motor features, motor fluctuations and gait disorders have the biggest impact on QOL (8). PD is however not just a movement disorder, and non-motor symptoms are both common and also play an important role in the patient's QoL.

The most effective drug against the symptoms of PD is levodopa, but its effect is limited on some of the symptoms (6;9). Bradykinesia and rigidity are usually the symptoms that respond best to levodopa, while tremor responds more variably. Motor complications, which can be divided into motor fluctuations and dyskinesias, is a common complication among patients who have received long term levodopa treatment (10;11). The strongest predictor for developing motor complications is duration and dose of levodopa treatment(12;13), and after 4-6 year of levodopa treatment, 40-50% of PD patients develop motor complications(12). Motor complications have a big impact the quality of life and patient disability, especially in the advanced stages of PD(11;14). Mobility, activities of daily living, stigma and communication are the most severely affected domains.

Pathology in PD

In the brain, the basal ganglia's role is related to movement control, by selecting, preparing and executing movements (18). In PD, there is a loss of dopaminergic neurons in substantia nigra pars compacta, which is the cause of the cardinal motor symptoms seen in the disease(15). However, pathology is not limited to this part of the brain, and several other extranigral parts may be involved, which is thought to cause levodopa-resistant motor

symptoms and nonmotor-symptoms (NMS)(16). In early stages of PD, the reduced dopamine production is compensated in several ways. The remaining dopamine neurons increase their activity, postsynaptic dopamine neurons become more sensitive, the amount of dopamine transporters is downregulated and the firing rate of basal ganglia neurons is modified (17). As the disease progresses, the dependency of external supply of levodopa increases.

Effect of levodopa treatment

Levodopa is the most effective symptomatic treatment of PD. Patients experience reduced disability and increased ability to maintain independent activities of daily living(19). It is also associated with enhanced QOL and improved mortality, making it an important tool in the treatment of PD (20;21). Long term chronic levodopa treatment is despite its usefulness commonly associated with motor complications(22). The motor complications are likely associated with pulsatile dopamine concentrations caused by oral levodopa treatment(23), and a more physiological approach could reduce the risk of motor complications. These complications are also a cause of considerable disability and limit the utility of the drug. In addition to causing motor complications, levodopa has limited or no effect on certain motor features and non-motor symptoms. Combining levodopa with a catechol-O-methyltransferase -inhibitor blocks peripheral levodopa metabolism, and could provide a more continuous distribution of dopamine in the brain, reducing the risk of motor complications(24)

Dopamine agonists

Dopamine agonists is a treatment option in the early stages of PD. Patients who started initial treatment with a long acting dopamine agonist had reduced risk of developing motor complications compared to those who started with levodopa(25). They are less potent than levodopa and are associated with more side effects, and do not prevent the development of motor complications once the patients are treated with levodopa (26).

Continuous dopaminergic stimulation

Fluctuating motor symptoms is an important factor to the decreased quality of life among PD patients (11). Continuous duodenal levodopa infusion is effective in treating patients with advanced PD, and improves both motor symptoms and NMS (27). Short term exposure to could improve QOL in patients with advanced PD, showing improvements in all domains except social support. It is suggested that this improvement might be due to the increased amount of time were the patient is “on”. This gives an improvement in disability, physical function and mobility, in addition to mental status, mood, social well-being and global QOL (28). There is also a reduced risk of developing motor complications in early disease with continuous dopaminergic stimulation (29).

Motor complications

Motor complications are a result of long term levodopa treatment and can be divided into motor fluctuations and dyskinesias. These complications have a big impact on the quality of life in the advanced stages of PD.

Motor fluctuations

Motor fluctuations are often referred to as on-off fluctuations and are relatively well documented. Patients in the “on”-phase has relatively good mobility and function, while they have relatively reduced mobility and function while “off”(30;31). They may alternate between disabling dyskinesias and disabling parkinsonian symptoms during the day. Initially in the early stages of PD, the duration of benefit following a dose of levodopa is long. As the disease progresses and levodopa treatment becomes chronic, the duration of benefit becomes shorter(32;33). Some patients may experience unpredictable on-off fluctuations as a result of this(22),and this is an important reason for surgical treatment.

Dyskinesias

Dyskinesias are either peak-dose, diphasic or dystonic. The most common levodopa-induced dyskinesias are peak-dose dyskinesias. They are involuntary movements that can include dystonias and myoclonus, occurring when the levodopa plasma concentration is at the maximum(34). Diphasic dyskinesias occur both when patients begin to approach the peak dose, and again when the concentration starts to fall(34). Dystonic dyskinesias are usually painful fixed postures occurring in the off-state(34). Dyskinesias may restrict the levodopa dosage as the therapeutic window narrows with disease progression and chronic levodopa treatment even though not all patients find them troublesome(34).

Nonmotor symptoms (NMS)

The impact NMS has on quality of life in PD is increasingly recognized, and as a consequence several aspects NMS have gained increased attention. Despite this, the non-motor symptoms of PD are both under-recognised and undertreated (35). The range of NMS is wide and includes neuropsychiatric symptoms, sleep dysfunction, autonomic symptoms, gastrointestinal symptom and sensory symptoms, including pain. In general, these non-motor symptoms increase in both severity and frequency with advancing age and progression of the disease(35) . Although the impact of NMS increases in advanced PD, it is also apparent in the early stages, and some symptoms may precede the motor symptoms (35)

Findings suggest that several non-motor symptoms have a dopaminergic contribution (36;37). Levodopa is however largely not an effective treatment of the NMS, but can limit the tendency of the symptoms to fluctuate along with the motor symptoms (38). Axial motor symptoms like falls, postural instability and dysphasia and NMS have been shown to progress together and is associated with disease progression(39). These symptoms are non-responsive to levodopa and dominates the advanced stages of PD, having a big impact on the patients disability and QoL(40).

As with motor symptoms, NMS can also fluctuate and cause more discomfort for the patient, but they are not as thoroughly investigated as motor fluctuations. The most common NMS fluctuations are anxiety (66%), drenching sweats (64%), lowness of thinking (58%) and fatigue (54%) (38). These fluctuations often coexist with motor fluctuations, and continuous

dopaminergic stimulation can probably have a beneficial effect in treatment of them, even though they to some degree are regarded as non-responsive to dopamine (38).

Neuropsychiatric symptoms

Neuropsychiatric symptoms in PD include anxiety, anhedonia, apathy, depression and dementia (41). The most frequent neuropsychiatric symptoms are anxiety and depression, which often coexist together with motor symptoms (42). These have a big impact on the quality of life, with depression being the biggest factor for quality in life in patients with PD(42). While the presence and frequency of neuropsychiatric symptoms in patients with PD appears to be unrelated to the disease staging, the severity of these symptoms increase with advanced disease (43). The frequency of behavioral, neuropsychiatric and cognitive disorders appears to be higher in patients with motor complications (42).

Anxiety

Anxiety is the second most common affective disorder in PD and is usually general anxiety disorders, panic attacks or phobias, such as social phobia (41;44) Increased anxiety is generally coexisting with depressed mood, and the correlation between depression and anxiety is strong (45). However, some patients reports anxiety and no depression, and vice versa. They both fluctuate with levodopa dose, and are most pronounced during off, and one treatment strategy is avoiding being “off” (38).

Depression

One of the most common NMS is depression, but the reported frequency of depression in PD varies in different studies. A meta-analysis has found that about 35% of patients with PD have clinically relevant depressive symptoms(46). In this study, major depressive disorder was present in 17% of PD patients, depressive symptoms in 22% and dysthymia in 13%. The prevalence of depression among patients with PD is higher than in both the general population and in patients with other chronic and disabling diseases(47).

The symptoms of depression include depressed mood, anhedonia and feelings of worthlessness or guilt. There are also somatic symptoms like changed appetite, sleep disturbances, psychomotor retardation and altered facial expression(48). In clinical setting, depressive symptoms in PD patients are often under reported and under-treated (49). One reason might be that some of these symptoms may also be evident in non-depressed PD patients as a part of PD, making it harder to differentiate between the two. It has been suggested that underdiagnosis of depression could be reduced by considering these symptoms as a part of depression rather than PD(48). However, by doing this there is a slight risk of overdiagnosing.

Several studies have proposed that depression is a prodromal syndrome of PD, and a review found a link between a history of depression and development of PD (50). Interestingly, there seems to be an increased risk of developing PD among people with anxious and pessimistic personalities(51). Those with depressive personality traits did however not have any increased

risks. Another study found an association between major clinical depression and rapid cognitive decline, also suggesting the pathophysiological link between PD and depression(52).

Mood fluctuations

Up to two third of patients with motor fluctuations also experience mood fluctuations (53). There is no standard way to determine whether a patient experiences mood fluctuations, and how severe they are. It has been estimated that 7% of all PD patients have clinically significant mood fluctuations (54). These tend to be related to motor fluctuations(53), with lower mood in off and higher mood in on. Those who experienced motor fluctuations are more commonly patients with a young age at onset of PD, longer disease duration. They are also more likely to have dementia, psychosis, motor fluctuations and clinical depression (54). A study showed that mood fluctuations preceded the change in motor function by several minutes, making it less likely that the fluctuations is just a psychological reaction to the motor fluctuations (45). Anxiety fluctuations often coexist with mood fluctuations, and they are probably as common(53;54).

Dopaminergic treatment of depression

Dopaminergic therapy has an effect on mood disorders and anxiety in PD (55). Pramipexole, a D3 dopamine agonist, has been shown to be effective against depressive symptoms without fluctuations. While the improvement was small, 80% of the effect was unrelated to the improvement of motor symptoms (56). As these also improve motor symptoms, initial treatment of depression in PD should probably consist of optimization of dopamine treatment(57).

Antidepressant treatment

SSRIs are the most widely used antidepressants in this patient group, but the evidence to determine whether there is an effect or not is insufficient(58). Atomoxetine, a selective noradrenaline reuptake inhibitor, has shown no antidepressant effect compared to placebo(59) although it did improve both global cognition and daytime sleepiness. Nortriptyline is a drug that has shown significant reduction of depression in this patient setting(60). In addition to reduction of depressive symptoms, it was linked with improved QoL. They suggested that antidepressant drugs with effect on both serotonergic and noradrenergic systems might be the preferred antidepressant treatment for patients with PD.

Pain

The prevalence of chronic pain increases with age, and some patients with PD have pains that are not related to their PD. Pain is often underreported and undertreated in a clinical setting(61), having a negative impact on the patient's QOL(62). The average intensity of pain in a study was 60mm on a 100mm visual analogue scale, while the average among control patients were half of this(61).

Motor fluctuations and dyskinesias are a major cause of pain in PD(63), and are along with central pain probably associated with PD. Pain in PD might manifest as central pain, oro-facial pain, limb pain or musculo-skeletal pain, usually more pronounced on the side most affected by motor symptoms. The most common pain related to PD is musculoskeletal pain, which possibly accounts for 70% of the reported pain, and pain seems to be related to female sex (64).

Pain in PD is linked to motor symptoms and often responds to antiparkinson medication. A recent review suggests that because pain in PD often fluctuates along with the motor symptoms, optimization of the antiparkinson therapy should be the first approach in treating all pains in PD(65). They proposed that a levodopa stimulation test could be performed to distinguish dopaminergically maintained pain from dopaminergic independent pain, to further improve the pain management.

Late stage PD

Patients with advanced-stage PD are a heterogeneous group, and the clinical presentation varies greatly in regards to the presence and severity of NMS, motor symptoms and motor complications. The duration of the disease seems to be the most important factor in reaching advanced-stage and with improved management of PD and increased general health, it is likely that there will be an increase in patients with late stage PD (66). In the later stages of PD, the main factor affecting disability and QoL is levodopa-resistant motor symptoms and NMS. Most of these symptoms currently lack effective treatment. In advanced parkinson, the motor complications have a reduced impact on QOL, as these can be treated by deep brain stimulation or because they attenuate naturally(4;40). The occurrence of falls, hallucinations, dementia and institutionalization indicate the start of rapid disease progression(66). Patients with an earlier onset of the disease has a longer disease duration, they respond stronger to levodopa and have increased severity of motor complications. Patients with later disease onset has a shorter disease course, worse levodopa response, but no motor fluctuations(67).

Staging

According to the Hoehn and Yahr scale, the definition of advanced-stage PD depends on disabling motor complications(68). This includes patients with bilateral disease, postural instability and physical dependence. Using the term late-stage has been proposed to describe patients with treatment-resistant motor symptoms or NMS who are highly dependent on caregivers(66). The proposed definition is a score on the Schwab and England scale of less than 50% during periods of adequate symptoms, which means that the patients needs help with half their chores and has difficulties with all activities.

Objectives

NMS has gained increasing attention, but much remains to be known. In advanced stages of PD, NMS has a greater impact on quality of life than the motor symptoms. Neuropsychiatric symptoms such as depression and anxiety, sleep disturbances and pain are both common and has the biggest impact on the patient's reduced QOL. There appears to be a correlation

between motor complications and certain NMS, making it plausible that dopaminergic pathways are involved in the development of NMS. While the fluctuations of motor symptoms are well known, NMS fluctuations are known to occur, but there is a lack of research done on this. Short-term fluctuations of NMS should be investigated further, and little research has been done on the field. This study aims to evaluate instruments for measuring short-term fluctuations of pain, depression and anxiety among patients with advanced PD, as illustrated by a few patients with advanced and complicated PD.

Methods

Patients/selection

To be able to measure short-term fluctuations of NMS in this study, patients had to experience fluctuations and have NMS. Selection criteria were that they had developed motor complications, and had a continuous duodenal levodopa pump and/or advanced PD. This was to ensure that the patients were both advanced stage and experienced motor complications. Patients were asked to participate in the study while they were inpatients at Akershus Universitetssykehus for control of their PD. In total three patients with advanced PD ended up participating in the study.

Instruments

Unified Parkinson's Disease Rating Scale (UPDRS) part 3 (motor symptoms) was used to objectively assess if the patients were in an on- or off-state, and patients were also asked how they considered their current function. 100mm visual analogue scales (VAS) were used for pain, depression and anxiety. The outer outcomes of the scale for pain were "no pain" and "worst imaginable pain". For depression it was "no lowered mood" and "worst imaginable depression", and for anxiety "no anxiety" and "worst imaginable anxiety". In addition, Hospital Anxiety and Depression Scale (HADS) was used as an additional outcome for depression and anxiety. Patients were asked to fill out the HADS questionnaire according to how they felt in the moment, rather than to try remembering what they answered the previous time. A questionnaire to assess their daily function was filled by the patients at the end of the study (see appendix). This questionnaire consisted of 8 questions, asking about their daily function and how frequently they have trouble with certain daily activities. The patient had to assign a score of 0-4 on each question, where 0 being that it never was an issue and 4 being a constant problem, giving them a total score from 0 to 32.

The patients were asked to participate in the study one day in advance, when they were admitted to the hospital. The instruments used in the study were used twice for every patient, once in "off" state and once in "on". To ensure that the patient were undoubtedly "off", the first set of UPDRS, VAS for pain, depression and anxiety and HADS was performed in the morning before the patients turned on their duodopa-pump or had their first dose of oral levodopa. The next set of UPDRS, VAS and HADS was performed during the day after several hours of levodopa treatment, when the patients were in both on as assessed by the

clinician and themselves. After collecting the second set of data, they were asked to fill out a form assessing their daily function.

Analysis

Analysis of the data is limited to descriptive statistics. Further statistical analyses were not performed because of the small number of patients included in the study. Missing values were imputed and exchanged for the average value of the answered question. Results where imputation was performed are presented both with and without the imputed values.

Ethics

The study was evaluated by REC, reference number IRB0000187, prior to startup. On 5.03.12. REC granted exemption from the ethical approval, as the project was evaluated as a quality project. The study was then passed by the Data inspectorate officer at Ahus, who approved the study on 27.02.12. In addition, all patients were asked to sign a consent form upon participation in the study.

Results

All patients were clearly off in the morning before their first dose, and experienced a high degree of motor symptoms. This was reflected both through their UPDRS score and how they felt. After a few hours of levodopa treatment, they all improved greatly, and patient 1 and 2 were having dyskinetic movements when they were examined the second time, indicating that they were around their peak dosage. All three patients were clearly “on”, and much more able to perform activities at the second examination. They were all able to complete the forms and VAS in both on and off, but patient 2 chose to not answer three of the questions in HADS in both “off” and “on”. The reason was that she found it difficult to answer those questions because she didn’t feel any of it at the moment.

All three patients were experiencing pain, anxiety and depressive symptoms to a variable degree both when “on” and “off”. In general there was a tendency of less NMS when “on” compared to “off”, both when looking at VAS and HADS. All patients had a lower VAS for anxiety and depression, and they also had a lower HADS score, further supporting the change in their mood. There was a trend towards a reduction of anxiety and depression. Pain as evaluated on a VAS, was however more individual. While two of the patients experienced slightly more pain, the third scored half as much on the VAS in “on” compared to “off”. It would seem that individual variation in the experience of fluctuating symptoms is great. While patient 1 and 3 experienced moderate to large fluctuations in depression and anxiety, patient 2 noted nearly no variation on the VAS for all three symptoms.

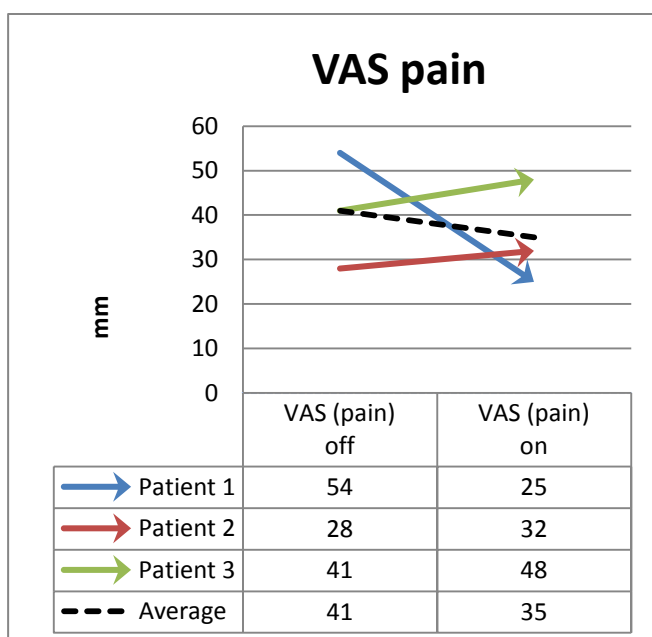
Tables and figures

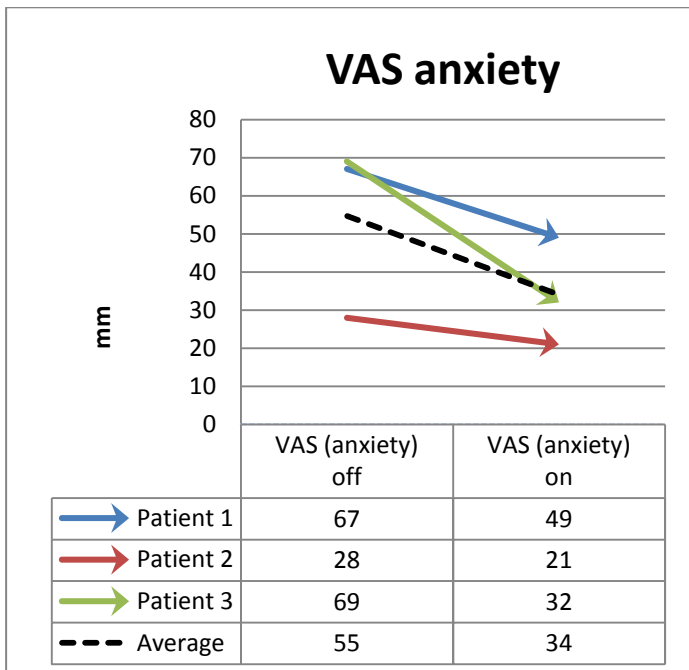
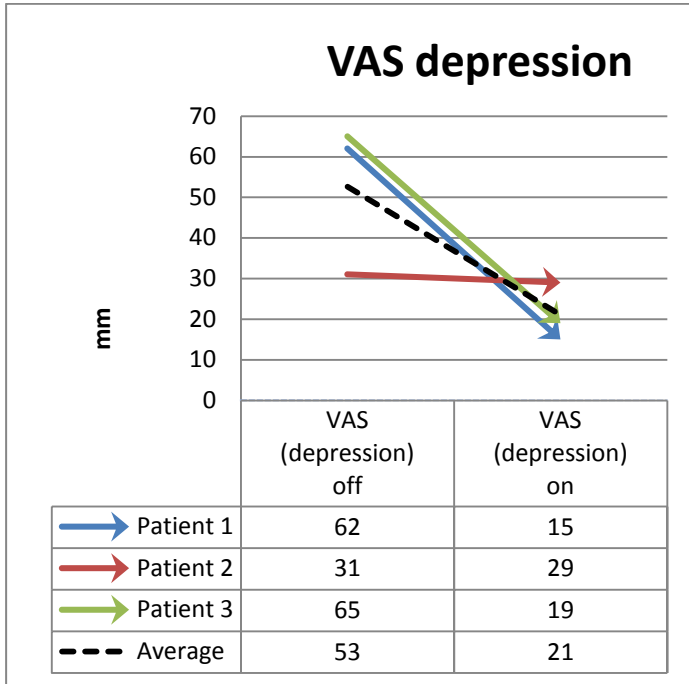
Patient	Born	Sex	Year of diagnosis	Year of duodenal pump	Questionnaire score
1	1943	F	2001	(march) 2012	13
2	1952	F	1997	2001	18
3	1937	F	2009	-	15

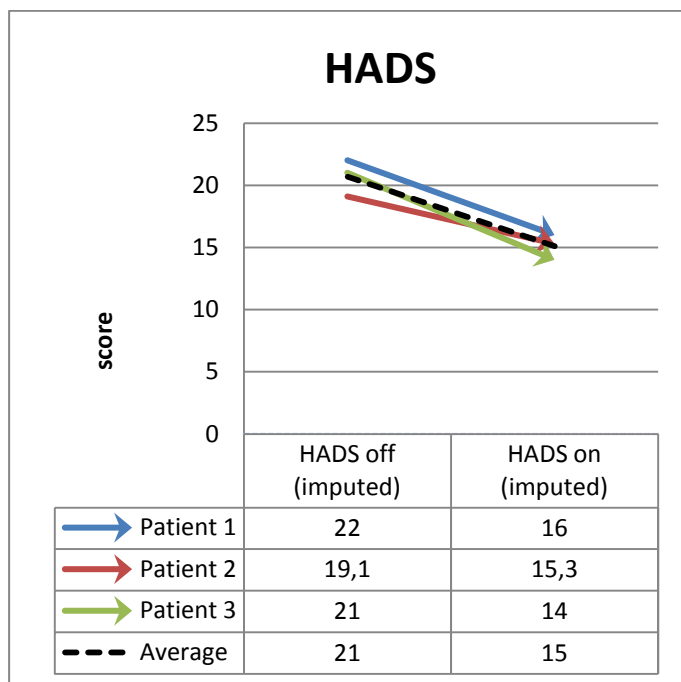
Patient	UPDRS off	UPDRS on	VAS (pain) off	VAS (pain) on
1	44	7	54	25
2	36	7	28	32
3	35	15	41	48

Patient	VAS (depression) off	VAS (depression) on	VAS (anxiety) off	VAS (anxiety) on
1	62	15	67	49
2	31	29	28	21
3	65	19	69	32

Patient	HADS off	HADS off (imputed)	HADS on	HADS on imputed
1	22	-	16	-
2	15	19.1	12	15.3
3	21	-	14	-







Discussion

The data from the study could not be used to find any statistical significant differences in the data from any of the VAS scores. A weakness in the study is the small number of patients included, making both significant and insignificant differences unreliable. There was a tendency towards reduction of pain, depression and anxiety on VAS and HADS in the “on” state when compared to “off” in the study, and this was also the general impression the patients were giving during examination. Even though not necessarily statistically significant, the tendency found in the study was consistent with other studies showing less NMS in “on” than “off”.

In the end, 3 patients participated in the study. Additional patients were initially intended, but some were excluded as they were having too great difficulties in participating and cooperating in the “off”-state.. In general, all patients were having severe motor symptoms before their levodopa dose. The included patients had advanced stage Parkinson disease, and were clinically ill and had a heavier load of symptoms than the average PD patient. The severity of their disease, symptoms and that it impacts their daily living was supported by the UPDRS motor examination and the questionnaire made for this study. They had a duodenal levodopa pump or indications for surgery, and were staying as inpatients at the hospital for optimization of their levodopa regime. They were experiencing some trouble talking and filling out the questionnaires in the morning, and appeared to be at a lower mood than later during the day. Even though patient 3 was diagnosed with PD in 2009, she had been experiencing symptoms for several years without receiving any diagnosis. She was initially suspected to have a parkinson plus condition, because of rapid progression and orthostatic symptoms. Considering her effect of levodopa and unilateral symptoms, this would seem less likely. She was not on treatment with duodenal levodopa-infusions and her levodopa dose was somewhat limited by orthostatic symptoms caused by the medication.

The aim of the study was to test the use of VAS and HADS on patients with advanced PD. The study did indicate that the use of VAS and HADS to detect short term fluctuations in PD patients could be for a larger scale study. VAS is commonly accepted as useful in detecting changes in pain, and there has also been validation studies for the use of VAS as a tool to detect both anxiety and depression(69) While the use of HADS has been validated as useful in a clinical setting of PD(70), there is a lack of evidence for the use of HADS to measure short term variations. Because of this, the findings related to HADS are interesting, but probably less reliable than the ones related to VAS. Patients in this study did appear to be able to independently fill out the questionnaire in both states, showing a slight decrease in score in “off”. Recall bias did not appear to be an issue.

An obvious weakness of the study was the small number of patients included. Because of this, no real conclusions can be drawn from the statistical data, as the population is too small to be representative. However, it is clear that some of these patients did in fact experience individual fluctuations of depression and anxiety, and to some degree also pain. In this case it cannot be generalized to another population. Another weakness is that all patients were female, as both depression and anxiety might be more common in females than in males (71).

While there has been increased focus on the NMS in PD and QOL, there are still aspects that need to be further explored. There have been some previous studies exploring the occurrence of short term fluctuations of mood and anxiety, including one study of 86 PD patients (72). In this study the collected data on an hourly basis for seven days , using VAS to rate mood, anxiety and motor state The results were that emotional and anxiety fluctuations were about as common as motor fluctuations. Even though the study used the VAS on mood to determine mood fluctuation in both directions, from “extremely sad” to “extremely happy”, it shows that VAS has been used to test the short term fluctuations in mood in patients with PD. Further studies needs to be done to validate the use of both HADS and VAS to assess the fluctuations of NMS.

Fluctuations of NMS in PD are known to occur and have a big impact on the patients QOL. It does seem apparent that improving and optimizing the patient’s levodopa medication regimen can both have an effect on reduction of motor complications, as well as improvement in fluctuations of NMS such as depression, anxiety and to some degree pain. Increased knowledge about the frequency and severity of fluctuations can help to increase the recognition and treatment of NMS. While some research has been done on the frequency of some of these fluctuations, especially on depression and anxiety, larger scale studies needs to be done on both the frequency and the severity of the fluctuations of these symptoms, in order to be better able to reduce the impact these symptoms have on the patients QOL.

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Appendix 1:

Spørreskjema:

Det er fem graderte svaralternativer per spørsmål (fra *ikke i det hele tatt* til *hele tiden*).

	Hvor ofte...	Aldri	Sjelden	Noen ganger	Ofte	Alltid
1	Har du vanskeligheter med å gå 100 m?					
2	Er du "off"?					
3	Er du overbevegelig?					
4	Har du vanskeligheter med å vaske deg, etc?					
5	Har du plagsomme kramper/spasmer?					
6	Kjenner du deg nedstemt?					
7	Tar du ekstradose?					
8	Er du fornøyd med din funksjon?					