

Impulse control disorders in Parkinson's disease

**Impulsivity and impulse control disorders in Parkinson's disease –
A pilot study of assessment instruments in a clinic population**

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Summary

This study consists of two parts: first, the thesis with a general theoretical overview of the topic. Second, the draft paper *Impulsivity and impulse control disorders in Parkinson's disease – A pilot study of assessment instruments in a clinic*.

The purpose of this work has been to contribute to the awareness of ICDs as a potential problem in Parkinson's disease (PD), and to investigate possible tools and their utility to assess this problem in a specialised neurologic policlinic in Norway. In the pilot study we translated the Questionnaire for Impulse-Compulsive Disorders in Parkinson's Disease (QUIP) and the Barrat Impulsiveness Scale (BIS-11) to Norwegian and administered them to a convenience sample of PD patients.

Statistical analyses was undertaken with SPSS version 15.0. The analyses showed comparable numbers of ICDs in our sample of patients compared with previous findings and we found a significant correlation between the presence of an ICD and the degree of impulsivity.

This study emphasizes the need for an increased awareness about ICDs and other compulsive disorders in Parkinson's disease as a possible side effect of their medication. The sensitive nature of these disorders requires a systematic and cautious approach, although an appreciation of their presence in a process of normalization seems equally important. Even though the pilot study was done on a small population after convenience sample our findings support previous studies that encourage clinicians to do routine testing for ICDs and other compulsive behaviours in PD patients.

Contents

Summary.....	II
Contents.....	III
Figures and tables.....	IV
Abbreviations.....	V
1.0 Introduction.....	1
1.1 Parkinson's disease.....	1
1.1.1 Anatomy and pathophysiology.....	1
1.1.2 Treatment of Parkinson's disease.....	3
1.1.3 The symptoms in Parkinson's disease.....	5
1.2 Impulse-control disorders in Parkinson's disease.....	7
1.2.1 Definitions.....	7
1.2.2 Prevalence of ICDs and other compulsive disorders in PD.....	7
1.2.3 Which patients are affected?.....	8
1.2.4 ICDs and the role of dopamine.....	9
1.2.5 Management of ICDs in PD.....	10
2.0 Methods.....	11
2.1 The questionnaires.....	11
2.2 Ethics.....	13
2.3 Choice of analysis.....	13
3.0 Results.....	13
4.0 Discussion.....	13
4.1 General discussion.....	13
4.2 Assessment of ICDs and other compulsive behaviours- utility of questionnaires.....	14
5.0 Conclusion.....	15
6.0 Litterature.....	17
Article: <i>Impulsivity and impulse control disorders in Parkinson's disease – A pilot study of assessment instruments in a clinic population.....</i>	<i>22</i>

List of figures and tables

In the article:

- Table 1:** Clinical features of the study population
- Table 2:** Reported compulsive behaviours
- Table 3:** Clinical correlates of ICDs
- Table 4:** Impulsivity and reported ICDs – screening with the formal cut-offs
- Table 5:** Impulsivity and a reported ICD – screening with the introductory question
- Figure 1:** Associations between impulsivity, using BIS-11 total score, and the presence of the report of no ICD vs 1 ICD and vs >1 ICD, using the introductory question for ICDs in the QUIP as screening tool

Abbreviations

PD	Parkinson's Disease
ICD	Impulsive Compulsive Disorder
DA	Dopamine Agonist
DRT	Dopamine Replacement Therapy
QUIP	Questionnaire for Impulse-Compulsive Disorders in Parkinson's Disease
BIS-11	Barrat Impulsiveness Scale
NMS	Non Motor Symptoms
DAWS	Dopamine Agonist Withdrawal Syndrome
QoL	Quality of Life

1.0 Introduction

First general literature on Parkinson's disease (PD) will be presented. This includes a brief introduction to the anatomy and pathophysiology, the treatments available and a summary of the main motor- and non-motor-symptoms of the disease. We will then look more deeply into impulse control disorders (ICDs) in the PD population.

1.1 Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease and is associated with a deficiency of dopamine in the basal ganglia. It is the most common cause of Parkinsonism with 80% of the cases. It was described by James Parkinson in his 1817 Essay on the Shaking Palsy with his descriptions of cases he had seen on the streets of London. Parkinsonism is characterised by three cardinal signs: rest tremor, rigidity and bradykinesia. Postural instability, seen later on in the progression of PD, is by some accepted as a fourth cardinal sign. The diagnosis of parkinsonism is clinical and given when two of the cardinal signs are fulfilled (1). The prevalence of PD varies depending on the study population and diagnostic criteria and it increases with age. It is thought to affect approximately 360 people per 100,000, with an incidence of 18 in 100,000 per year. It is uncommon before the age of 30 and the prevalence peaks after the age of 60 (2).

While the cause of PD is still unknown, the possible underlying mechanisms, causing especially the motor symptoms, are partly revealed. First one has to look into the anatomy and functions of the basal ganglia.

1.1.1 Anatomy and pathophysiology

Circuits of the basal ganglia

The basal ganglia are situated in the basal centre of the brain and include the substantia nigra, the striatum (nucleus caudatus and putamen), thalamus, globus pallidus and nucleus subthalamicus. There are dense internuclear connections within the basal ganglia and it is generally agreed that there are three major circuits; the sensorimotor, the associative, and the limbic (3 p. 2126-2127). All three circuits contain two main pathways where striatal activity is translated into output from the pallidum. This translation is done by a direct pathway and an indirect pathway which includes the nucleus subthalamicus. This is considered to be the site of origin for the motor problems we see in PD patients and can be used as a way of explaining the two different pathways: The motor cortex sends out signals to make us move, to control these movements, to not be abnormal and uncontrolled; the signals pass the basal ganglia. The striatum receives the movement command from the cortex and sends out a brake signal to the globus pallidus which again sends a new signal to the thalamus. This signal is modulated by the direct and the indirect pathway; the striatal signal either flows directly to the internal part of the globus pallidus (GPi), or first traverses the external globus pallidus (GPe) and nucleus subthalamicus before it reaches the GPi. The GPi receive inhibitory signals from the direct pathway and excitatory signals from the indirect pathway. The sum is transmitted as an inhibitory signal to the thalamus which again has efferent excitatory fibres back to the cortex. To put this schematically, this means that with the cortex signals alone we move uncontrolled;

with the signals from the cortex and the striatum alone we freeze and cannot move; but with the modulation within the pallidum we sort of have a brake for the brake, also called disinhibition, and can send finely adjusted signals back to the cortex, and ultimately to our executive peripheral nerve endings to make us move properly. The function of the associative circuit is assumed to be mainly cognition and the limbic circuit which involves the limbic structures is thought to involve processes of emotions and motivation (3 p. 2127).

The limbic system

The limbic system is considered to be the basis of motivational and emotional processes as opposed to the cognitive and conscious systems in the brain (4 p. 461). The limbic system consists of structures both in the neocortex and also the so-called basal forebrain, included the nucleus accumbens, the amygdala in the temporal lobe and the insula. The amygdala is shown to have an important role in the establishment of links between stimuli and their emotional value. The corticomedial nucleus of the amygdala receives afferent dopaminergic fibres from the ventral tegmental area (VTA) which is located dorsomedially to the substantia nigra. Furthermore the amygdala has efferent fibres to the ventral striatum which also receives dopaminergic fibres from the VTA (4 p. 462-464) Experiments with rodents suggest that relations between the basolateral amygdala and the ventral striatum are necessary for establishing stimulus-reward associations. This will be further explored later in relation to dopamine and learning (4 p. 467)

Pathophysiology

Parkinson's disease predominantly attacks the substantia nigra, more precisely the pars compacta (SNc), but also the ventral tegmental area (VTA). The SNc holds the brain's largest collection of dopamine-containing neurons (4 p. 331). These neurons degenerate in PD, observed microscopically as neuronal loss, gliosis, and extracellular pigment, which results in a deficiency of dopamine. Nigral cells diminish with age in every person. The difference is that the speed of nigral cell loss is so accelerated in the PD patient compared with an age-matched control. The cell number is reduced to as little as 30 per cent (5 p. 919). In the remaining neurons, one can find characteristic cytoplasmic inclusions, called Lewy bodies. The main component in Lewy bodies is the α -synuclein and it is neurotoxic for the cell (5 p. 920) There are familial forms of PD where the coding for synuclein is attacked, but for the most part PD is sporadic and so the aetiology is unknown. This said, the natural tendency of α -synuclein to aggregate is likely enhanced by genetic factors controlling the protein synthesis but also due to environmental factors such as aging, oxidative stress and toxic exposures as well as secondary processing and degradation (3 p. 2134). Braak et. al (6) proposed in 2003 a theory that PD evolves in 6 stages and that the characteristic motor symptoms develop as late as stage 3-4 with the pathophysiologic involvement of substantia nigra. This theory is based on Lewy body deposition and not neuronal degeneration and is not without controversy (7). According to Braak's staging concept the deposition of Lewy bodies begins in the olfactory bulb and the anterior olfactory nucleus in stages 1-2. PD patients have reported a loss of smell prior to the appearance of motor symptoms (8). Together with rapid eye movement behaviour disorder (RBD), constipation, and depression the olfactory troubles are signs that may precede the motor symptoms (reviewed in 7).

Dopamine and dopamine receptors

The role of dopamine on neuronal excitability in the basal ganglia is not fully understood, but the most studied basal ganglia connection is the dopaminergic nigrostriatal pathway which is also the highway for dopamine in the CNS. The striatal neurons express dopamine receptors and in response dopamine modulates the corticostriatal signals (4 p. 334-335).

Dopamine is a catecholamine synthesised from L-tyrosine in the nerve cell bodies of SNc. It functions as a neurotransmitter, or a modulator, as it binds to dopamine receptors on the G protein in neural cells. There are two families of dopamine receptors, the D1 and the D2. The main difference between them is related to G protein binding. The D1 family, consisting of the D1 and D5 receptors, connects to the stimulatory G protein and thus increases cAMP production. We find the D1 receptors primarily in the caudate, putamen, nucleus accumbens, and olfactory tubercle. The D5 is predominantly found in the hippocampus and hypothalamus. On the contrary, the D2 family, consisting of D2S, D2L, D3, and D4, is linked to the inhibitory G protein, thus decreasing the intra cellular concentration of cAMP. The D2 receptors are found primarily in the same locations as the D1, the D3 receptors are expressed in the striatum and in the limbic areas, and the D4 receptors we find in the frontal cortex, midbrain, amygdala, medulla, and to some extent in the basal ganglia (9 p. 892-894). To complicate the picture of D1/D2 as respectively stimulating/inhibiting the synthesising of cAMP there are also characteristics in the way dopaminergic neurons fire and the implication this has on the dopamine receptors. The effect of dopamine is thus dependent on the receiving receptor's properties, their location in the CNS, and probably on the way the dopamine is released from its cell of origin (4 p. 335). It is also of crucial interest to see what activates the nigrostriatal neurons to release dopamine; many of the nuclei having efferents to the substantia nigra actually change their activity in relation to arousal, motivation and emotionally driven behaviour (4 p. 336)

1.1.2 Treatment of Parkinson's disease

Dopamine Replacement Therapy (DRT)

Ever since the discovery of dopamine deficiency as the main cause of parkinsonism in PD, medication with dopamine replacement has been the number one treatment of the symptoms in PD with levodopa as the most effective agent. Nevertheless, there is still no treatment that can stop the degenerative process of PD, treatment is limited to managing the symptoms and primarily the motor-symptoms.

Levodopa

Dopamine itself does not cross the blood-brain barrier but its immediate metabolic precursor levodopa (L-3,4-dihydroxyphenyl-alanine) does (10 p. 443). Given alone, levodopa is almost entirely metabolized by dopa decarboxylase extra-cerebrally; distribution together with a dopa decarboxylase inhibitor is therefore necessary. Levodopa is transported over the blood-brain barrier by a membrane transporter for aromatic amino acids and is converted to dopamine, by decarboxylation, mainly in the presynaptic terminals of dopaminergic neurons in the striatum. Thus, effective levodopa treatment is dependent on residual dopaminergic neurons. After release, dopamine is either transported back into the dopaminergic terminal or metabolized by the enzyme monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT). Thus, a way to prolong the time of action of dopamine is to inhibit these enzymes. Levodopa medication is often distributed together with either a MAO-inhibitor or a COMT-inhibitor. There are combinations available, including levodopa, a dopa carboxylase inhibitor, and a COMT inhibitor (Stalevo) (10 p. 444). Although levodopa is by far the most efficient medication for the motor symptoms of PD and the responsiveness to levodopa is considered a diagnostic criterion by many neurologists (5 p. 922), the effect is not permanent. As the disease advances, the nigral neurons get fewer and fewer and as a result there are not enough places for levodopa to store and to get metabolized to dopamine. As a result the patient will

experience the so-called on-off phenomenon where the changes from hypokinesia to normal mobility and to dyskinetic movements are fast and unpredictable. The therapeutic window for levodopa treatment will get smaller and smaller and eventually one will have to look for supplements or alternatives. Continuous administration of liquid levodopa through a duodenal probe is an alternative at this stage (11).

Dopamine agonists

As medical research has made progress other types of dopamine replacement therapies have become available: the dopamine agonists are the main alternative as well as a supplement to levodopa medication. The dopamine agonists are associated with fewer dyskinetic motor complications (5 p. 922) and with the unfavourable development of levodopa treatment in mind, the DA have found a role both in initial treatment and as a modifier to the effects of levodopa later in the disease. The dopamine agonists act directly on the dopamine receptors in the striatum, thus they are not dependent on residual dopaminergic neurons in the substantia nigra. For oral administration, four agonists are available; *bromocriptine*, *pergolide*, and the more selective *ropinirole* and *pramipexole* (12 p. 535). Bromocriptine acts on the D2 class of dopamine receptors and partly on the D1 family (12 p. 535). Pergolide stimulates directly both D1 and D2 class receptors (10 p. 447). Ropinirole is a newer preparation and relatively selective as a D2 class agonist. Pramipexole is also selective to the D2 class, more specific to the D2 and the D3 receptors. Both ropinirole and pramipexole have little or no activity on D1 receptors (12 p. 535) Aside from their selectivity, the new preparations also are tolerated better by the patient and give fewer side effects such as nausea, hypotension, and fatigue than the older less selective ones. This said, a variety of side effects are reported for these new dopamine agonists, most pronounced are hallucinations, nausea and somnolence, as compared with levodopa (13). More recently the dopamine agonists have been coupled with impulse-control disorders and other compulsive behaviours in PD patients as they are seen more often in this population than in the general population (14). We will look more deeply into this subject later on in this thesis.

Anticholinergic agents

Before the discovery of levodopa, anticholinergic agents were widely used in the treatment of PD. The mechanism of the therapeutic actions is not fully understood, but it is likely that they act on the interneurons in the striatum. The effect of these agents is mostly seen in early PD or as a supplement to dopaminergic therapy. Their side effects are a result of their anticholinergic properties; sedation, mental confusion, constipation, urinary retention, and blurred vision (12 p. 537-538))

Deep brain stimulation

This therapy involves the implantation of electrical stimulators in the posterior and ventral part of the subthalamic nucleus (5 p. 924). The recruited patients are those with a need for frequent levodopa medication with unacceptable dyskinesias experiencing a constant on-off phenomenon. Improvement is seen in all motor features of the illness, but as with all surgery there are considerations due to complications. Breakage of the wire, haemorrhage into the basal ganglia, and local infections have occurred, but such complications are rare (5 p. 925).

Neuroprotective treatments for Parkinson's disease

A direct treatment for the neurodegeneration in PD is yet to be found. But several studies have suggested different preparations as neuroprotective in PD. Amongst the medications studied are ropinirole, pramipexole, levodopa, and the MAO inhibitors selegiline and rasagiline (5 p.

923). Results in recent studies are still debated and the uncertainty concerning the relationship between different outcomes should be appreciated (12 p. 538).

1.1.3 The symptoms in Parkinson's disease

In this section the major motor features of PD will be described before we move on to the non-motor symptoms in PD patients.

The motor features of PD

As the onset and progression of PD is lurking in its nature, the first symptoms of the disease might be overlooked. This may be the reason for *rest tremor* as the most well-known sign of PD onset, and relatives might notice it as a one-sided slow tremor, most often seen in the upper limb. The tremor is rhythmic with a frequency of 3 to 5 Hz and is due to alternating contraction between agonist and antagonist muscle groups. (3 p. 83) The tremor normally disappears at complete rest and with intended movements of the arm, but increases with emotional stress (5 p. 83). The cog-wheel effect, as a well-known clinical finding in PD patients, is most likely a palpable tremor combined with the next major motor symptom; rigidity. The *rigidity* in PD patients is defined as a velocity independent increase in passive tone as opposed to spasticity which is length-and-velocity-dependent (15 p. 74). The muscles of the patient are firm and tense and can be variable resistant to passive movements. Together with the third cardinal sign, *bradykinesia* is well established that their cause lies in the typical PD lesions of the nigrostriatal system (9 p. 63). Bradykinesia and akinesia might be the most disabling motor symptoms for the PD patient. Akinesia or hypokinesia refers to a loss or decrease of normal muscular tonicity and responsiveness. It has been expressed by different characteristic hallmarks of PD; reduced habitual movements, infrequently blinking, a masked face with loss of expression, drooling and the loss of arm swing while walking. The bradykinesia refers to a general slowness to the execution of every movement. Together with hypokinesia it is the manifestation of a PD patient in off mode, i.e. without effective medication. They are literally unable to initiate or execute any voluntarily movement, at the most severe.

The non-motor features of PD

James Parkinson gave the following description of what he had observed in the streets of London early in the nineteenth century: "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured."(16). Although Parkinson was quite precise when it comes to the motor features of the disorder the non-motor symptoms were not at all appreciated at this point in medical history. It is now well established that non-motor symptoms (NMS) are common at all stages of PD and that they have a great impact on the patients' quality of life. The NMS of PD come in all sorts of variation and the list is extensive. Some of them are known to be dopamine-dependent, many are non-dopaminergic and some of them are due to dopamine replacement therapy (DRT) (17 p. 4). They can be divided in order of their manifestation: neuropsychiatric symptoms, sleep disorder and symptoms, fatigue, sensory symptoms, autonomic dysfunction, gastrointestinal symptoms, drug-induced NMS, and non-motor fluctuations (7). We will elaborate further only a selection of the most common NMS seen in PD.

Dysautonomia

As reviewed by Chaudhuri et. al (18) dysautonomia occurs with varying severity in PD but up to 50 % of PD patients report that autonomic problems have severe impact on their daily lives. It includes orthostatic hypotension, constipation, bladder dysfunction, erectile dysfunction, dribbling of saliva, and dry eyes.

Constipation

GI-symptoms in PD are part of the autonomic symptoms and include amongst others dribbling of saliva, dysphagia, and constipation. Constipation may precede motor-symptoms of PD and Abbot et. al found that among 7000 men, those who reported constipation during a period of 24 years had a threefold risk of developing PD after a mean interval of 10 years from initial constipation (19).

Sexual dysfunction

Sexual dysfunction as part of autonomic problems in PD refers mainly to erectile dysfunction which is reported in up to two-thirds of the male PD population (7). Hypersexuality and increased sexual fantasy is also found in PD patients but is thought to be linked to dopamine replacement therapy and will be reviewed later in this text.

Neuropsychiatric symptoms

Depression

As one of the most common psychiatric problems in PD depression has a major impact on many PD patients' lives. As reviewed by Chaudhury (18), the prevalence of depression in PD varies from 10-45 % depending on the criteria used. The aetiology of depression in PD is unclear, but the explanation of depression solely as a response to disability is rejected (17 p. 186). Therapy is not sufficiently studied, but large clinical trials are upcoming and should improve the way depression is handled in PD (17 p. 190).

Cognition and cognitive dysfunction

According to a review by Emre M. (20) the prevalence of dementia in PD affects about 40 % of patients. The clinical features involve impaired attention and memory; impaired visiospatial functions; and as the most prominent feature, impaired executive functions such as problem solving, concept formation, and planning. Language is for the most part preserved, but personality changes are part of the syndrome. The underlying mechanism of dementia in PD has been a subject of controversy, but more recent studies point to Lewy-body-type degeneration as the main pathology (20).

Sensory symptoms

Pain

Pain was appreciated as early as 1877 as a wearying part of PD. Charcot put it this way "...it is also a cruel disease since it causes distressing sensations" (17 p. 315). About two-thirds of PD patients are affected by sensory or painful syndromes and the mechanisms are multifactorial. Explanations stretch from central dopaminergic deficiency to non-dopaminergic mechanisms, and from pain directly linked to motor features such as rigidity. Pain can also be linked to anti-parkinsonian medication (17 p. 319-321). As causes are complex so are the strategies of management, but of crucial importance is the recognition of the patient's suffering, education, and support (17 p. 323).

1.2 Impulse-control disorders in Parkinson's disease

Over the last decade it has been observed that Impulse Control Disorders (ICDs) occur more frequently in patients with Parkinson's disease (PD) than in the general population (21, 22). The disorders involve hypersexuality, binge-eating, compulsive buying, and pathological gambling and have been coupled with a quite strong relation to dopamine replacement therapy, and to dopamine agonists (DA) in particular (14). Other compulsive behaviours investigated and found in PD patients are punding, hobbyism, walkabouts, and compulsive medication use (reviewed in 23).

1.2.1 Definitions

Of the impulsive-compulsive behaviours, pathological gambling is the only disorder included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) as an ICD Not Elsewhere Classified (24). A lot of different terms have been used to define these disorders in PD patients, as "dopamine dysregulation syndrome", "hedonistic homeostatic dysregulation", dopamimetic drug addiction, "compulsive behaviours" and "repetitive behaviours" (reviewed in 25). However, the term ICD has been applied to cover the four major ICDs that are reported to occur in PD patients (23) as they all are characterized by the same failure of impulse control which is not better described by any other psychiatric condition (25). The other related disorders seen in PD patients do not have a formal definition in the DMS-IV, but are characterized by different forms of compulsivity and repetition and they have also been seen in relation to Dopamine Replacement Therapy (DRT) (23).

An Impulse-Control Disorder (ICD) is defined as "the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others" (24 p. 663). Pathological gambling is the most common ICD (26). Having an ICD can have potentially devastating consequences for both patient and the patient's family, in terms of economy and psychosocial status (27). The compulsive behaviours found in PD patients include *punding* which can be described as repetition of specific, purposeless behaviours (23), often related to a person's interests or occupation earlier in life (21), for example examining, sorting, ordering, or arranging objects. *Hobbyism* has similarities with punding but involves higher-level repetitive activities, like writing, painting, gardening, or working on projects. *Walkabout* refers to walking or driving with no specific purpose (23). *Compulsive medication* is characterized as an addiction-like self-medication of dopamimetics (22).

1.2.2 Prevalence of ICDs and other compulsive disorders in PD

A recent review (22) based on 98 reviewed reports found a mean overall prevalence of ICDs in PD patients of 10%, during the period 2000 and January 2013. All patients were on DRT. 2.5% reported more than one ICD. The DOMINION study (14), the largest epidemiological evaluation of ICDs in PD, found in their cross-sectional study of 3090 patients with PD, an overall prevalence of ICD of 13.6%. The prevalence reported for each ICD were as follows: gambling 5 %, compulsive sexual behaviour 3.5%, compulsive buying 5.7%, and binge eating disorder 4.3%. 3.9% of participants had 2 or more ICDs. In an Italian study (28) patients

treated for PD were 25 times more likely to have pathological gambling than the general hospital controls. In the review by Callesen et al (22) the overall prevalence found for each ICD was: pathological gambling and hypersexuality 3.5% each, compulsive buying 2.5%, and binge eating 2.6 %. The other impulsive-compulsive behaviours in PD have not been as well studied and numbers differ substantially. In one study (29) compulsive medication was identified in 3.4 % to 4 % in PD patients, whereas the review by Callesen et. al (22) found a prevalence of this disorder of only 0.4 % of all patients included in the studies reviewed. Prevalence of punding has been identified at varying degrees, some finding 14 % (30), in other cases only 1.4% (31). Other compulsive behaviours together, such as punding and hobbyism were identified in 3.7 % (22). The overall prevalence of these various disorders range from 6 % to 15.5 % in PD patients compared to a prevalence of ICDs of 1.1 % to 1.6 % in the general population (reviewed in 22). The rest of this text will primarily refer to ICDs since their presence in PD are more well documented than the other compulsive behaviours.

1.2.3 Which patients are affected?

Even though ICDs are seen with higher prevalence amongst PD patients than in the general population, the relation to PD is still somewhat unclear. Is it PD itself as a facilitator? Is it dopaminergic preparations? Or are there yet unknown factors which predispose for ICDs in this population? DA is not solely used in PD. In conditions like restless-legs syndrome, prolactinoma and fibromyalgia the patients also benefit from these types of preparations. Findings show that ICDs have been identified also in DA treatment of these diseases (32-34), sometimes with even higher prevalence than in PD populations. The PD population on dopaminergic medication other than dopamine agents still has a higher prevalence than the general population (35). The question is still why is it only a small group of PD subjects medicated with dopaminergics that is stricken by these disorders? It has been suggested that there is a susceptibility present in the segment of PD patients developing an ICD. Antonini et. al (36) found similar prevalence for impulsivity and ICDs in newly diagnosed drug-naïve PD patients compared with healthy controls. Another study (37) found an increased rate of novelty-seeking in newly diagnosed PD patients after 12 weeks of dopaminergic treatment as compared to their drug-naïve scores. Both these studies suggest that PD patients do not have higher impulsivity than the general population before starting treatment with dopamine replacement therapies. Other personal traits studied are cognitive functions, more specifically; PD patients' difficulties with executive functions and the risk for developing an ICD (reviewed in 38). Further longitudinal follow-up studies are required to investigate if it is the same at-risk population that develops ICDs after starting medication for PD, and who represents the remaining percentage which gives a higher prevalence of ICDs in medicated PD patients than in the general population.

In addition to impulsivity, factors have been sought that can predict the onset of ICDs in PD patients. Weintraub et. al (14) showed in their cross-sectional study an association between younger ages (<65 years), being a smoker, a family history of gambling problems, being unmarried, and living in the United States as compared to Canada, and the presence of an ICD in PD patients. When it comes to gender, both male and female score equally regarding ICD prevalence, but there is unequal distribution between different types of ICDs. Males reported more tendencies to hypersexuality, whereas females comprise a larger share of compulsive buying and binge eating (14). Even though referred to as predisposing factors (39) this can, as Weintraub et al also point out, only be seen as associated factors as the study was not designed to define etiological risk factors of ICD in PD. A recent review by Vriend et. al (40)

link depression in PD to the presence of an ICD as they frequently coincide. They find increasing evidence that depression and ICDs develop in the same susceptible PD patients possibly as a result of dysfunction of the ventral striatum and other brain areas involved in motivation and reward. Thus a depressed PD patient might be more vulnerable to acquire an ICD and vice versa. This last point leads us to the role of serotonin in PD (reviewed in 22), although it is beyond the scope of this thesis.

1.2.4 ICDs and the role of dopamine

As already highlighted, DRT in PD has been coupled with the presence of an ICD, most notably the relation with DA, but there is also connection to levodopa dosage, especially in combination with a DA (14). We will now look deeper into theories concerning dopamine's role in ICDs within the PD population. Already elaborated earlier in this text is the possible role of meso-corticolimbic pathways of dopamine relative to reward and reinforcement behaviour. We also know that PD patients suffer from a pronounced dopamine deficiency due to loss of dopaminergic neurons in the SNc and the VTA. This loss has been linked to degeneration in the frontal-striatal tracts (41, 42), and a possible result is impairment in executive abilities among PD patients.

Dopamine and learning

ICD's have been compared with substance addiction and investigators have proposed they should be included in the same group of reward-based disorders (17 p. 215). In the habit theory, substance addiction is seen as a process that initially starts with the behaviour as a goal directed response, and that reward-based learning drives the sequence into habitual and compulsive behaviours, eventually without voluntary control (43, 44). The limbic system is considered to be the basis of motivational and emotional processes in the brain as opposed to cognitive and conscious systems (4 p. 461). And the amygdala, in the limbic system, is considered necessary for learning of the association between stimuli and reward or punishment as positive and negative outcomes, respectively (4 p. 467). Experiments with rodents suggest that relations between the basolateral amygdala and the ventral striatum are necessary for establishing stimulus-reward associations (4 p. 467). It has also been proposed that learning is driven by expectations of future reward and punishment and that the dopaminergic neuron's fluctuating output signals changes or produce errors in the predictions of such future events (45). In a study from 2004 (46) Frank et. al found evidence that the ability to learn from negative outcomes is decreased when on dopamimetic medications, and that the ability is actually reversed compared to patients not on medication. In another study (37), it was found that in newly diagnosed PD patients without ICDs, the non-medicated patients were impaired at learning from positive outcomes, and the newly medicated patients, taking dopamine agonists, were impaired at learning from negative outcomes. In two other studies (47, 48) it was found that dopamine agonists enhanced learning from gain outcomes in PD patients with ICDs, although the findings to negative outcomes were contradictory. Deep brain stimulation (DBS), as a treatment for Parkinson's disease, has also shown a relation to increased impulsivity, even though they take much lower doses of medication (49). As reviewed by Callesen et. al (22) this last subject is still object of disagreement and controversies.

Distribution of dopamine receptors in the brain in relation to DRT

As already elaborated, there are several different dopamine receptors identified in the human brain, and in the dorsal striatum the expression of receptors consists predominantly of D1 and

D2 receptors (23), whereas the ventral striatum has a higher expression of the D3 receptor, found widely also in the rest of the limbic system (50). This should dictate that if we stimulate primarily D3 receptors we also affect the limbic system and therefore influence reward and learning outcomes. The same follows for D1/D2 stimulation, which should alleviate mainly motor symptoms in PD without too much impact on emotions and motivation. Interestingly, several studies have also indicated that the D2/D3 dopamine agonists, most widely used, pramipexole, ropinirole and pergolide (22), are particularly related to ICD symptoms (25, 51-53). Voon et. al (54) also reported a prevalence of PG in PD patients of 0.7 % when treated with levodopa alone and 13.7 % when on mono therapy with dopamine agonists. This is supported by Weintraub et. al (14) who found a prevalence of up to 17.1 % among PD patients treated with dopamine agonists relative to 6.9 % in patients not treated with dopamine agonists. The combination of levodopa and dopamine agonist use is indicated as a reinforcing factor as it has been associated with an increased likelihood of 50 % of an ICD when medicated together (14). The total levodopa equivalent daily dose (LEDD, levodopa and dopamine agonists) is also seen to be higher in the PD population with an ICD (22). This coupling to levodopa dosage is supported by a study (55) on hemi-parkinsonian rats showing D3 receptor induction as a response to levodopa administration, thought to be mediated by repeated D1 receptor stimulation.

Dopamine and the overdose theory

In PD the dorsal striatum is the most affected by dopamine deficiency. Compared to the dorsal activity, ventral striatal dopamine levels are relatively preserved (56). From this observation follows the hypothesis, called “the overdose theory,” that with medication dispensed to improve motor symptoms due to dorsal striatal deficiency this might cause an “over-dosing” in ventral cortico-striatal cognitive and limbic pathways (57). According to this theory, efficient function is dependent on a eu-dopaminergic level where both lower and higher levels will impair functional outcomes (56). PD patients with ICDs are seen to have problems with cognitive tasks that rely on ventral striatal activation (23), an observation that seems to strengthen this theory. If we take into account the distribution of dopamine receptors already elaborated and the theories concerning ICDs and reward-based learning, the overdose theory is in accordance with the relatively higher prevalence seen in PD patients on DRT compared with the general population.

All this said it is important to emphasize both that the dopamine systems in the brain are extremely complex and are not fully understood. The habit theory is criticised due to the clear difference between automatic, habitual actions in animal models and the strongly motivated and compulsive ICDs in humans (17 p. 220). Therefore one should be cautious of coming to too simplistic conclusions.

1.2.5 Management of ICDs in PD

Having an ICD can have great impact on a patient’s life, with potentially devastating psychosocial consequences (27). The first step in the management of an ICD is to assess and diagnose it. For this purpose different tools have been tested. In the cross-sectional study of 3090 PD patients, The Massachusetts Gambling Screen score was used for current problem/pathological gambling, the Minnesota Impulsive Disorders Interview score for compulsive sexual behaviour and buying, and the DSM-IV research criteria for binge-eating disorders (14). The Dopamine Dysregulation Syndrome-Patient and Caregiver Inventory was

developed as a screening tool to assess a wide range of impulsive-compulsive behaviours in PD (58) and in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (UPDRS) there is one single item to cover excessive gambling, sexual behaviour, hobbyism and punting. In addition there is one question concerning hobbyism (59). Research indicates that one single question is not valid as a screening tool for ICDs in PD (60).

The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) is a self-administered screening questionnaire, developed and validated (15) by researchers at the University of Pennsylvania, and exists both in a non-rating scale version and a rating scale version. Both have been validated (61, 62).

When one has identified an ICD it is the reduction of DA that is the primary strategy (reviewed in 22). Case reports indicate the ending of ICDs after reduced doses of existing DA treatment, especially with complete discontinuation of this specific medication (63). This said, one must be aware of the possibility of complications in relation to DA withdrawal. Clinical symptoms are anxiety, panic attacks, fatigue, sleep disturbance, and medication cravings (64). This is called the DA withdrawal syndrome (DAWS) and is a severe condition specific for DA and cannot be improved by levodopa or other PD medication. Even though several treatments have been tried out in search for a better management of ICDs in PD, no clinical trials support the use of psychiatric preparations (64).

2.0 Methods

Methods are described in our article (65). This chapter will only give a more detailed description of some aspects.

2.1 The questionnaires

The QUIP and its validation by Weintraub et al. (61)

The QUIP (Questionnaire for Impulse-Compulsive Disorders in Parkinson's Disease) is a questionnaire developed by researchers at the University of Pennsylvania. They designed the questionnaire by reviewing existing screening and diagnostic instruments for ICD's and other compulsive behaviours, obtained expert advices on ICD's in PD, and from an expert in questionnaire development they structured the ICD section to be consistent with the diagnostic criteria described in the Diagnostic and Statistical Manual of mental Disorders (DSM-IV-TR). The structure of the QUIP is described in our article. After modifications based on feedback from 10 researchers and 5 PD patients, they validated the final version by testing it on 157 PD patients from 4 movement disorders centres. After filling out the QUIP the patients were evaluated through a "gold standard" interview for different types of impulsive and compulsive behaviours. The interviewers were blinded for the patients' QUIP-results. Cut-off points were set to 1-2 \geq affirmative responses depending on the category. They found that the QUIP had a minimum of 80 % sensitivity and specificity for each of the 4 ICD's, and since a patient often has more than one ICD the sensitivity for discovering a person with any ICD increased to 97 % when combining the four ICD's questioned. For the hobbyism section both sensitivity and specificity were > 90 %. The median time for filling out the QUIP was 5 minutes. D. Weintraub et al. emphasise in their article that the QUIP was designed as a screening tool and not as diagnostic rating instrument. The negative predictive value for each ICD was high (98-100 %) so a negative screen seems to imply the absence of any ICD with a great degree of certainty. As the authour's point out, a low positive predictive value can be compensated for by a follow up interview. They also validated a short version of

the QUIP with even higher sensitivity and specificity. The QUIP is rated at a 12th grade reading level.

The translation of the QUIP to Norwegian

The QUIP was translated to Norwegian for the purpose of this pilot study. For improvement, the Norwegian translation has been re-translated to English by five different persons, everyone with Norwegian as their mother tongue, but with English as an equivalent to this. Four of the English versions have then been compared separately with the English original by four native English speakers. The result of this back-and-forth translation has been mainly small comments, some relating to semantics and some with more relevance according to structure and aesthetics. Due to this, small modifications of structure have been made in this study. A semantic evaluation is in progress, but this will be completed after the distribution and collection of questionnaires in the pilot study. To fully validate the QUIP both a more thorough elaboration of the text as well as a test-retest study and a follow-up interview will be needed.

BIS-11

The Barratt Impulsiveness Scale (BIS-11) is a 30-item self-report questionnaire assessing the personality/behaviour construct of impulsiveness (66), originally developed by Barratt (67) to analyse the relationship between anxiety and impulsiveness. It was constructed to measure impulsivity as a unidimensional personality trait, but is later changed and developed to include several dimensions (68). The current Barratt scale, BIS-11, proposes that impulsivity is a construct of three broad dimensions: motor, non-planning, and attentional impulsiveness. The BIS-11 is structured to assess long-term patterns of behaviour and has been used to assess trait levels of impulsivity across a variety of populations, including substance-dependent individuals as well as normal populations (66). The BIS-11 asks about the frequency of impulsivity-related behaviours and each item is scored on a 4-point scale. Even though an understanding of the relative contribution of each of the subscales is necessary to understand a person's level of impulsiveness, the majority of studies using the BIS-11 have reported only the total score (66). The higher the summed score for all items, the higher the level of impulsiveness (68). There are no filler items. The BIS is in its 11th revision (68) and is now the most commonly administered self-reported measure specifically designed to assess impulsiveness (66). Stanford et. al (66) suggest that the BIS-11 should be viewed as a standard point of reference in research on impulsiveness. The BIS-11 has been translated to Norwegian and a process of validation is presently in progress (unpublished).

Clinical assessment

Each patient was assessed clinically by a neurologist specialised in movement disorders. The diagnoses were based on the individual case history; on paraclinical and imaging examinations for most patients including DAT scans and brain MRI. In addition, response to dopaminergic medications and disease progression over time was assessed. All patients had parkinsonism. For the present study, patients were also diagnosed as “possible Parkinson plus” as well as more certain multisystem atrophy (MSA) or progressive supranuclear palsy (PSP). In addition, presence of fluctuations, hallucinations, and cognitive reduction/dementia were noted. Clinical staging was done according to Hoehn and Yahr (69).

2.2 Ethics

The study received an exemption from ethics approval by the Regional Committee for Medical and Health Research Ethics, due to its design as quality assurance of an already established treatment. All patients were nevertheless asked to sign a form of consent. Participation was voluntary; all questionnaires were anonymous, and based on individual informed consent.

2.3 Choice of analysis

All analyses were performed with SPSS version 15.0. As this pilot study did not have enough power required for more analytical statistical analysis mainly descriptive statistics were used. When appropriate, Student's t test and chi-2 test were used for numerical and categorical data respectively.

3.0 Results

See article

4.0 Discussion

4.1 General discussion

Parkinson's Disease is the most common form of parkinsonism and the second most common neurodegenerative disorder (1). It has primarily been recognised for its implications on motor functions and the cardinal signs are used as diagnostic criteria in the clinic (1). Symptomatic management of motor symptoms are somewhat adequate after the introduction of levodopa, later on dopamine agonists and now also liquid administration of levodopa and deep brain stimulation. The NMS however are still not subject to either adequate acceptance or management (70). In one study (71) NMS rested undisclosed in 50% of cases due to embarrassment, unawareness of the relation to PD and consultation time mostly occupied by discussion on motor symptoms. Whilst this is true, they have been identified as the main predictors of poor quality of life (QoL) in PD patients (72). In the PRIAMO study (72), a large multicenter study assessing NMS and their impact on PD patients QoL, they found that 98.6% of patients with PD had one or more NMSs. The most common were fatigue (58%), anxiety (56%), leg pain (38%), insomnia (37%), urgency and nocturia (35%), drooling of saliva, and difficulties in maintaining concentration (31%). The mean number of NMS per patient was 7.8 (range, 0–32). The neuropsychiatric problems were found to have the most negative impact on Quality of Life (QoL). Impulsive-compulsive behaviours were not examined in the PRIAMO study but are in the literature categorised as part of the neuropsychiatric symptoms (70). The fact that they were not part of this extensive study emphasises the need for increased awareness. The impulsive compulsive behaviours range, as we have seen, from hypersexuality and compulsive buying, to repetitive behaviour, and compulsive use of medication. These behaviours are problematic for patients but also for caregivers and are often not expressed since they might be socially unacceptable,

embarrassing and a source of financial distress. In one study a mean loss of more than \$ 100 000 was reported as a result of pathological gambling behaviours in PD patients (27). In recent years, several findings show that Impulse Control Disorders (ICDs) occur more frequently in patients with Parkinson's disease (PD) than in the general population (14, 73-77) and that there is a correlation to PD therapy. Other associations seen are younger age, a history of gambling (14), depression (40, 73, 76, 78), anxiety, novelty-seeking and impulsivity (78). This last finding is supported by literature that couples impulsivity to biased learning of positive/negative outcomes and that dopaminergic neuron's fluctuating output signals changes or cause error in the predictions of such future events (45). The "overdose theory" refers to the relatively preserved levels of dopamine in the ventral compared to the dorsal striatum, and that PD therapy dispensed to improve dorsal activity due to this dorsal striatal deficiency (56, 57) might overload the ventral striatum which is related to learning from different outcomes (4 p. 467). This last observation which is based on that efficient function is dependent on a eu-dopaminergic level, where both lower and higher levels will impair functional outcome, (56) is strengthened by the findings that depression seems to be developing in the same vulnerable group of patients as do ICDs. Vriend et. al (40) propose a model for the role of dopamine in these disorders where the limbic cortico-striatal-thalamocortical circuit can be symbolized by a coin where one side has low activity resulting in PD-related depression and on the other side high activity might induce ICDs.

There are several instruments available to assess NMSs in PD, some of them more specific towards PD than others (70 p. 29). When it comes to ICDs and other compulsive behaviours in PD, several general rating scales, questionnaires and diagnostic criteria have been used (14, 24, 58-60), but a specific tool was up to recently not available. The correlation between ICDs and impulsivity also suggested this parameter as a possible screening tool for these disorders. Maybe one should also consider screening for depression in PD patients in the search for persons vulnerable for the development of an ICD when using DRT.

4.2 Assessment of ICDs and other compulsive behaviours - utility of questionnaires

As mentioned there is to our knowledge no validated tool in use in Norwegian clinics to assess ICDs and other compulsive behaviours in PD patients. Whilst we know that these problems are associated with embarrassment for many and devastating socioeconomically consequences for some (71), this should be considered a part of routine clinical care for PD patients. The aim of this study was primarily to raise awareness about ICDs as a possible problem in PD. As part of this we wanted to look into how these problems can be assessed in the clinic. With the correlation between ICDs and impulsiveness in mind, in this pilot study we have used the QUIP, specific for ICDs and other compulsive behaviours in PD as well as a general impulsiveness scale, the BIS-11, where patients are asked for more general traits of impulsivity.

There are some issues to note in relation to the questionnaires. First, the patient needs to be able to read and write, at least to make a cross in the right place. For many PD patients this is not possible, either due to motor fluctuations, impaired vision, reduced motoric precision, cognitive reduction, or other symptoms of late stage PD. This may impair the screening of these problems in the most severe PD patients. This problem is partially resolved as the QUIP is designed with the possibility to be filled out together with the patient's close relative or by an informant alone. Studies (75, 77) however show moderate agreement between patient and

informant, although with better sensitivity for ICDs than for the other behaviours. This may be due to minimization of symptoms, hiding of undesirable behaviours, and a lack of awareness. This said, a sensitivity of almost 100 %, regardless if completed by patient or informant was found when a reported ICD was controlled with a follow-up interview (77). Negative predictive values are thus high, a negative screen seems to be reliable, but a positive screen needs a follow-up interview to examine symptoms in more detail.

Second, and in continuation of this, some of the questions, especially in the ICD section are sensitive, asking about compulsive sexual behaviour and pathological gambling. One example is: “1. Do you or others think you have an issue with too much sex behaviours (such as making sexual demands on others, promiscuity, prostitution, change in sexual orientation, masturbation, internet or telephone sexual activities, or pornography)?” Both patient and informant may feel embarrassed and this might bias the responses. We experienced both that a patient’s closest relative were not aware of the presence of these kind of problems and that patients were embarrassed by the questions towards the research assistant, emphasising his or her negative screened questionnaire.

In our pilot study (65) we found a significant correlation between a positive screen for one or more ICDs and the impulsivity score on the BIS-11. This suggests that a general impulsivity score may be used in screening for vulnerable PD patients when it comes to ICDs. The questions in the BIS-11 are much more concealed and were not experienced as embarrassing by our respondents. Two examples of statements are: “I do things without thinking” and “I make-up my mind quickly”. This said, the scoring system of the BIS-11 is more complicated than for the QUIP.

Third and finally, are some issues with practical implementation. The QUIP is estimated to have a completion time of 5 minutes (61). With the possible need of a separate room, time for explanation and especially with probable practical problems due to PD in mind, demands on time in the clinic may be problematic.

There is already a screening tool for NMS in PD used in Akershus University Hospital, a Norwegian version of the Non Motor Symptoms Questionnaire (NMSQuest) (79). The questionnaire is sent to patients with complicated PD before their scheduled control and they bring the questionnaire already filled out to the hospital. Patients are asked about a wide range of NMSs including dribbling, constipation, pain, hallucinations, and depression. There is only one question in relation to ICDs, about increased sexual drive. Additional questions to an NMS screening should be considered as well as distributing the QUIP to patients in advance. This would solve the problem related to time consumption. Distributing the questions in advance could lower the threshold to talk about these subjects, raise awareness among both health workers and patients, but also educate patients in the possible presence of such symptoms in PD, and so potentially relieve guilt and shame.

This said, the Norwegian QUIP and BIS-11 still need validation and one needs to consider if the QUIP is the best instrument, if the BIS-11 may be an alternative, or if adjustments or development of a different type of screening tool is necessary.

5.0 Conclusion

In this thesis we have first elaborated some theoretical aspects of Parkinson’s disease and then studied the NMS of PD, showing that they are frequent and underreported. The NMS are not

subject to neither adequate acceptance nor management and this is despite the fact that they are identified as main predictors of a poor quality of life. We then studied in further detail the ICDs and other compulsive behaviours in PD. Several studies show that a substantial portion of Parkinson patients have an ICD and there is a strong association between with the use of dopamimetics and the presence of an ICD.

Having an ICD can cause great distress for both patient and care giver and may have devastating social and economic consequences. The different ICDs can involve embarrassment and are often not socially accepted and might therefore be minimized by both patient and the patient's relatives. Asking about ICDs is sensitive and the delicate nature of these disorders might impede aspects of the clinical practice. A screening tool for ICDs would possibly alleviate this sensitivity and be an important improvement in the assessment.

In our pilot study we tested the utility of the QUIP and the BIS-11. Both instruments rely upon the patient's ability to read and write, and the practical implementation needs some consideration. The QUIP was useful but has some weaknesses in its direct nature which might possibly be perceived as offensive by some patients. ICDs in PD are shown in previous studies to be associated with higher levels of impulsivity and in our pilot study we found a significant correlation between the impulsivity score and the report of ICDs. This suggests impulsivity screening with BIS-11 as a possible way to identify the vulnerable patients at risk of acquiring an ICD.

In conclusion we urge that awareness should be raised towards impulsive-compulsive disorders in PD as a possible side-effect of DRT. Even though our pilot study was conducted on a small population after convenience sample, our findings support previous studies that encourage clinicians to do routine testing for ICDs and other compulsive behaviours in PD patients.

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Impulsivity and impulse control disorders in Parkinson's disease – A pilot study of assessment instruments in a clinic population

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Abstract:

Objectives: to contribute to the awareness of impulse control disorders (ICDs) as a potential problem in Parkinson's Disease (PD) and to investigate possible tools and their utility in assessing this problem within a specialised neurologic policlinic in Norway.

Material and methods: The Questionnaire for Impulse-Compulsive Disorders in Parkinson's Disease (QUIP) and the Barrat Impulsiveness Scale (BIS-11) was distributed to a convenience sample of patients in the context of routine clinical care for their Parkinson's disease or as part of the diagnostics of a parkinsonistic disorder.

Results: Utility: Practical considerations regarding the completion of the QUIP and the BIS-11: First, patients need to be able to read and write. Second, the presence of a close relative or an assistant might be associated with embarrassment and thus underreporting of socially unacceptable behaviours. Third, the time requirement might be a problem.

Numbers: Sixteen (39.0%) patients reported an ICD. Two (4.9%) patients reported more than one ICD. There was a significant correlation between reported ICD and the patient's score on the BIS-11 (linear regression; adjusted r^2 0,40 and $p < 0,0001$).

Conclusions: A substantial portion of Parkinson patients may have an ICD. The assessment of ICDs poses some problems both in clinical practice and in research. The QUIP is a useful tool in the assessment of such disorders, but a general impulsiveness scale as BIS-11 may also function as a screening tool, although both instruments need thorough validation of their Norwegian translations before a potential national implementation is recommended.

Keywords: Impulse-control disorders, impulsivity, Parkinson's disease

Introduction

Parkinson's Disease (PD) is a progressive neurodegenerative disorder and is associated with a deficiency of dopamine in the basal ganglia due to loss of dopaminergic neurons in the substantia nigra zona compacta and the ventral tegmental area in the midbrain (1 s.331). PD is responsible for about 80% of cases of parkinsonism, characterised by the cardinal signs rest tremor, rigidity and bradykinesia. When James Parkinson defined what he called the Shaking Palsy by observing patient cases on the streets of London in early 19th century he described "the senses and intellects" as being uninjured (2). It is now well established that this is not the case in Parkinson's disease (PD) and that non-motor symptoms (NMS) might actually be present prior to the first motor symptoms (3). The non-motor features range from neuropsychiatric symptoms like depression, dementia, apathy and anxiety to sleep disorders and autonomic symptoms like sexual dysfunction, constipation, sweating, bladder disturbances and dribbling saliva (4). The NMS is shown to impair quality of life significantly and compared to motor-symptoms, assessment and treatment are insufficient (5).

Over the last decade it has been observed that Impulse Control Disorders (ICDs) occur more frequently in patients with Parkinson's disease (PD) than in the general population (reviewed in 6, 7). The disorders involve hypersexuality, binge eating, compulsive buying and pathological gambling and have been coupled with quite a strong relation to dopamine replacement therapy (DRT), and to dopamine agonists (DA) in particular(8). Other compulsive behaviours investigated and found in PD patients are punding, hobbyism, walkabout and compulsive use of medication (reviewed in 9). The DOMINION study (8), the largest epidemiological evaluation of ICDs in PD, found in their cross-sectional study of 3090 patients with PD an overall prevalence of ICDs of 13.6%. In a recent review (7) the overall prevalence found for each ICD was: pathological gambling and hypersexuality 3.5% each, compulsive buying 2.5% and binge eating 2.6 %. All patients were on dopamine replacement therapy (DRT) and 2.5% reported more than one ICD. The same review reports a prevalence of ICDs of 1.1% to 1.6 % in the general population. The other compulsive behaviours in PD have not been as well studied and numbers differ substantially.

Having an ICD can have great impact on a patient's life, with potentially devastating psychosocial consequences (10). The first step in the management of an ICD is to assess and to diagnose it. For this purpose, in a study setting, several general rating scales, questionnaires and diagnostic criteria have been used (8, 11-14). Researchers at the University of Pennsylvania found that there were no good tools available for the assessment of ICDs in PD and as a response they developed the Questionnaire for Impulse-Compulsive Disorders in Parkinson's Disease (QUIP), a self-administered screening tool. The QUIP exists both in a non-rating scale version, long and short version, and a rating scale version. Both have been validated (15, 16). In Norway there is to our knowledge no validated tool for assessing ICDs in PD patients.

The aim of this study has been to contribute to the awareness of ICDs as a potential problem in PD, and to the possible introduction of a tool to assess this in Norway. In the pilot study we translated the QUIP to Norwegian and administered it to a sample of PD patients to fill out, in the context of routine clinical care. Patients were also asked to complete the Barrat Impulsiveness Scale (BIS-11). We were interested in the utility of the QUIP and secondly if this instrument were able to capture comparable numbers of ICDs in a specialised neurologic polyclinic in Norway as seen in previous studies. We were also interested to see if there was any correlation between the impulsivity score and the presence of an ICD.

Material and methods

Patients and setting

The study was performed in a University Hospital in Norway which covers approximately 490 000 inhabitants. A convenience sample of 44 patients was assessed in a specialised neurologic polyclinic in the hospital between September 2012 and March 2014. Patients were identified in the context of routine clinical care for their Parkinson's disease (PD) or as part of the diagnostics of a parkinsonistic disorder. Each patient was asked to fill out the questionnaires after their scheduled appointment and there was a separate room available for this purpose.

Measures

Clinical assessment

Each patient was assessed clinically by a neurologist specialised in movement disorders. The diagnoses were based on individual case history; on paraclinical and imaging examinations including for most patients DAT scans and brain MRI. In addition response to dopaminergic medications and disease progression over time was assessed. All patients had parkinsonism. For the present study, patients were also diagnosed as "possible Parkinson plus" as well as more certain multisystem atrophy (MSA) or progressive supranuclear palsy (PSP). The presence of fluctuations, hallucinations and cognitive reduction/dementia were noted. Clinical staging was done according to Hoehn and Yahr (17).

BIS-11

To assess impulsivity we used the Barratt Impulsiveness Scale (BIS-11), a 30 item self-reporting instrument to assess impulsiveness, originally developed by Barratt (18, 19). The BIS-11 asks about the frequency of impulsivity-related behaviours and each item is scored on a 4-point scale. The BIS-11 is designed to measure three theoretical substrates of impulsiveness; Attentional Impulsiveness, Motor Impulsiveness, and Non-Planning Impulsiveness. The higher the summed score for all items, the higher the level of impulsiveness (18). There are no filler items. The BIS-11 has been used to assess levels of impulsivity across a variety of populations, including substance-dependent individuals as well as normal populations (reviewed in 20). The BIS-11 has been translated to Norwegian and a process of validation is presently in progress (unpublished).

The QUIP

To assess ICDs and other compulsive behaviours we used the QUIP, a self-administered screening questionnaire, developed and validated (15) by researchers at the University of Pennsylvania. The questionnaire consists of three parts; first a section with five questions (including an introductory question, defining and exemplifying each ICD) for the four ICDs reported in PD (gambling, sexual, buying, and eating behaviours). Then follows a section with three specific introductory questions and two additional questions for hobbyism, punting, and walkabout; and finally a third section with five questions concerning compulsive medication use. The QUIP asks about behaviours observed at any time since the onset of PD that lasted at least 4 weeks. All questions are statements about whether different behaviours apply and the respondent is required to answer "yes" or "no". Based on the validation of the QUIP (15), the following cut-offs were used to represent a positive screen: pathological gambling (any 2 of the 5 items); hypersexuality (any 1 of the 5 items); compulsive buying (any 1 of the 5 items); binge-eating (any 2 of the 5 items); for the second section (any 1 of the 3 items); for the medication section (positive on question 1 and 4). For the purpose of this study the QUIP was translated to Norwegian.

Statistical analysis

All analyses were performed with SPSS version 15.0. Descriptive statistics were the main output. When appropriate, Student's t test and chi-2 test were used for numerical and categorical data respectively. For multiple group comparisons we used ANOVA with Bonferroni corrections for multiple testing.

Ethics

Participation was voluntary, all questionnaires were anonymous and based on individual informed consent. The study received an exemption from ethics approval by the Regional Committee for Medical and Health Research Ethics due to its design as quality assurance of an already established treatment.

Results

Forty-four patients were asked to fill out the QUIP. One patient had to end before completion due to severe cognitive problems. Three patients were too tired after their scheduled appointment and refused. Twenty-seven patients filled out both the QUIP and the BIS-11. Of the 41 QUIP respondents the mean age was 69.3 (95% CI 66,5-72,1) years and the median duration of PD was 5.0 (IQR: 9) years. Relevant clinical features of the study population are detailed in Table 1.

Table 1: Clinical features of the study population

n:	41
Gender n (%):	male 28 (68.3%) female 13 (31.7%)
Age, mean (95% CI):	69.3 (66,5-72,1) years
PD duration, median (IQR):	5,0 (9) years
Hoehn and Yahr stage, median (IQR):	2,5 (1,0)
Possible Parkinson Plus:	16 (39 %)
Other diagnoses:	PSP: 1 (2.4%) MSA: 4 (9.8%)
Medication, n (%):	Levodopa alone: 17 (41.5 %) DA alone: 4 (9.8 %) Levodopa and DA: 13 (31.7 %) No medication: 7 (17.1%)
Fluctuations:	14 (34.1%)
Hallucinations:	5 (12.8%)
Cognitive reduction:	11 (28.2)

Abbreviations: IQR, interquartile range; PD, Parkinson disease; DA, dopamine agonist, CI, confidence interval

Frequencies of ICDs and other compulsive behaviours

Sixteen (39.0%) patients reported an ICD sometime during PD. The most common ICDs reported were compulsive buying followed by hypersexuality and binge eating while the most common other compulsive behaviours were hobbyism followed by punning (Table 2). Males (n = 11/28, 39,3%) and females (n=5/13, 38.5%) reported the same presence of an ICD during PD, but there were some differences within the categories of ICDs and other compulsive behaviours, although without significance.

Table 2: Reported compulsive behaviours

	Patients (n=41)
	n (%)
Any ICD	16 (39)
• Gambling	0
• Sex	7 (17.1)
• Shopping	9 (22)
• Eating	2 (4.9)
Multiple ICDs	2 (4.9)
Positive introductory question, ICD	13 (31.7)
Hobbyism	6 (14.6)
Punding	3 (7.3)
Walkabout	0
Compulsive medication	0

Abbreviation: ICD, impulse control disorder

Presence of an ICD in relation to clinical correlates

Of the 41 QUIP respondents, seven (17.1%) patients were not taking any Parkinson medication; four (9.8%) patients used only a dopamine agonist (DA); 17 (41.5%) patients used levodopa in mono-therapy; and 13 (31.7%) patients used a combination of levodopa and a dopamine agonist. 53.8% of patients using both levodopa and DA reported an ICD compared to 38.1% in the group on mono-therapy with either levodopa or DA. Patients who scored positive for any ICD were slightly younger, although no statistical significance was found. Small differences without significance were seen between patients with/without fluctuations, with/without hallucinations, with/without cognitive reduction and with/without a possible diagnosis of Parkinson plus. See Table 3.

Table 3: Clinical correlates of ICDs

	Total (n=41)	ICD (n=16)	No ICD (n=25)	p-value
Male sex, n (%):	28 (68.3)	11 (39.3)	17 (60.7)	0.96
Age, mean (95% CI):	69.3 (66,5-72,1)	66.8 (62,8-70,7)	70.9 (67,0-74,8)	0.14
Hoehn and Yahr stage, median (IQR):	2.5 (1,0)	2,5 (1,5)	2,5 (1,4)	
PD duration, median (IQR):	5,0 (9) years	4,0 (13)	5,0 (9)	
Medication, n (%):				
• Levodopa alone:	17 (41.5%)	6 (35.3%)	11 (64.7%)	0,75
• DA alone:	4 (9.8%)	2 (50%)	2 (50%)	0,64
• Levodopa or DA	21 (51,3%)	8 (38.1)	13 (61.9)	0,48 ^a
• Levodopa and DA	13 (31.7%)	7 (53.8)	6 (46.2%)	0,48 ^a
• No medication:	7 (17.1%)	1 (14.3%)	6 (85.7%)	0,22
Possible Parkinson Plus, n (%):	16 (39 %)	4 (25%)	12 (75%)	0,32
Fluctuations, n (%):	14 (34.1%)	7 (50%)	7 (50%)	0,33
Hallucinations, n (%):	5 (12.8%)	3 (60%)	2 (40%)	0,35
Cognitive reduction, n (%):	11 (28.2)	3 (27.3%)	8 (72.7)	0,48

Abbreviations: ICD, impulse control disorder; IQR, interquartile range; PD, Parkinson disease; DA, dopamine agonist, CI, confidence interval

^a Comparison of combination therapy and mono-therapy with either DA or levodopa

Impulsivity measures and ICDs

Twenty-seven of the QUIP respondents also filled out the BIS-11. There were higher summed scores for impulsivity within the patient group who screened positive for any ICD. No significance was found when using the formal cut-offs. Results summarized in Table 4. Nevertheless, when using only the introductory question for the presence of an ICD, screening responses came out with a significant correlation with BIS-11 score, see Table 5. There was also a significant correlation between whether a patient reported no ICD, one single ICD, or multiple ICDs and the patient's score on the BIS-11. (Linear regression; adjusted r^2 0.40 and $p < 0.0001$) See Table 6 and Figure 1.

Table 4: Impulsivity and reported ICDs – screening with the formal cut-offs

	ICD n=11	No ICD n=16	p-value
	Mean (95% CI)	Mean (95% CI)	
BIS-11 total score for impulsivity	63.0 (58.0-68.0)	57.3 (53.0-61.6)	0.074
• Attentional impulsivity	16.6 (14.3-18.8)	15.0 (13.3-16.7)	0.233
• Motor impulsivity	21.6 (19.3-23.9)	18.6 (16.9-20.3)	0.027
• Non-planning impulsivity	24.8 (22.3-27.3)	23.6 (20.8-26.5)	0.527

Abbreviations: ICD, impulse control disorder; CI, confidence interval

Table 5: Impulsivity and a reported ICD – screening with the introductory question

	ICD n=9	No ICD n=18	p-value
	Mean (95% CI)	Mean (95% CI)	
BIS-11 total score for impulsivity	66.4 (61.3-71.6)	56.2 (52.8-59.5)	0.001
• Attentional impulsivity	17.3 (14.8-19.9)	14,8 (13.3-16.24)	0.053
• Motor impulsivity	22.4 (20.2-24.7)	18.6 (17.0-20.1)	0.005
• Non-planning impulsivity	26.7 (23.0-30.6)	22.8 (20.7-24.9)	0.043

Abbreviations: ICD, impulse control disorder, CI, confidence interval

Table 6: Impulsivity and the report of single/>1/no ICD – introductory question

	Single ICD n=7	>1 ICD n=2	No ICD n=18	p-value ¹
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
BIS-11 total score for impulsivity	64.6 (59.5-69.6)	73.0 (-3.2-149.2)	56.2 (52.8-59.5)	0.001 ^a
• Attentional impulsivity	16.0 (14.5-17.5)	22.0 (-16.1-60.1)	14.8 (13.3-16.24)	0.006 ^b
• Motor impulsivity	21.1 (20.0-22.3)	27.0 (1.6-52.4)	18.6 (17.0-20.1)	0.001 ^c
• Non-planning impulsivity	27.4 (22.6-32.3)	24.0 (11.3-36.7)	22.8 (20.7-24.9)	0.085

Abbreviations: ICD, impulse control disorder, CI, confidence interval

¹ ANOVA with Bonferroni corrections: ^a Post Hoc Test: No ICD vs. single ICD: $p = 0,024$, No ICD vs. >1 ICD: $p = 0,006$; ^b Post Hoc Test: No ICD vs. >1 ICD: $p = 0,005$, Single ICD vs. >1 ICD: $p = 0,035$; ^c Post Hoc Test: No ICD vs. >1 ICD: $p = 0,001$, Single ICD vs. >1 ICD: $p = 0,041$

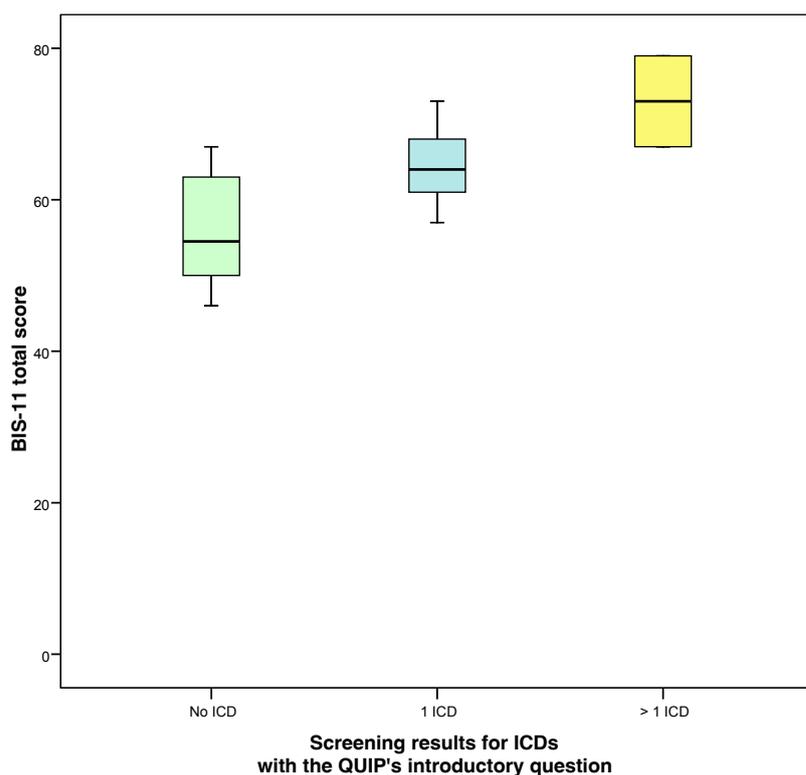


Figure 1 Associations between impulsivity, using BIS-11 total score, and the presence of the report of no ICD vs 1 ICD and vs >1 ICD, using the introductory question for ICDs in the QUIP as screening tool.

Observations during completion of questionnaires – utility of instruments

Most patients had no practical problems filling out the QUIP and the BIS-11. Some patients had difficulties reading or writing, or both, due to their PD, and needed help to complete. The research assistant supported the patient in these situations. In some cases, there was a sense of embarrassment in relation to the QUIP-questions, as they involve behaviours like hypersexuality, pathological gambling, binge eating, and compulsive shopping. One patient's closest relative expressed surprise over her partner's positive screen for hypersexuality. Although we strove to make patients fill out questionnaires without their closest relative beside them this was not always feasible. Some patients with negative screenings wished to emphasise this to the research assistant.

Discussion

The purpose of this pilot study was primarily to investigate the utility of an assessment tool for ICDs and other compulsive behaviours in PD patients in a Norwegian clinic, and to increase the awareness of these problems. On a secondary level we were interested to see if reported ICDs and correlated clinical features, as well as impulsiveness, were comparable with previous findings. We will discuss the latter first.

Sixteen (39.0%) patients in our study reported an ICD sometime during PD. Two (4.9%) patients reported more than one ICD. Several studies have used the QUIP in the assessment of impulsive compulsive behaviours in PD patients (21-24). Our reported prevalence of any ICD seems slightly higher than previous findings; in Finland they found a prevalence of 34.8% (24), in Denmark the prevalence was 21.6 % - both using the QUIP through a postal survey (21); in Japan they found a prevalence of 28% (22); and in a Malaysian clinic they reported a prevalence of 23.5% (23), when responses from patient and caregiver were combined. Only

the Japanese study carried out follow-up interviews for the patients that screened positive on the QUIP. They found the same tendency to overestimation as Weintraub et. al when it comes to self-reporting alone, with low positive predictive values (15, 22). This emphasises the need for a follow-up interview to assess whether an ICD is present and to elaborate the severity of symptoms and the need for management. On the other hand, negative predictive values were almost 100% for all behaviours, suggesting that if patients are screened as negative, it is highly likely supports that they do not have a history of ICDs or other compulsive behaviours.

Our results found some correlations with younger age, a combination therapy of levodopa and DA, and the presence of an ICD. This correlates with previous findings (8, 21, 24). These were not statistically significant result; this may be due to too little power in this pilot study.

We found a significant correlation in this pilot study between a positive screen for any ICD, when using the introductory question, and the BIS-11 score. We found this to be of interest since the shortened version of the QUIP uses only the four introductory questions and one additional question for each ICD. Cut-offs are set to 1 positive item out of 2, and the sensitivity and specificity is found to be even higher than for the long version which is used in this pilot study (51). In phase II of the DOMINION study, a multicentre case-control study was undertaken (25), and found similar correlations using the same assessment tool for impulsivity, supporting this correlation. This suggests the possibility of an impulsiveness score as a screening tool for patients' vulnerability of acquiring an ICD. It might be less sensitive for a patient to report general impulsive acts in a questionnaire than a tendency to more specific behaviours, for example increased sex drive. This said, the scoring of the BIS-11 is complicated, and the original purpose of developing the QUIP was to have a tool that asks for these behaviours in PD patients specifically (15). The task might be to lower the threshold to talk about such symptoms rather than further concealing them as potential embarrassing features of PD.

When it comes to the utility of the QUIP there are some considerations to note. First, the patient needs to be able to read and write. This is not always the case in PD and might be a source of underreporting in the most severely affected patients, although a close relative might function as informant. Moderate agreement between patient- and informant-reporting has been reported when using the QUIP, although negative predicative values for patient/informant combined were found to be almost 100%, suggesting that a negative screen essentially rules out the presence of an ICD (26). Secondly, some of the questions are quite sensitive, for example asking about sexual promiscuity. This needs to be taken into consideration because patients may feel uncomfortable filling out the form with a close relative nearby, or with the doctor in the next room soon to look at the results, or with a nurse assisting in the completing of the questionnaire. We experienced both disclosure of ICDs unknown to the closest relative and expressed embarrassment toward the research assistant, with the patient emphasising his or her negative screen. This illustrates the need for an considered and sensitive approach to these issues, although an appreciation of their presence in the process of normalization seems equally important. Thirdly, the potential time requirement and practical problems associated with the completion of questionnaires may complicate the implementation of such an instrument.

This study has several limitations. First, the study population is small and it was derived by convenience sample in routine clinical care in a specialised neurologic polyclinic. The sample of patients is therefore not necessarily representative for PD patients, either in the clinic or in the general community. Second, some patients had problems filling out the forms as a

consequence of motor fluctuations or late stage PD, and required help; some with reading, some with writing, and some with both. This might have affected their responses. The same goes for the patients that either needed or wanted their close relative to be with them when filling out the form. Third, in the process of translation, a long and a shortened version of the Norwegian QUIP was used in the beginning of this pilot study. All questions used in the short version were identical to the corresponding questions in the long version. In the statistical work three “absent questions” in the short version have been set as missing in the data set and the questions present were scored as in the long version. This should have few implications; if any, this may give a slight underreporting rather than the other way around. Fourth, it is emphasised in the validation of the QUIP (15) that the questionnaire is meant solely as a screening tool, thus a follow-up interview is necessary after any positive responses to determine the range and severity of symptoms. Within the limits of this pilot study such an interview was not feasible. This might result in too high prevalence as the QUIP has a tendency to overestimate (21). On the other hand, the personal contact of either a research assistant or a close relative during completion might have had the opposite effect. Fifth and last, the Norwegian QUIP and BIS-11 were not validated, thus further validation studies may be necessary.

In conclusion, a substantial portion of Parkinson patients have an ICD. The assessment of ICDs presents some problems both in clinical practice and in research. The different behaviours are associated with embarrassment and guilt and they are largely neglected in the clinic, but they can have potentially devastating social and economic consequences. Therefore we urge that awareness should be raised towards these disorders as a possible side-effect of DRT. The QUIP is a useful tool in the assessment of such disorders, but a general impulsiveness scale as BIS-11 may also function as a screening tool, although both instruments need thorough validation of their Norwegian translations before a potential general implementation can be recommended. Even though this pilot study was done on a small population after convenience sample, our findings support previous studies that encourage clinicians to do routine testing for ICDs and other compulsive behaviours in PD patients.

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Conflicts of interest

No conflict of interest to declare.

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