Depression in Parkinson's disease

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Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder affecting 100 to 150 persons per 100 000 inhabitants. The diagnosis during lifetime is based on clinical examination and the cardinal features are rigidity, resting tremor, bradykinesia and postural instability. However, there is growing evidence, that PD should not be appreciated solely as movement disorder. The underlying brain changes also result in autonomic, sensory and neuropsychiatric disturbances.

These neuropsychiatric symptoms include sleep disturbances, apathy, attention deficits, cognitive dysfunction, dementia, psychotic symptoms and depression. Depression is the most common neuropsychiatric complication in PD and has been shown to be a major determinant of impaired quality of life, often independent from the severity of the motor symptoms.

Depression has commonly been considered as a "normal" psychological reaction to the functional impairment and poor prognosis related to a chronic neurological disease. However, persons suffering from diseases with comparable functional impairment are less likely depressed, and depression is usually not associated with functional impairment, and may even occur before PD is diagnosed. Therefore, intrinsic mechanisms, specific to PD, likely contribute as well. Several aspects of depression in PD remain to be explored, including the clinical symptom profile, risk factors and its biochemical basis. The objective of this dissertation is to explore several of these aspects, based on the unique longitudinal PD cohort in Stavanger established in 1992. First, in the general part, after a brief introduction of PD, an overview is given about the prevalence, clinical characteristics and treatment options for depression in PD.

List of publications

Ehrt, U., Bronnick, K., De Deyn, P.P., Emre, M., Tekin, S., Lane, R., Aarsland, D., 2007. Subthreshold depression in patients with Parkinson's disease and dementia--clinical and demographic correlates. *Int J Geriatr Psychiatry*, 22, 980-5.

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Contents

1. Parkinson's disease: A brief Introduction

1.1 Definition and diagnosis

Parkinson's disease (PD) is a chronic-progressive and disabling neurological disorder and the second most common neurodegenerative disease after Alzheimer's disease. Pathologically, PD is defined by nigrostriatal loss of dopaminergic cells and Lewy bodies in the surviving cells on autopsy. It is manifested clinically by a broad spectrum of motor and non-motor features. The four cardinal features of PD can be grouped under the acronym TRAP: tremor at rest, rigidity, akinesia (or bradykinesia) and postural instability. This syndrome is labeled "parkinsonism" and may also occur in other medical conditions than idiopathic PD, such as dementia with Lewy bodies, cerebrovascular disease, the so called parkinsonian plus syndromes or as side effect after administration of neuroleptic medication. The presence of akinesia and one of the other symptoms are considered sufficient for the clinical diagnosis of parkinsonism. Diagnostic criteria have been developed by the UK Parkinson's Disease Society Brain Bank and the National Institute of Neurological Disorders and Stroke (NINDS) [1]. Other diagnostic criteria for clinical subgroups of the disease classified at different levels of confidence were proposed by Larsen et al. [2]. Flexed posture and motor blocks (freezing) have been included among classic features of PD [3]. Despite recent advances in imaging and genetics of PD, its diagnosis is typically based on the presence of a combination of cardinal motor features, associated and exclusionary symptoms, and response to levodopa [4]. The Unified Parkinson's Disease Rating scale (UPDRS) is the most established scale for assessing motor dysfunction, disability and impairment [5].

1.2 Epidemiology

Incidence and prevalence of PD increase with age, but published numbers vary widely across studies and countries, which is probably due to differences in methodology and diagnostic criteria. However, metaanalyses indicate that about 1.6% of persons 65 years of age or older are affected by the disease [6]. The best incidence studies give a rate of about 17 per 100 000 per year in the overall population, the highest incidence is generally between 70 and 79 years of age [7]. In a recent incidence study covering near ¼ of the total Norwegian population, Alves et al. found the annual incidence rate to be 12.6 per 100 000 inhabitants, age-adjusted to the 1991European population structure [8]. There is good evidence that men are, in general, about 1.5 times more likely to develop Parkinson's disease than women, this difference is not the same across different studies, and is more pronounced in (and possibly restricted to) people with an older age of onset and in Western populations [9]. Healthcare costs for the management of PD are substantial. The direct health care costs of PD in the United States were estimated at $10,349 per patient per year and are expected to rise in the future due to the aging population worldwide, and following this, the increasing number of affected patients [10].

1.3 Clinical presentation and course

Disease presentation is usually unilateral and insidious. Although there are wide inter-individual variations, the course of disease is relentlessly progressive, with gradually increasing motor symptoms, and development of a range of non-motor symptoms, increasing functional impairment and disability, such as autonomic dysfunction, pain, skin problems, sleep disturbances and neuropsychiatric symptoms (see below) [11]. Patients suffering from PD live with significant functional impairment, a poor health-related quality of life (HRQOL), and increased mortality compared with the general population [11 12].

1.4 Pathology

In addition to the defining loss of nigrostriatal dopaminergic neurons, a wide range of other brain regions and neurotransmitter systems are involved, and according to the Braak hypothesis [13], there is a sequential rostral progression of the pathological involvement. Brain stem nuclei such as serotonergic raphe nuclei, the adrenergic locus coeruleus, as well as dopaminergic nuclei such as ventral tegmental area are involved in the majority of cases. The major cholinergic nuclei in the basal forebrain and limbic structures are also involved rather early in course, and in the final stages, neocortical involvement is common. Whereas the nigrostriatal pathology is the main cause of the motor symptoms, the widespread extra-striatal pathologies probably contribute to the wide variety of non-motor symptoms in PD [14-16], although the exact relationship between non-motor symptoms and brain changes are poorly understood.

1.5 Etiology

Etiology is largely unknown, but it is hypothesized that PD is caused by interplay of genetic and environmental causes. Recent insights into genetics of Parkinson's disease (PD) have enhanced our understanding of basic disease mechanisms, for example the central role of α-synuclein, the key element of the Lewy body. Mutations in the α-synuclein gene (SNCA) were found in autosomal dominant PD. Several other mutations have been identified, and contribute to familial cases of PD. For example, mutations in the parkin gene contribute in the pathogenesis of early onset autosomal recessive parkinsonism [17]. However, the majority of PD cases are sporadic, suggesting that genetic factors are multifactorial.

1.6 Management

The current treatment of PD is mainly medical and its aim is to alleviate the symptoms. A cure is not available. Treatment of Parkinson's disease is complex

because of the chronic-progressive course of the disease and the wide range of motor and non-motor symptoms demanding different strategies. Drugs include l-dopa, dopamine receptor agonists, anticholinergic drugs, and antiglutamatergic drugs [18]. L-dopa remains the treatment of choice. There is an ongoing debate how early in the course of the disease one should initiate medication [19]. The early use of dopamine agonists is beneficial in younger Parkinsonian patients. Nonergot dopamine agonists have milder side effects. Dopamine agonists, catechol-o-methyltransferase inhibitors, amantadine and apomorphine have differing but beneficial roles in the management of levodopa side effects [19]. These drugs can improve motor symptoms in the majority of cases, although the underlying pathological process is probably not affected. However, with the progression of the disease, the effect is usually less pronounced, and adverse events and drug-related complications such as motor fluctuations with on-off periods, dyskinesias, psychosis and delirium occur in many patients and limit the usefulness of these drugs,

Since basal ganglia circuits and their disturbances in PD became better understood, stereotaxic surgery has had a renaissance in PD [20]. One important breakthrough in this field has been the introduction of high-frequency stimulation (deep brain stimulation, DBS), a method that has substituted the classical lesioning methods previously used in stereotactic and functional neurosurgery [21]. The most common targets for DBS are subthalamic nucleus (STN), internal pallidal segment and ventrointermedial thalamic nucleus [20]. Transplantation of dopamine-producing cells may become another surgical approach for treating PD when the technical and ethical problems related to this method are resolved.

1.7 Psychiatric symptoms in Parkinson's disease

Non-motor symptoms of PD have been increasingly recognized as a major cause of disability. In addition to autonomous dysfunction and pain, neuropsychiatric disorders including cognitive impairment are particularly common [11]. A wide variety of neuropsychiatric symptoms occur in PD, including visual hallucinations [22], anxiety

[23], depression [24 25], apathy [26], cognitive impairment [27], and impulse control disorder [28 29]. These symptoms tend to cluster into syndromes, and typically affective, psychosis and apathy syndromes have been identified in PD [30]. Depression is the most common psychiatric disorder diagnosed in patients with Parkinson's disease [31], and is the topic of the current thesis.

2. Depression as psychiatric disorder

The term depression is used to describe a mood, a symptom, a symptom constellation (syndrome) as well as a group of specific psychiatric disorders. Due to the absence of reliable biological markers, the diagnosis of the specific psychiatric disorder depression is still based exclusively on symptoms and signs.

Major depressive disorder (MDD), dysthymic disorder (DD), minor depression and depression not otherwise classified (DDNOS) are the group of disorders in the Diagnostic and Statistical Manual for Mental Disorders of the American Psychiatric Association characterized by depressive symptomatology [32].

The diagnosis of major depressive disorder or major depression (MD) requires the presence of depressive mood or loss of interest and pleasure in once-pleasurable activities for at least 2 weeks, accompanied by a varying combination of other depressive symptoms, among them loss of appetite, sleeping disturbances, concentration difficulties, psychomotor restlessness, feelings of worthlessness or guilt (the exact criteria are displayed in Table 1). Some individuals experience only one single episode, but often, individuals suffer from multiple major depressive episodes. Severe depressive illness may be accompanied by psychotic symptoms, such as a break with reality, hallucinations, and delusions.

Minor depression is a mood disorder with fewer symptoms and less impairment compared with major depression. DSM research criteria for minor depression are in the DSM-IV appendix and require the presence of only two of nine symptoms (see table 1). Depressive episodes may occur once in a person's lifetime, but more often, they are recurrent. Dysthymia or dysthymic disorder are less severe conditions with depressive symptomatology that may not disable a person but can hinder one from functioning or feeling well. They are considered as rather chronic disorders. To diagnose it, symptoms have to be present for two years or longer. People with

dysthymia may also experience one or more episodes of major depression during their lifetimes.

Table 1) DSM-IV-TR criteria for major and minor depression

Depressive episode	Criteria
Major depressive episode	A. Persistence and general pervasiveness of 5 or more of 9 potential symptoms during the same 2-week period that represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure that is present most of the day, nearly every day, as indicated by either subjective report or observations made by others. 1) Depressed mood 2) Markedly diminished interest or pleasure in all, or almost all, activities 3) Loss or gain in weight or appetite 4) Insomnia or hypersomnia 5) Psychomotor agitation or retardation 6) Fatigue or loss of energy 7) Feelings of worthlessness or excessive or inappropriate guilt 8) Diminished ability to think or concentrate, or indecisiveness 9) Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide B. Symptoms do not meet criteria for a DSM mixed episode (presence of phenomena of both a manic and a depressive episode). C. Symptoms cause clinically significant distress or functional impairment. D. Symptoms are not due to the direct physiological effects of a substance or a general medical condition. E. Symptoms are not better accounted for by bereavement.
Minor depressive episode	Requires only 2 of the 9 symptoms above, but one must be either depression/sadness or loss of interest/pleasure.

3. Epidemiology, course and consequences of depression in PD

The differential diagnosis of depression in PD is broad, including states of demoralization, adjustment disorders, major mood disorders (major depression, dysthymia, or bipolar disorder), minor depression, and depressive symptoms not fulfilling diagnostic criteria (subsyndromal depression). In addition, apathy and fatigue may mimic depression. Depression has a major impact on functional ability as well as on the quality of life of PD patients and their caregivers [33-36]. In some studies, depression was revealed as the strongest predictor for impaired quality of life [34 35]. Depression is also associated with lower cognitive functioning and increased mortality [37 38]. Despite this, in many PD cases, depression is not diagnosed sufficiently and thus, under-treated [39 40].

The prevalence of depression or depressive syndromes in PD reported in the literature varies widely, ranging from 2.7% to 76% [24 41 42]. Several reasons for this variation can be given, for instance the nature of the study population, how depression is defined and the way it is diagnosed. Also the applied statistical methods may influence the numbers. Studies in outpatient and inpatient samples tend to report higher prevalence rates, whereas rather lower prevalence numbers are reported in studies measuring depressive symptoms in community-based studies. Studies using diagnostic criteria for depression strictly, such as DSM IV or the International Classification of Diseases (ICD) of the World Health Organization (WHO) yield the lowest rates [41].

Furthermore, the approach to such criteria may influence prevalence numbers. Important depressive symptoms like insomnia, weight loss psychomotor retardation or loss of energy are also frequent symptoms in PD, sometimes in the absence of depressed mood [43]. One has to choose either an “inclusive” approach and to consider such ambiguous symptoms as belonging to the depressive syndrome or not to do so and choosing the “exclusive” approach, which yields lower prevalence rates. This problem is discussed more in detail in the section “Diagnosis of depression in PD”.

Self-report rating scales tend to give higher prevalence rates than observer-rated instruments. Prevalence rates are influenced by the syndromes included in the study: major depressive disorder only or less severe syndromes such as dysthymia and minor depression. When using point-prevalence, the rates are lower than in studies using monthly or lifetime prevalence.

There is a lack of a systematic review of prevalence studies taking all these factors and the different settings and approaches to diagnosis of depression in PD into account, which make it difficult to estimate the extent to which depression is accompanying PD.

Neither the prevalence nor the severity of depression seem to have any clear relationship to the course of PD. Patients both in early and late phases of the disease can suffer from depression. It was even shown that depression, especially major depression (MD) may predate the onset of the motor symptoms [44].

Little is known about the natural history of depression in PD. The existing longitudinal data suggest that in some patients the course is chronic or variable with repeated remissions and relapses of depression and that the more severe cases seem to become chronic. Starkstein et al. found that 56% of patients with MD still suffered from MD at follow up, and 89% were still depressed when also cases with minor depression were included [45]. In another study, cases with less severe depression were more likely to be significantly improved at follow up than those with severe depression [46]. Limitations with the few longitudinal studies are that the cohorts were small and selected, and that follow-up time was rather short. Thus, further studies with more adequate design are needed.

4. Clinical Characteristics of depression in PD

4.1 The psychopathological pattern of depression in Parkinson's disease

Several studies have explored the hypothesis that the symptom profile of depression in patients with PD differs from that in patients without PD. From a theoretical point of view; it has been suggested that the neurotransmitter disturbances underlying depression in PD may differ somewhat from those in 'common' depression regarding localisation, distribution and severity [47] and that such differences result in a specific phenomenological symptom pattern. This would have clinical implications, since modern antidepressants provide differential pharmacological strategies targeting specified depressive symptoms, e.g. specific monoamine transmitter disturbances. As early as in 1923, Friedrich H. Lewy described depressive patients with PD to be moody, irritable and weepy from a clinical view [48]. More recent studies focusing on the clinical features of depression in PD, reported distinctive characteristics in PD-related depression with less classical 'endogenous' depressive symptoms such as feelings of guilt, suicidal ideation, but more somatic symptoms such as anxiety, sleep disturbances and concentration difficulties. "Atypical depression" accompanied by anxiety or comorbid anxiety disorders were reported by Schiffer et al. [49]. Brown found that depression in PD was characterized by loss of interest and poor concentration in one study [50] and by a low degree of feelings of guilt and self blame and a relative lack of delusions and hallucinations in another [51]. Ehmann et al. compared depressive symptoms in 45 PD patients to those in 24 matched patients with other chronic disabling diseases not involving a loss of central monoamines and not differing on a measure of functional disability [52]. PD subjects had significantly higher BDI total scores and higher scores on BDI items reflecting cognitive-affective and somatic depressive symptoms. According to the authors, these findings support

the hypothesis that depressive symptoms in PD are not solely a psychological reaction to disability.

In contrast, other studies found the psychopathological features of depression in patients with and without PD to be similar and therefore likely to have a common pathogenetic basis. The difference in some aspects of symptomatology might be due to some additional pathogenetic factors, although this would not necessarily confirm the hypothesis that depression in PD is a distinct subtype of depressive disorders [53 54].

To date, few studies have directly compared the phenomenology of depression in PD and MD. Such information may help in diagnosing depression in PD and enhance our understanding of the underlying neurochemistry of depression in PD, with potential therapeutical implications.

4.2 Depression and its association with other clinical features in Parkinson's disease

Attempts have been made to understand the underlying neurobiology of depression in PD by examining its relationship to other clinical features. Depressed patients with PD are more likely female [25] and to have a history of former depression [55], and patients with motor symptoms on the right side and assumed left brain pathology were more depressed than those with left-sided symptoms [55]. In a series of studies, depression was more frequent in those subjects with a predominant akinetic-rigid syndrome than in those with a predominant tremor or mixed phenotype [56 57]. In a small study study by Menza et al., temporary dysphoria and anxiety were found to follow motor fluctuations [58]. Most patients rated themselves worse during off-states, and better during on-states on a mood scale. Such brief mood disturbances commonly do not meet the criteria for an existing mood disorder, but are often experienced as distressing by the patients. This effect was stable in the majority of patients, regardless of concomitant dyskinesia, but some worsened again, when the on-state was accompanied by dyskinesia. Thus, such mood fluctuations can be an expression

of central dopaminergic changes and a direct effect of levodopa therapy on mood, or alternatively, as a psychological secondary change associated with disability due to motor symptoms [59]. The results argue also for a complex etiology of depression in PD.

Mayeux et al. reported that depressed patients with Parkinson's disease were younger than non-depressed patients [60]. This finding has been replicated by others [61 62], even after controlling for the duration of PD [62].

However, the findings are conflicting, and consensus has not yet been reached regarding the clinical correlates of depression in PD [63].

Common comorbid non-motor symptoms of depression in PD are cognitive impairment and dementia, anxiety, psychosis, apathy, sleeping and sexual disturbances [25 31 64-67]. Several studies have explored the relationship between depression and cognitive impairment, both in the general population and in PD. Starkstein et al. reported that depression scores in patients with PD accounted for most of the variance in MMSE score and had more impact on cognitive function than age and duration of illness. However, only patients with PD and major, but not minor depression scored significantly lower on MMSE than non-depressed patients [55]. In the Stavanger community-based sample, Tandberg et al. found that a MMSE score <24 increased the probability of major depression by 6.6 [66]. It is not yet clear whether the cognitive deficits are a result of severe depression or vice versa in PD. A relationship between depression and cognitive impairment has been reported also in patients without PD [68]. Starkstein et al. assessed PD patients prospectively and found that the depressed subgroup showed a significant steeper decline on cognitive function than the non-depressed subgroup. However, patients treated for depression had a milder decline of their cognitive scores than untreated patients, suggesting that adequate management of depression may delay cognitive impairment [45].

5. The diagnosis of depression in PD

5.1 Clinical criteria

Depression is usually diagnosed according to the criteria of the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders [69] or the ICD-10 Classification of Mental and Behavioral Disorders [70]. However, the diagnosis of a depressive disorder according to DSM IV or ICD-10 cannot be made, when depression is "due to a general medical condition". No guidelines are given for how to apply this criterion. Especially in PD this exclusion criterion is difficult to apply in individual patients, since it is usually unclear whether or not a symptom is caused by the somatic disease. Therefore, the strict use of these criteria in PD would exclude a significant part of patients with clinically significant depressive symptoms [71] and cannot be applied without restrictions. In the revised version of DSM (DSM IV-TR) the authors recommend diagnosing "mood disorder due to Parkinson's disease". However, researchers in this field have stated for a long time that there is a need of clear diagnostic criteria for PD related depression.

Many depressive symptoms like insomnia, weight loss, psychomotor retardation or loss of energy are also frequent symptoms in PD, even if the patient doesn't report depressed mood [43]. Therefore, symptom overlap between depression and PD is a well-known diagnostic problem in PD and assessments exclusively based on observer or self-ratings, are therefore of questionable validity [72]. Moreover, many of the depressive symptoms have a lower specificity in PD. Concentration difficulties, sleeping problems, psychomotor retardation or loss of energy are symptoms typical for both PD and depression. Therefore, when diagnosing depression in PD, one has to choose an exclusive or a more inclusive approach. The latter allows including also the somatic ambiguous features which may be interpreted as depressive symptoms or as being part of the neurological disease. Sleeping difficulties or restlessness are such symptoms. However, the inclusive approach results in higher depression rates. It may

also be difficult to diagnose depression in patients with cognitive impairment, which is common in PD, due to reduced ability to abstract thinking, self-awareness and communication abilities.

Thus, the recently recommended provisional diagnostic consensus criteria for depression for in PD were gratefully welcomed [71]. Modifying DSM-IV criteria for MD, the participants of an expert workshop recommended: (1) a rather inclusive approach to symptom assessment to enhance reliability of ratings in PD and avoid the need to attribute symptoms to a particular cause; (2) the inclusion of subsyndromal depression in clinical research studies of depression of PD; (3) the specification of timing of assessments for PD patients with motor fluctuations; and (4) the use of informants for cognitively impaired patients.

5.2 Psychometric measurements

Cut-off values from different depression scales or DSM criteria have commonly been used to diagnose depression in PD. However, the most common depression scales assess psychopathological as well as somatic symptoms, which do not necessarily represent depressive symptoms in patients with PD. When choosing an "inclusive" instead of an "exclusive approach", (see above), one has to consider sleeping problems or concentration difficulties as depressive symptoms which consequently leads to higher depression scores.

The expert group mentioned above [73] concluded that there are validated and widely accepted depression scales to be used in patients with PD, such as Beck Depression Inventory (BDI), Hamilton depression rating scale (HAM-D), and MADRS. Less data was available on Center for Epidemiologic Studies Depression Scale (CES-D) and Cornell Scale for Depression in Dementia (CSDD). Observer-rated scales (e.g., HAM-D and Montgomery-Åsberg Depression Rating Scale [MADRS]) have better psychometric properties than self-rated scales. Depression scales are useful as screening instruments and rating scales, and to follow symptoms over time.

Depending on whether high sensitivity or high specificity is required, adaptations of cut-off scores can be necessary. For screening purposes, HAM-D, BDI, Hospital Anxiety and Depression Scale (HADS), MADRS, and Geriatric Depression Scale (GDS) are recommended. HAM-D and MADRS as well as the BDI and the Zung Self-Rating Depression Scale (SDS) are more useful and valid when assessment of severity is important. Of note, a rating scale can only supply but never substitute the clinical diagnosis, and thus, the diagnosis of depression should ideally not be exclusively made by a score on a scale. Structured clinical interviews such as SCID, MINI etc can be used in addition, but have not yet been validated in PD. There is not one generally accepted, "best" depression rating scale for PD patients. MADRS, GDS, and CSDD may be useful in patients with dementia. A complicating issue is the fact that patients often perceive their condition differently in an off period than during an on period. Accordingly, fluctuations should be recorded, and also any variation in depression related to such fluctuations. Although the HAMD has several ambiguous items, which can be expression of both depression and PD, such as insomnia, agitation or gastrointestinal symptoms, by using adjusted cut-offs, it has shown the best psychometric properties compared to DSM-IV criteria. The HADS and GDS have fewer overlapping, somatic items and therefore, may be better when comparing patients at different stages of PD. In line with the NINDS recommendations [71] "loss of pleasure" or anhedonia is more specific to depression, while "loss of interest" is also considered as a symptom of apathy and often occurs in patients without depression. More research is required on the sensitivity, specificity, and positive and negative predictive values of each scale for major depressive disorder in PD, in particular the Cornell Scale for Depression in Dementia (CSDD) scale and the CES-D[73]. Additionally, studies examining the validity of depression rating scales against the recently recommended criteria for depressive disorders in PD (see below) are needed [71].

In general, the observer should score answers on the scales using an inclusive approach. When using rating scales, patients should be instructed not to attribute their symptoms to either PD or depression. Observers should choose an "inclusive

approach", even if this potentially leads to higher scores. An exclusive approach may lead to an underestimation of depression severity. The experienced clinician should reflect on this problem. There are no sufficient instruments to identify minor or subsyndromal depression, recurrent brief depressive disorder or dysthymia which often occur in PD. The impact of age, cognitive impairment, apathy, and cultural differences on the validity of depression scales has to be studied further.

6. Aetiology of depression in PD

6.1 Biological versus psychological explanations

There is no complete understanding of the pathophysiology of depression in PD yet. Like de novo depression, depression in PD is a condition with heterogeneous etiology which can be explained on different physiological levels, molecular, genetic, cellular, and behavioural. Modern research often focuses only on one level, and a comprehensive understanding and evaluation of the growing evidence from genetic, pathological, pathobiochemical and imaging studies therefore becomes more and more difficult for the single researcher.

Already James Parkinson stated in his original publication, that patients may become demoralized by the disease. Later on, Friedrich H. Lewy and Pierre Janet described an explicit association between PD and depression from a clinical view [48] [74]. At that time, depression was understood as a psychological reaction related to the trauma of having this neurological disease.

At first sight, to react with depression seems understandable when suffering from a chronic, progressive, disabling disease, and the patients self often attribute their sadness to the disease. The high prevalence of depression especially in patients with early disease onset could be understood as the illness' negative effect on their job situation, economic security and quality of life [75]. If depression was solely determined by functional impairment, however, depression should become more common and more severe in later stages of the disease, i.e. the more severe the impairment, the more severe the depression. However, studies examining this relationship show conflicting evidence. Robins found that PD patients were much more depressed than chronically disabled control patients with an even more severe grade of physical handicap. And, within the PD group, depression was unaffected by the severity of the disability [76]. Menza and Mark studied 104 patients with PD and 61 control subjects with equal disability scores, and found that PD patients were more depressed. Functional disability was correlated with depression and explained 9% of the

variance in depression. Depression was correlated with “harm avoidance” a personality trait related to central serotonergic systems but not with novelty seeking, a trait related to dopaminergic pleasure and reward systems. These results were discussed as support for the hypotheses that both physiologic and psychological factors contribute to depression in PD and that serotonergic dysfunction may be more important than dopaminergic pathways [77].

Depression in PD and depression without PD have much in common. Depression as a rather homogenous psychopathological condition is unspecific regarding etiology. When treating the single case, it is difficult to attribute the patient’s depression to either ‘biology’ or ‘psychology’. Several studies have aimed to disentangle psychological and biological factors contributing to depression in PD. More of didactic reasons, researchers often construct their discussions around the dichotomy question: is it biology or psychology? However, it is more likely that a “mixed model”, which takes both pathophysiological changes associated with PD and psychosocial aspects into account, is more appropriate. Serra-Mestres and Ring showed that the pathophysiological changes in PD lead to an increased vulnerability to react to negative emotional stimuli with depression. Patients with more severe forms of PD and more prefrontal cognitive dysfunction are more vulnerable to the distracting effects of external negative stimuli. According to the cognitive model of depression, these patients are at high risk of developing clinical depression [78].

Nilsson et al. showed in a large register study on more than 200 000 individuals, that PD patients had a higher risk of developing major depression compared with patients having other medical illnesses with a comparable degree of disability [79], suggesting that disease-related brain changes are more important than reaction to disability for the development of depression in PD. Cole et al. found depression to be related both to illness severity and functional impairment. The association was significant in men, but not in women and stronger in patients with early disease onset and those with right-sided PD; implicating that also biological alteration contributes [80]. Brown et al. examined a sample of PD patients at two occasions. Depression and disability were

associated on both measure points. Depression was more severe in patients with a rapid disease progression and fast functional impairment and rather independent on the absolute change in disability [51]. Schrag et al. found similarly results, i.e. higher depression scores associated with advancing disease severity, especially recent self-reported deterioration, akinesia, occurrence of falls, self -reported cognitive impairment and the feeling of stigmatization. Therefore, treatment of depression should consider the patients' own perception of their disease [81].

6.2 Pain and depression in PD

Chronic pain, an unpleasant or distressing sensory experience, is a common, but often underreported problem in patients with PD [82]. However, not all clinical descriptions of PD mention pain. In some patients, pain becomes severe enough to overshadow the motor symptoms of the disorder. Ford classified these painful sensations into 5 categories: musculoskeletal pain, neuritic or radicular pain, dystonia-associated pain, primary or central pain, and akathitic discomfort. Additionally, there is a central pain syndrome, likely intrinsic to PD, however, its precise mechanism is unknown, and a correlation with pathology has not been made [83]. When carefully questioned, more than half of all people with PD report painful symptoms and various forms of physical discomfort. In a large study on 450 PD patients, two thirds had chronic pain. 26% had pain unrelated to PD ("non-PD-pain", caused mainly by osteoarthritis), while 39.3% had chronic pain related to PD ("PD-pain"). Parkinsonian patients with "PD-pain" were younger at PD onset, had more motor complications and more severe depressive symptoms [82].The patients may experience aching, stiffness, numbness and tingling at some point in the course of the illness. In another study, 269 (67%) of 388 consecutive parkinsonian patients, presented sensory or painful syndromes [84]. Among them, 94% had muscular pain, stiffness 85%, cramps, pseudo-cramps, spasms 3% and various myalgias 7%, 51% presented osteoligamentar "rheumatologic" pain. Restless legs or akathisia were also described (10%). Surprisingly, less defined and localized neurogenic painful syndromes, like paresthesia, dysesthesia, burning sensation and

itching were less frequent (8%). For some patients pain and discomfort are so severe that they overshadow the other problems caused by the disease. Since pain is known to contribute to depression in elderly people in general [85], it is likely that such an association also exists in patients with PD. However, very few studies have explored this hypothesis, and the available studies are based on small and selected samples and have reported inconsistent results [86 87]. Pain was among the major predictors of impaired quality of life in patients with PD [88]. The complexity and pathophysiology of pain in PD still remains poorly understood. Thus, given the potential treatment implications, there is a need for further studies to explore the association between pain and depression in PD.

6.3 Brain changes of depression in PD

Patients who are later diagnosed with PD are more likely to have suffered from a previous depression than people who do not develop PD [89]. This can only be explained by biological risk factors. These individuals do not know that they will get the disease, they do not suffer from disabling symptoms, thus, there is no psychological stress related to the disease yet. Therefore, in addition to being an understandable psychological reaction to the disease and functional impairment, depression in PD is probably also etiologically related to disease specific factors. Several of the brain lesions in PD have been discussed as potential contributors to depression in the general population. In the following, I will focus on some of these potential disease specific pathways, which have been explored in autopsy and imaging studies as well as genetic and cerebrospinal fluid studies.

6.3.1 Serotonin

Since the first studies into the pathophysiology of PD, the involvement of non-dopaminergic neurotransmitter systems has repeatedly been described [90-93], reviewed by Leentjens [94]. Serotonergic dysfunction is associated with idiopathic depression, although the relative importance for the etiology of depression is not yet clear. Given

the serotonergic model of depression [95], it seemed plausible to examine serotonergic mechanisms and their relationship to depression in PD as well. Mayeux and co-workers were prompted to enunciate the "serotonin hypothesis" by their own finding of decreased concentrations of 5-hydroxyindolacetic acid (5-HIAA), a serotonin metabolite, in the cerebrospinal fluid of depressed PD patients [96]. This finding was later replicated by Mayeux itself [47], while Kuhn et al. could not confirm it [97]. However, several other neurochemical, neuropathological or imaging studies, in vivo or post-mortem supported the serotonergic theory.

Depression has been reported to be associated with genetically polymorphisms, particularly of the serotonergic systems. Patients with the short allele of the serotonin transporter promotor scored significantly higher on both depression and anxiety measured by the Hamilton Depression and Anxiety Scales [98 99]. Neurochemical involvement seems to vary between patients, depending on how much neurodegeneration has progressed in the relevant brain areas. More severe serotonergic neuronal cell loss in the dorsal raphé nucleus (DRN) was observed in PD patients with depression [100]. Reduced echogenicity using transcranial sonography (TCS) in the mesencephalic raphé, also representing loss of serotonergic neurons and suggesting an involvement of the basal limbic system, was found to be associated with depression in PD [101]. Using postmortem immunohistochemical analysis, Halliday et al. reported the first chemically identified loss of serotonin neurons in the median raphe nucleus of the pons and of substance P-containing preganglionic neurons in the dorsal motor vagal nucleus [102]. It can be speculated, that such loss of serotonergic neurons may partly explain depression.

^{11}C WAY-100635 and PET reveals reduction in nucleus raphé 5-HT(1A) receptor binding in both depressed and non-depressed PD patients, but depressed patients have a greater reduction in cortical binding, reflecting post-synaptic 5-HT_{1A} receptor dysfunction and supporting previous indirect evidence that serotonergic neurotransmission is decreased in PD [103]. However, given the therapeutic potential of

manipulating serotonergic receptor systems, their relationship with depression in PD needs to be further explored.

6.3.2 Noradrenalin

Noradrenaline has been suggested to be associated with symptoms of idiopathic depression [104]. The locus coeruleus is the major noradrenergic structure in the brain. From there, widespread noradrenergic neurons project to limbic areas and other regions. Greater degeneration within the locus coeruleus in depressed versus non-depressed PD patients has been reported [105].

Increased $\alpha 1$ and $\beta 1$ receptors and decreased $\alpha 2$ receptors have been described in prefrontal cortex of demented and depressed PD patients and seem to be related to lesion of the noradrenergic pathways from the locus coeruleus to the cortex [106]. Surprisingly, loss of neurons in the locus coeruleus was found in the caudal portion of the nucleus, which projects to the spinal cord. Remy et al. employed ^{11}C-RTI-32 PET to compare depressed with non-depressed PD patients [107]. ^{11}C-RTI-32 binds mainly to the dopamine transporter (DAT) in the striatum and a decrease of ^{11}C-RTI-32 binding reflects loss of catecholaminergic innervation in the corresponding regions of the brain. In this study, the depressed group had lower ^{11}C-RTI-32 binding than the non-depressed group in the locus coeruleus and in several regions of the limbic system including the anterior cingulate cortex, the thalamus, the amygdala and the ventral striatum. The authors concluded that a specific loss of dopamine and noradrenaline innervations of the limbic system may be crucial for the etiology of depression in PD.

6.3.3 Dopamine

Depression has also been linked to the dopamine system, and one theory of depression in PD is the “dopaminergic” hypothesis which was introduced by Fibiger [108]. This theory was based on evidence from several studies indicating that the mesolimbic-mesocortical dopamine projections play an important role in reward and

reinforcement processes in both animals and humans. Fibiger linked the fact that mesolimbic and mesocortical dopamine projections degenerate in PD to the reduced ability to experience pleasure or reward (i.e. anhedonia) as cardinal features of PD and suggested that damage to these reward-related systems may contribute directly to the high incidence of depression in PD [108].

In the earliest stages of the disease, before the onset of motor symptoms, mesocortical, and mesolimbic dopaminergic pathways are also affected [109]. These projections mediate self reward mechanisms, and damages here result in a reduced ability to experience pleasure or reward (i.e. anhedonia), a core symptom of depression.

Both serotonergic and cholinergic systems have an inhibitory effect on dopamine, and a reduction in the activity of serotonergic and cholinergic systems can compensate the dopaminergic lesions initially. However, subsequently, cholinergic and noradrenergic neurons begin to degenerate, albeit to a less extent. These processes may be relevant for the development of depression and may also explain why depression often precedes the motor symptoms.

The limbic system with its nuclei and connections is a crucial anatomical substrate for emotions. These limbic centres and nuclei are supplied with dopaminergic innervation arising from the ventral tegmental area (field A10). In PD there is variable loss of dopaminergic neurons in the ventral tegmental area (VTA) [110], thus, the connections with the limbic system and also the orbitofrontal cortex are interfered [111]. Winter et al. tested the influence of dopaminergic systems and their interrelationship with serotonergic systems in depressionlike behavior in a rodent model. Lesions in the substantia nigra pars compacta (SNc) and VTA increased depressive-like behavior in rats. Both citalopram and l-Dopa could reduce such behavior [112]. This suggests a direct involvement of dopaminergic lesions of either the SNc or the VTA but also serotonergic pathways in dopaminergic cell loss-induced depression.

Tyrosine hydroxylase (TH) is the enzyme responsible for catalyzing the conversion of the amino acid L-tyrosine to DOPA. DOPA is a precursor for dopamine which in turn is a precursor for noradrenaline. The nigrostriatal loss of TH, dopamine and dopaminergic neurons in PD lead to changes, which may also directly or indirectly damage the forebrain catecholamine fibers and induce depression.

The reported efficacy of dopamine agonists, especially pramipexole, against depression in PD (see below under management) also support the dopaminergic hypothesis.

6.3.4 Acetylcholine

Evidence from epidemiological [25] and pathophysiological studies [113 114] suggest a relationship between depression and dementia in PD. In longitudinal studies, depressed PD patients had greater cognitive decline compared with non-depressed patients [45 115]. Depression in PD is associated with a quantitative but not qualitative worsening of cognitive deficits [116]. This suggests that a common mechanism might underlie both the affective and the cognitive disturbances. Bohnen et al. reported in vivo findings suggesting that cholinergic degeneration may play a significant role in the cognitive decline in PD [117]. Therefore, the same group raised the question whether also depression is, at least in part, associated with cholinergic hypofunction. In dynamic PET studies, applying the [11C]methyl-4-piperidinyl propionate (PMP) radioligand, a selective substrate for AChE hydrolysis, an association between depressive symptoms and cortical cholinergic denervation was found, even after controlling for cognitive impairment [118].

If depression was a risk factor for dementia, two theoretical explanations for this are (1) the comorbid mood disorder is an expression of more widespread neurodegeneration, or (2) the treatment used for the depression contributes to the pathological process leading to dementia. Regarding the latter, tricyclic antidepressants with their anticholinergic properties may influence cognition both due

to the cholinergic blockade, which is associated both with cognition and depression in PD [118], but also with an accumulation of Alzheimer-like pathology [119].

Loss of cholinergic neurons occurs early in PD, and is considered to be a key factor in the development of dementia in PD [120]. Not surprisingly therefore, there is evidence from clinical studies that use of anticholinergic drugs is a risk factor for dementia in the general population [121] and worsening cognition in people with dementia [122 123], but very few studies exist in PD. Preliminary data from a small cross-sectional study indicate such an effect in PD [124]. This is consistent with findings that PD patients who had received long-term treatment with anticholinergic drugs had significantly higher cortical plaque and tangle densities compared to patients either untreated or receiving only short-term treatment [119]. Prospective, longitudinal studies are needed to explore the hypothesis that tricyclic antidepressants and other drugs with anticholinergic activity contribute to cognitive decline in PD. This is of particular relevance given the recent trial suggesting that nortriptyline is effective for depression in PD [125].

6.4 Structural and functional imaging

The recent development of a range of novel imaging technologies have contributed importantly to the investigation of brain changes associated with clinical symptoms in PD. To image the many structural and neurochemical changes in PD means either mapping alterations in brain structure or function. MRI can reveal structural changes like volume reductions. Functional imaging (Positron Emission Tomography - PET, single-photon emission CT [SPECT], functional MRI, and proton magnetic resonance spectroscopy) is applied to detect and characterize regional changes in brain blood flow, metabolism, and receptor availability or binding [126]. Structural MRI studies have demonstrated an association between regional atrophy and dementia [127] and mild cognitive impairment [128] (Beyer), but have not yet contributed to the brain changes underlying depression in PD.

Experimental studies have shown that diffusion tensor MRI (DTI) may contribute to the early diagnosis of Parkinson's disease (PD) and that fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values on DTI in the basal ganglia and frontal areas are different in PD patients compared with healthy controls [129]. In a study comparing PD patients with and without depression, the depressed subjects showed significant reductions in FA values in the bilateral anterior cingulate bundles [130].

As mentioned above, Lewy body pathology can affect the serotonergic cells in the median raphe [13]. However, a positron emission tomography study using 123I-beta-CIT SPECT failed to show a relationship between serotonergic median raphe HT1A binding or brainstem serotonin transporter (SERT) binding and the presence of depression in PD [131] . The finding of reduced frontal 5-HT1A binding in PD patients with depression is consistent with previous reports from Mayberg et al. who, using PET studies, found regional cerebral glucose metabolism reduced in depressed compared with nondepressed patients with PD [132]. The authors suggested that depression in PD is associated with dysfunction in the caudate and orbital-inferior area of the frontal lobe and that disruption of basal ganglia circuits involving the inferior region of the frontal lobe may affect the regulation of mood.
Studies using transcranial sonography (TCS) have provided evidence of alterations in the mesencephalic midline structures in patients with unipolar depression and depression in Parkinson's disease (PD). Berg et al. examined 31 PD patients with MRI and transcranial sonography (TCS). A significant reduction in mesencephalic midline echogenicity of depressed compared to nondepressed PD patients was detected on TCS images [101]. Brainstem midline structures comprise fiber tracts and nuclei of the basal limbic system. Following this, the authors interpreted their finding as supporting the hypothesis that the basal limbic system is involved in mood disorders in PD.

7. Management of depression in PD

During the last three decades, several new treatment options for the management of depression were described. Novel psychosocial, psychotherapeutic and pharmacologic strategies have significantly transformed the choice of treatment of the depressive patient. Similarly, since the introduction of "first-generation" antidepressants, the tricyclic drugs and monoamine oxidase inhibitors, the number of different antidepressant drugs has grown dramatically. Newer classes of drugs include the selective serotonin reuptake inhibitors (SSRI), serotonin-noradrenalin reuptake inhibitors (SNRI), dopamine-noradrenalin reuptake inhibitors, serotonin modulators, noradrenalin-serotonin modulators, and selective noradrenalin reuptake inhibitors (NRI). Compared with traditional antidepressant drugs, newer drug classes such as SSRIs and SNRIs offer improved tolerability to therapy with a high level of efficacy. But all antidepressants produce unwanted effects including drowsiness, dry mouth and urinary retention and cardiac arrhythmias, gastro-intestinal upset and others, especially in the elderly patient with comorbid conditions such as PD. The choice of an antidepressant is guided not only by its efficacy, but should also take into consideration safety and potential side effects.

However, in patients with PD and depression, the choice of treatment is difficult due to the limited empirical evidence to support treatment strategies. This was highlighted in a Cochrane review in 2003 [133]. Although some evidence was added since then, there is still limited evidence available.

Depressive symptoms in PD often remain undiagnosed and untreated. In one study, 37% of subjects with PD receiving an antidepressant still met criteria for Major depression, thus, even when delivered; treatment is often inadequate or ineffective [39]. Furthermore, psychosocial support or psychotherapy was not provided to patients not responding on pharmacotherapy. There are several possible explanations for this situation, including poor cooperation with psychiatric services, misinterpretation of

symptoms or ignorance toward psychiatric symptoms. Moreover, the lack of evidence of treatment strategies may result in a kind of nihilism in the face of depression in PD. In the following, the existing evidence on treatment of depression in PD is reviewed.

7.1 Psychosocial and psychotherapeutic strategies

Very few systematic studies have explored the effect psychosocial treatment strategies on the development or treatment of depression in PD. During the course of PD, many patients with PD become dependent from care. Dealing with the negative consequences of PD and managing the functional impairment, especially in late stages of the disease, is important and might reduce the risk for depression in some patients. Negative consequences of the disease, such as difficulty in dressing, difficulty turning, falls, autonomic disturbance particularly urinary incontinence have been found to be associated with depression and predict poor quality of life [88]. An association between lack of social support and depression has been found in elderly people [134]. Sufficient social support is an effective buffer against stress related to suffering. Cheng et al. investigated the correlation of social support, measured by a standardized scale, with depression in PD and corrected for potential confounding factors such as disease severity and duration. Unfortunately, 'social support' was not defined in detail, but both subjective experience and objective circumstances were considered. The results suggest that adequate social support may improve depression [135]. 'Social support' can probably be provided by professional and informal caregivers such as family or friends. Whether Cognitive Behavioral Therapy (CBT) is effective against depression in people with this complex degenerative condition is still an open question. The available evidence is not strong, but we assume that the efficacy literature of psychotherapies in older adults with other chronic diseases also applies to the PD population [136]. Patients with PD and depression are a vulnerable, often neglected group. This would appear to provide a sound clinical basis to attempt to confirm the validity of CBT in this population [137].

7.2 Pharmacotherapy

A review on the treatment of depression published by the Quality Standards Subcommittee of the American Academy of Neurology in 2006 identified 36 studies, of which only 6 studies fulfilled the defined criteria of study design and outcome measures [138]. Only one study qualified for Class I evidence (randomized, doubleblind, placebo-controlled) [139], two studies for Class II [140 141] and three for Class III evidence [142-144]. All were randomized controlled trials, and included amitriptyline, nortriptyline, citalopram, fluoxetine, sertraline, pergolide, pramipexole, and nefazodone. Three of the studies used placebo comparators. No significant benefit of citalopram or sertraline was found over placebo, but lack of benefit was maybe related to methodological limitations [139 141]. Fluoxetine and nefazodone revealed equal efficacy for depression, but this study was not placebo-controlled, and thus, one cannot conclude whether either drug was effective [144]. Patients treated with pramipexole improved significantly more than patients treated with pergolide on measures assessing depression [143]. In a study comparing amitriptyline with fluoxetine, patients randomized to amitriptyline significantly improved (change in HAM-D of 14), while those treated with fluoxetine did not [142]. However, dropout rates were greater in the amitriptyline group due to side effects. In an early study of nortriptyline, the authors report a significant improvement in depression compared to placebo [140]. However, it is impossible from the publication to determine if this difference was significant. After discussion of the strengths and limitations of the most relevant trials, it was concluded, that “there is insufficient evidence to make recommendations regarding treatments for depression in PD” [138].

Weintraub et al. reviewed the available antidepressant studies in PD [145]. Relevant studies were analyzed and effect sizes were compared with those from antidepressant studies in elderly patients without PD. While active treatment in general was superior to placebo in depressed elderly patients without PD, this was not the case in PD. However, both active treatment and placebo had large effect sizes in PD.

Traditionally, effect size or *Cohen's d* index is the difference between patient and control group means, within each study or comparison, expressed in standard deviation units. Weintraub et al. used "effect size" as the change from baseline for each study. This large placebo effect was also shown in two of the very few adequately designed placebo-controlled randomized trials with SSRI in depressed PD patients [139] [141]. Old age and a diagnosis of major depression seem to be associated with a better response to any antidepressant treatment. Newer antidepressants are well tolerated in PD. The repeated observation that SSRIs is less effective for depression in PD than in non-PD patients is used as an argument against an exclusive serotonergic hypothesis of depression in PD [145].

A recent placebo-controlled trial, funded by the US National Institute of Health, compared nortriptyline up to 75 mg, paroxetine CR up to 37,5 mg, and placebo in patients with PD and depression [146]. Although the largest study in this population, even this trial is small by clinical trial standards. Efficacy was assessed by the change in HAM-D. Compared to placebo, the treatment effect of nortriptyline was significant for both the overall change in the HAM-D and in the percentage of responders, while that of paroxetine CR was not. The effect size of nortriptyline was large (1.20, based on HAM-D) and the number needed to treat for nortriptyline was 3.5 based on response status. In addition, nortriptyline improved social functioning, sleep, and anxiety. Patients on paroxetine CR had significantly more side effects than placebo, but those on nortriptyline did not, although both drugs were well tolerated. Nortriptyline acts as a dual reuptake inhibitor, inhibiting reuptake of both serotonin and noradrenalin, whereas paroxetine CR is a selective serotonin re-uptake inhibitor. These results provide additional evidence to the theory that the noradrenergic system is involved in depression in PD [107], and the authors speculate that the noradrenalin transporters may play a role. The noradrenalin reuptake transporter is responsible for removing dopamine from the synapse in the prefrontal cortex. If these transporters are blocked by nortriptyline, dopamine levels can increase, facilitating dopaminergic function. Until now, SSRI has been the first line choice for depression in PD. The results of this trial suggest a re-evaluation of this clinical practice.

Dopamine agonists, especially pramipexole, have shown anxiolytic, antidepressive and antianhedonic effects in experimental and clinical investigations [147-150]. These effects are likely related to dopamine agonists having specific action on D(2) and D(3) receptors in the mesolimbic system and prefrontal cortex [151]. Recently, pramipexole was even recommended as a first-line treatment in patients with PD and depression [152]. Treatment with dopaminergic drugs does not, however, consistently alleviate depression in PD [153]

7.3 Biological, non-pharmacological agents

7.3.1 Electroconvulsive therapy

Electroconvulsive therapy (ECT) is the most effective treatment of idiopathic major depression and has been recommended for treatment of both depression and motor symptoms in PD. Faber and Trimble reviewed 27 studies published until 1991 and concluded that approximately 70% of PD patients showed improvement in psychiatric disturbances (including depression) across the studies reviewed [154]. Only one of the 27 was a controlled study, which included 11 patients with PD but without psychiatric co-morbidity. The majority of studies were single case reports and none of the other studies included more than 7 patients. In a retrospective chart review Moellentine et al. studied 25 patients with PD receiving ECT for psychiatric co-morbidity (major depression with and without psychosis, anxiety disorder and dementia). The results were compared with those of 25 patients without a comorbid neurological condition [155]. In this study, ECT improved depression, anxiety, cognitive status and overall global functioning in both groups. In addition, motor functions were improved in 56% of the PD patients. However, 56% of the PD patients experienced complications compared to only 12% in the comparison group. The positive response to ECT in PD is often rapid [156 157] but may be short-lived. However, maintenance ECT may contribute to a sustained effect [158]. Transitory cognitive worsening is the most common side-effect, and some patients may experience

delirium, urinary retention, choreiform movements, and falling [155 159 160]. The precise mechanism of action of ECT on both depression and motor symptoms is unknown; one hypothesis is that ECT stimulates different neurotransmitter systems, including the D2 receptor. The seizures induced by ECT can increase both noradrenaline and serotonin levels in the brain [161]. Noradrenaline increases dopamine levels in the basal ganglia which may explain the positive effects on motor function [162].

7.3.2 Transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) of the cerebral cortex has shown some antidepressive effect in treatment resistant patients with idiopathic depression [163]. RTMS has also been suggested as a potential treatment option for both depression and the movement disorder in PD. Cardoso et al. compared the neural changes after successful therapy of depression in PD with TMS with the changes after successful treatment with fluoxetine by event-related functional magnetic resonance imaging (fMRI) methods [164].

Both rTMS and fluoxetine had a significant, similar mood improvement. Reduction of depressive symptoms was related to reduced activity in selected brain areas after rTMS, whereas increases were found in other areas after fluoxetine treatment, leading the authors to conclude that antidepressant effects of rTMS and fluoxetine in PD are associated with changes in different areas of the depression-related neural network.

7.3.3 Deep brain stimulation

During the last 20 years, deep brain stimulation (DBS) of selected nuclei such as subthalamic or thalamus, has become established as a safe and efficacious treatment option in movement disorders [165]. Indications for DBS are PD, essential tremor and dystonia. Case reports suggest that major depression and also obsessive-compulsive disorder may respond to DBS [166]. On the other side, depression, hallucinations, cognitive impairment, mania, and behaviour change were reported as side effects after DBS [166]. Particularly thalamic and GPi stimulation may cause suicidal

behaviour. Therefore, patients should be monitored cautiously for suicidal thoughts pre- and post-operatively.

In summary, until recently the evidence for treating depression in PD has been very limited. The recent study suggesting that nortriptyline is effective is encouraging, however, but the findings need to be confirmed in larger studies. Although other treatment, such as ECT and psychotherapy, may be helpful for some patients, the evidence is still very limited.

8. This study

8.1 Aims of this study

The overall aim of this project is to explore key aspects of depression in PD where there is currently limited knowledge, including epidemiology, clinical profile, classification, aetiology and treatment-related factors. To obtain such information we have

1) In study 1 performed a systematic review of available epidemiological data and explored the frequency of depression in PD

2) In study 2 explored the symptom profile of depression in PD, testing the hypothesis that depression in PD differs from that in elderly depressed people without PD

3) In study 3 explored depressive symptoms in patients with PD without major depression, i.e. sub-threshold depression, and examined its relationship to other clinical features in PD.

4) In study 4 examined the relationship between pain and depression in PD, testing the hypothesis that pain is significantly associated with depression in PD.

5) In study 5 examined the relationship between the serotonin systems in different brain areas with depression, testing the hypothesis that depression in PD is related to changes in 5HT1a receptors in neocortical regions.

6) In study 6 explored the use of drugs with anticholinergic properties in patients with PD to test the hypothesis that treatment with tricyclic antidepressants and other drugs with anticholinergic activity is associated with a more rapid cognitive decline.

8.2 Methods

8.2.1 Design

The present studies are parts of a research programme on different aspects of PD, consisting of a sequence or combination of overlapping studies with different study designs. Cross-sectional survey was used for studies 2 and 3. Studies 4 and 6 were longitudinal cohort studies. Study 1 was a systematic review and Study 5 a clinical-pathological study.

8.2.2 Methods for the systematic review

A systematic literature search was carried out in Medline using PubMed. The entire time scale was used up to February 2007. Key words were "Parkinson", "depression," "prevalence", and "incidence." In total 272 articles were retrieved. After exclusion of papers with limited methods, 104 articles were included and underwent quality assessment. The included articles were read in full and quality rated by three of the authors Jennifer Reijnders, Uwe Ehrt and Dag Aarsland. When the raters could not agree on a rating, consensus was achieved after discussion. If consensus was not reached, articles were reassessed by the last author Albert Leentjens who made a final decision. The quality assessment used criteria adapted from Aarsland et al. [167].

8.2.3 Patient selection

Several different patient and control samples were used for this thesis. Most studies were fully or in part based on a community-based prevalence sample, sample 1. In September 1992 a prevalence study was initialized with the aim to detect all patients with PD in Rogaland County, Western Norway. Information from general practitioners, nursing homes, district nurses, health workers and the Rogaland Parkinson's Society was collected, and an extensive search in relevant hospital files was performed to achieve complete ascertainment of patients with PD in this region. About 400 patients with symptoms suspect for PD were systematically registered and

examined by neurologists, who were proficient in diagnosing and treating movement disorders. In the first instance, 245 out of the 400 were diagnosed with PD according to clinical criteria published by Larsen et al. [2]. The total crude and age-adjusted PD prevalence rates were calculated to be 110.9/100 000 and 102.4/100 000, respectively [168]. As part of this study, 100 healthy elderly people were randomly selected and represent a healthy control group.

The patients included were examined with a standardized examination program in 1993, 1997, 2001 and yearly after 2001. In this study we used only data from the first three assessment points. During follow up, 6 patients were re-diagnosed as not suffering from idiopathic PD and therefore excluded from analysis. From some patients, we could not collect complete data at follow up. Those had to be excluded from some but not all of the longitudinal studies.

Study 4 and 6 are exclusively based on Sample 1, and Study 4 also included the healthy control group. In other studies, we included control groups or included data from other collaborating research centres. The 111 PD patients of the subsample from The Netherlands in study 2 were recruited from the neurological outpatient department in Maastricht and were assessed between 1995 and 2001. A comparison group consisting of 100 consecutively patients referred to the Old Age Psychiatry outpatient clinic at Stavanger University Hospital, Norway suffering from at least mild depressive symptoms with a MADRS score ≥7, were also included. In study 3, Patients were recruited from research centres in 11 European countries and Canada to participate in a multicentre trial of rivastigmine for Parkinson's disease Dementia (PDD).

8.2.4 Diagnosis and rating of PD

In sample 1, PD was diagnosed by neurologists with special expertise in movement disorders according to criteria published by Larsen et al. [2]. Until now, 27 of the total PD population have come to autopsy, and the diagnosis of PD was confirmed neuropathologically in all cases [169] (R. Perry, personal communication). The PD

patients of the Dutch sample from study 2 and the patients from study 3 were diagnosed on the basis of the UK-Parkinson's Disease Society Brain Bank (UK-PDS-BB) criteria [170]. The clinical examination of motor symptoms consisted of a complete Unified Parkinson's Disease Rating Scale (UPDRS) [5] and the Hoehn and Yahr disease staging [171]. Based on the UPDRS subscores, tremor-dominant (TD), akinetic-rigid (AR) and indifferent motor subtypes were defined, following procedures used in previous studies [172]. Furthermore, right and left side motor subscores were computed according to procedures published before, by adding the respective scores for right and left-sided motor symptoms on UPDRS items 20–26 [31]. These clinical subtypes were used in some analyses in studies 3 and 4.

8.2.5 Diagnosis and rating of depression

Depression was rated in sample 1 by a neurologist using the MADRS [173] and the Beck Depression Inventory (BDI) [174]. The MADRS was originally designed as an instrument, which should be particularly sensitive to psychopathological change resulting from drug treatment [173]. The ten items (apparent and reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, depressive and suicidal thoughts) are completed during a clinical interview. The clinician first asks broadly phrased questions about the topic of the item and afterwards more detailed ones which allow a precise severity rating (from 0-6). High inter-rater reliability was reported in several studies. Studies gave the impression that the MADRS performed comparably or even better than HADS or HRDS, in terms of general validity and reliability [175 12457]. The MADRS focuses mainly on psychic and less on somatic symptoms compared with several other scales, which is an advantage in settings where physically ill patients are assessed.

The BDI is a 21-question multiple-choice self-report inventory, one of the most widely used instruments for assessing presence and severity of depression, especially in a scientific context. The 21 items of the BDI intend to cover depressive symptoms in line with DSM-IV criteria. Each question has a set of at least four possible answer choices, ranging in intensity. For example: (0) I do not feel sad; (1) I feel sad; (2) I

am sad all the time and I can't snap out of it; (3) I am so sad or unhappy that I can't stand it. When the item is scored, a value of 0 to 3 is assigned for each answer and then the total score determines the severity of depression.

The BDI has a relatively broad coverage of the somatic symptoms of depression, which may lead to false-positive results among persons with physical illness. However, as described above, in our study we used cut-offs validated in PD patients which should reduce this concern.

Both instruments have been shown to be valid depression scales in patients with PD, and cut off scores are available to identify depressive disorders according to DSM IV criteria [176 177]. MADRS scores ≥18 and BDI scores ≥17 indicate the presence of major depression with relatively high specificity.

The MADRS was also used as rating scale for depression in the subsample from our collaboration centre in The Netherlands (study 2).

The patients from study 3 had no major depression according to exclusion criteria. To assess depression, item 4 of the 10-item Neuropsychiatric Inventory (NPI) was used [178]. The NPI addresses ten specific psychopathological, noncognitive domains, among them depression. Regarding depression, a positive answer on the introducing question “if the patient seems to be depressed or says that she/he is depressed” is the precondition to ask further. Then follow several questions focusing exclusively on the mood symptoms of depression. Does the patient often cry? Is he suffering from feelings of guilt, hopelessness, and suicidal ideas and so on. Finally, an informant rates the severity of depression on a scale from 1–3 and the frequency of depression from 1–4. A composite score is the product of frequency and severity, yielding a score ranging from 1–12. A score of 4 or higher is usually considered to represent clinically significant severity of symptoms.

8.2.6 Diagnosis of dementia and cognitive assessment

Cognition was assessed by means of the Mini Mental State Examination (MMSE) scores [179] and in study 3 additionally with the Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS–cog) [180]. These are cognitive screening tests designed primarily to assess cognitive decline in patients with Alzheimer's disease, but in particular the MMSE has also frequently been used for PD. The scales focus on memory, language, praxis, attention and other cognitive abilities. High scores represent high cognitive functioning on the MMSE and low performance on the ADAS.

8.2.7 Techniques used to study brain tissue

Post-mortem brain tissue was obtained from 27 patients with dementia and parkinsonism, consisting of 10 patients with dementia with Lewy bodies (DLB) from the Newcastle (UK) dementia case register study [181] and 17 PDD patients from sample 1, along with 9 controls. Coronal brain slices were flash frozen in liquid nitrogen before being stored at – 70 °C. Inferior (Brodmann area, BA20) and superior (BA36) temporal cortices were removed. Brain membranes were prepared [182] and binding of [3 H]8-hydroxy-2- ipropylaminotetralin (8-OH-DPAT) to the 5-HT1A receptor was performed following the methodology previously described [183].

8.3 Results

8.3.1 Study 1

We identified 104 relevant studies, 22 studies focused primarily on the prevalence of depression in PD; the remaining 82 studies had other primary objectives but also reported on the prevalence of depression in the study sample. There were 16 population-based studies, 3 studies in general practices, 2 studies in nursing homes, 71 studies on outpatient samples, 5 studies in hospital inpatient settings and 7 studies

used patients from different settings. Different diagnostic criteria for depression were used: 31 studies used a structured or semistructured interview to establish DSM criteria, 20 studies used DSM criteria without a structured interview, 38 studies used a cut-off score on a depression rating scale, and 15 studies used no or inadequate criteria to diagnose depression.

Of the 104 studies, 51 fulfilled our operationalized quality criteria and were included. After excluding studies based on the same, cumulative or joint databases, 36 studies were included in the review. Overall, major depressive disorder was present in 17% of patients, minor depression in 22%, and dysthymia in 13%. The prevalence of clinically significant depressive symptoms was 35%. For major depressive disorder, population studies report significantly lower prevalence rates than studies in outpatient samples and hospital inpatient settings. The reported prevalence of major depressive disorder in studies using a structured or semi structured interview to establish DSM criteria ranges from 2.3% to 55.6% with a weighted mean of 19%. In studies using DSM criteria without a structured interview the prevalence rates of major depressive disorder ranges from 2.9% to 7.7% with a weighted mean of 7%. In studies using a cut-off on a depression rating scale, the rates were higher, between 13% and 89% with a weighted mean of 42%.

8.3.2 Study 2

One hundred and forty-five patients with PD, 76 cases from sample 1 and 69 cases from our collaboration group in Maastricht, The Netherlands, fulfilled the inclusion criteria. The depressed comparison subjects without PD were older than the patients with PD, but did not differ significantly for sex distribution, MMSE score and total MADRS score. The comparison subjects had MD (mild, moderate or severe), some of them were at time of assessment in partial remission. Fourteen patients with PD in the Stavanger group (18.4%) received antidepressants (13.2% a TCA, and 5.2% mianserine), whereas 83% of the controls took antidepressants (45% an SSRI, 24% mianserine, 13% TCA, 2% lithium, and 25% other antidepressants). Medication data

were not available for the Maastricht cohort. PD patients or control subjects who received antidepressant medication differed significantly from subjects not receiving antidepressants with respect to gender distribution, age, MMSE score, and MADRS single item and sum scores. All MADRS sub items were significantly correlated with the sum score in both PD and non-PD patients (Pearson coefficient r range 0.26–0.79, all p-values <0.005). 43.5% of the Maastricht sample fulfilled MD criteria, compared to 10.5% of the Stavanger patients with PD (taken together 26.2%). Since the patients from Maastricht were more depressed, we formulated a model with study site as covariate (MANCOVA). The omnibus analysis showed significant greater between-group than within-group differences regarding the MADRS score profile In this model patients with PD had less reported sadness, slightly less loss of energy,, more concentration problems, less feelings of guilt and lower score on item 8, disturbed affective reactivity (anhedonia).

8.3.3 Study 3

Depression item on the NPI was assessed in 538 patients (35% females) and these were included in the study. 116 patients (21.6%) had a NPI depression score ≥4 indicating clinically relevant depressive symptomatology, and constituted group with PD related dementia and depression. Depressed patients were more likely to be female (p=0.025), and were younger both at onset of PD (p=0.017) and at assessment (p=0.003) than non-depressed patients. They were more likely to receive antidepressants (41.4% vs. 22.5%; p<0.0001) and benzodiazepines (27.6% vs 17.3%; p=0.011) than non-depressed patients. Since female patients were more depressed than male patients, clinical correlates of depression were explored in male and female patients separately. There were no significant gender differences regarding age, age at onset, PD duration, UPDRS score, Hoehn and Yahr stage and NPI total score. However, male patients performed better on cognitive rating scales than female patients as demonstrated on the ADAScog score [mean 22.8 (SD 10.0) vs 25.5 (SD 10,5); t=2.852; p<0.005] and MMSE [sum score 19.6 (SD 3.9) vs. 18.7 (SD 3.6); t=2.585; p<0.01]. The association between depression and younger age both at

assessment and at onset of PD was confirmed in male ($p<0.01$) but did not hold true for female ($p=0.397$) patients. Similarly, males with left-sided parkinsonism scored higher on depression than those with right-sided PD [NPI item 4 score 1.99; SD 2.57 vs. 1.16; SD 1.92 ($p=0.014$)], whereas no difference between right- and left-sided PD was found in females ($p=0.23$).

8.3.4 Study 4

152 (67%) of the 227 included PD patients vs. 39% of the comparison subjects suffered from pain as assessed by the Nottingham Health Profile ($p<0.001$). PD patients with pain had more severe depressive symptoms, indicated by higher mean scores on both MADRS and BDI. Patients with pain and also had more severe motor symptoms, longer disease duration, and lower MMSE score than those without pain. No significant differences were found regarding sex distribution, age and use of analgesics. Even after adjustment for potential confounders, pain was significantly associated with BDI.

Both the MADRS ($p<0.00001$) and BDI sum score ($p<0.0005$) correlated significantly with pain. Multiple linear regression analyses with BDI and MADRS as dependent variables were significant even after adjusting for sex, age, PD duration, UPDRS III score and MMSE score. The effect of pain severity (partial correlation with depression severity) was significant in the model with MADRS ($p=0.014$) and a trend in the model with BDI ($p=0.056$).

Compared to patients with a tremor-dominant (TD) subtype, patients with an akinetic-rigid (AR) type more commonly reported pain (72 % vs. 48%; $p=0.002$). AR patients also had more severe depression according to MADRS sum score than TD patients ($p<0.0001$).

8.3.5 Study 5

67% (n=18) of the DLB/PDD patients had experienced clinically significant depression over the course of the illness (4 DLB, 14 PDD). 5HT1A density was 60% higher in BA36 in combined DLB/PDD patients with depression, compared to those without. This difference was significant (p=0.005). Subgroup analyses were hampered by the small sample sizes, but in the PDD group, 5- HT 1A density was significantly higher in BA36 in those with depression compared to the small number of patients without (p = 0.042). We could not detect a significant difference in 5-HT 1A density or affinity in either BA20 or BA36 between DLB subjects who had experienced depression during the course of the disease and subjects who had not.

8.3.6 Study 6

The 235 PD patients used a total of 99 drugs, and 29 of these drugs were classified as having clinical relevant anticholinergic activity (AA). At baseline, 102 of the 235 patients (43.4 %) received at least one drug with AA. The most frequently used drugs with AA were antidepressants (n=84), cardiovascular agents (n=80), anxiolytics and sedatives (n=61), and antipsychotics (n=44). Seventy-two subjects (30.6%) were taking more than one drug with AA. At baseline, patients taking AA agents had significantly lower cognition (MMSE median 25) and higher depression scores (MADRS median 9) than those not taking AA agents (28 and 6, respectively). Total AA load correlated significantly with MMSE (Spearman rho=-0.205, p=0.002) and MADRS (Spearman rho = 0.321, p<0.001). Using linear regression analysis, after adjusting for age and gender, MADRS (standardized beta 0.291, p<0.001) but not MMSE score remained significantly associated with the AA load in a linear regression analysis. In longitudinal analyses, the median change in MMSE over the full 8-year period in subjects who had used AA drugs at some point (n=62) was 8 points (IQR 16), whereas those who had not used AA drugs at any assessment (n=22), declined only 1 point (IQR 6.75). This difference was significant (Mann Whitney test z=-2.3, p=0.021). The correlation between total AA load during the 8

years (ie sum of AA load at all three assessments) and the change in MMSE score was significant (Spearman rho=0.26, p=0.017). In the linear regression analysis, after adjustment for potential confounders, the association between AA load and MMSE decline remained significant (Beta 0.154, SE 0.072, standardised Beta=0.217, p=0.036; total model F=5.4, p<0.001).

8.4 Discussion

8.4.1 Methodological critique

The primary goal of epidemiological research is to provide evidence on the incidence, prevalence and progression of diseases, and to find associations with risk factors in the population. For example, linkages between smoking and lung cancer or heart disease and the consumption of certain fats were found by epidemiological research. The careful interpretation of such data is the basis for the establishment of causality, and thus, a precondition for identifying groups at high risk or the development of both prevention and treatment strategies. Epidemiological data on the highest level of quality represent the general population. However, for several reasons, including resources, the researcher may have to lower one's ambitions and employ alternative methods. Such limitations may involve the patient selection and completeness of case-ascertainment, but also the case definition and diagnostic accuracy and methods of measurement. In the following I aim to mark some basic methodological topics and discuss critically the specific methodological problems in our study related to study design, patient selection, case definition and statistics.

8.4.2 Study design and patient selection

For a study to be methodologically sound and feasible in relation to the study purpose it is required to use the right design. There are some standard terms for study design

which are related to different epistemological levels. One can distinguish between experimental (such as double-blind randomised controlled trial) and observational studies, which can be retrospective record reviews or prospective studies. Furthermore, studies can be cross-sectional or longitudinal.

In this thesis, a variety of study designs were used to explore different aspects of PD and depression. First, a prevalence study (community-based) was conducted to estimate the prevalence of PD in the population of Rogaland/Norway. Subsequently, the cohort was examined longitudinally (longitudinal cohort study) over time. However, the assessments at a single point in 1993, 1997, and 2001 and so on, are cross-sectional studies. So, even if some of the studies presented in this thesis represent cross-sectional data, it is important to stress that it contributes to the quality of data, that these data are based on a unselected cohort followed prospectively for many years. This increases the diagnostic accuracy of PD and dementia.

Another matter of discussion is, if the chosen operational procedure employed in a prevalence study really results in a complete detection of all subjects of interest. Moreover, it is important to know where the study subjects come from and if they are an appropriate group to study to address the research question of interest. It is of interest to know how the study subjects are selected. Are they a sub-sample from a larger population based study or are they taken from a selected randomized controlled trial? A typical selection bias is to base studies on groups from in- or outpatient samples or include patients based on retrospective hospital charts. Such samples are usually biased, since for example nursing home patients or patients treated by the general practitioner are underrepresented. Accordingly, such study samples may be younger and have more severe or more atypical features than the general population of patients.

In our study, to ensure a case-ascertainment as complete as possible, all available information regarding specific diseases were considered. This included hospital files, but also information from the Rogaland Parkinson's Society, all general practitioners, health workers, district nurses and nursing homes from the recruitment. However,

early cases not diagnosed yet were not included. In general, door-to-door surveys may be the best method with the highest level of response and they also ensure to target persons not consulting their general practitioner. However, taken our resources into consideration, we think, our approach of patient selection was the best possible and that nearly all individuals in our study area suffering from PD in January 1993 were included.

During the first years of follow up, the time interval between the study visits was four years. Such a long test-interval leads to relatively high attrition rate in this rather old and frail population, primarily due to death. Attrition due to other causes was very low. Thus, we think that even in our follow-up sample selective attrition is not a confounder, and that the group is representative for the PD population in the region.

8.4.3 Diagnosis of PD and psychometric methods

The application of appropriate diagnostic and rating instruments is another essential condition in epidemiological research. In our study, we aimed to apply standardized and well established instruments with adequate psychometric properties.

The diagnosis of PD is still based on clinical examination. With the exception of dopamine transporter scan, which was not available at the start of the main study, there are no biomarkers yet which can ascertain the diagnosis during lifetime. Clinical examination includes a careful disease history and the application of diagnostic criteria. One aim in epidemiological research is to detect all patients with the disease which has to be studied (sensitivity). For the experienced clinician, it is usually not difficult to identify patients with parkinsonism, although mild and atypical cases can be difficult to identify. It may be more difficult and therefore a larger methodological issue in PD research, to achieve high specificity, i.e. to exclude all those cases with conditions mimicking idiopathic PD, like parkinsonism in DLB or frontotemporal dementia , vascular parkinsonism, parkinsonism as side effect after

administration of specific drugs, essential tremor and parkinsonism as clinical syndrome in the so-called Parkinson plus syndromes.

The gold standard in the diagnosis of PD is the application of UK-Parkinson's Disease Society Brain Bank (UK-PDS-BB) criteria [170]. These criteria were used in study 2 and 3. In our sample 1, PD was diagnosed regarding to diagnostic criteria published by Larsen et al. [2]. When published in 1993, these criteria were one of the first attempts to systematize the diagnosis of PD, and their accuracy was later supported neuropathologically in 22 cases that came to autopsy [169], and subsequently by a further 7 cases (Robert Perry, personal communication). Moreover, there are no substantial differences between UK-PDS-BB criteria and the criteria used in our study.

Another important term in epidemiologic research is *validity*. To study the validity of a rating instrument means to investigate the extent to which the instrument measures what we want it to measure. For example does a questionnaire designed to measure depression on an ordinal scale actually measure depression as defined by diagnostic criteria? And even if validity has been demonstrated previously, has it been demonstrated in the setting we want to apply it in? A scale which has been validated for use among younger adults may not be valid if used among elderly patients with neurological diseases or in other countries. The depression rating scales we used in our study are widely used and accepted depression measures. They have subsequently been validated for patients with PD against the gold standard, DSM IV criteria for "depressive disorder". Cut-offs for the use of both MADRS (14/15) and BDI (13/14) to discriminate between depressed and non-depressed subjects have been recommended [176 177]. At lower cut-offs, the scales have higher sensitivity and are useful screening instruments, at the cost of a low specificity. Vice versa, at higher cut-offs the specificity becomes higher, but the sensitivity lower. These features suggest that they are good diagnostic instruments.

While the MADRS represents a clinician-based rating scale, the BDI is a self-report method. The choice between clinician-based or self-rating instruments is complex.

The latter are easier to administrate and do not require skilled interviewers. But their use as diagnostic instruments is restricted by confounders like personality traits. On the other hand, for methods of measurement in which the role of an observer is crucial, inter-rater reliability (IRR) should be considered. This is relevant if several raters administer an instrument, a common situation in multi-centre clinical trials or longitudinal studies. Two observers may rate the same phenomenon different, if not trained sufficiently. Another situation reducing IRR is when the subject answers differently dependent on the social style or personality of the interviewer or the presentation of particular questions (interviewer bias). The use of fixed wording questions is one method reducing interviewer bias.

Generally, it is important to improve agreement between observers by training and using the same observer when making 'before' and 'after' measurements on the same subject. In our department, we are training the psychometric measures we use regularly, which enhances IRR. However, no systematic attempts to establish IRR coefficients were made in the current studies.

In study 3, we examined depressive symptoms in patients drawn from a randomized controlled trial, who did not suffer from “major depression”. Our study purpose was planned post-hoc, i.e. after the original study was conducted. The depression item from the NPI [178], was available to assess depression. The psychometric properties of the NPI depression item have not yet been established in PD. One strength of this item is its focus on the psychological and behavioural sign and symptoms of sadness and guilt rather than somatic items or anxiety. The instrument is highly structured with scripted questions and anchored responses. However, one should not diagnose specific psychiatric disorders based upon the NPI, although we believe that it can be used to detect clinical relevant depressive symptoms. In fact, the introducing question in the NPI depression domain: “does the patient seem depressed or does he say that he is depressed” is commensurable with the question which previously has been shown to perform remarkably well in depression case-finding studies [184]. In other

words, it is likely that a person, who answers “yes” on the question “are you depressed?” in fact, is depressed.

In study 4 on the relationship between pain and depression, the items related to pain were selected from the NHP. A genuine pain measure was not used. Originally, the NHP was constructed to measure “perceived health”. However, in studies to estimate its concurrent validity, the NHP pain section correlated with 0.78 with the McGill Pain Questionnaire [175], supporting its validity as a measure of pain.

Cognitive functioning was assessed with MMSE in our studies. This well studied instrument is used all over the world and is brief enough for routine clinical use. In general, validity results appear to be good [185]. Some limitations have to been taken into consideration. The MMSE has floor and ceiling effects. Low educational level predicts lower scores. It may also miss impairments resulting from right hemisphere lesions [186]. However, the biggest concern in our study is related to the limited discriminant validity of the MMSE when used to assess cognitive impairment of the subcortical type, which is typical in PD. Especially in the early stages of dementia, these patients more often exhibit executive and visuo-spatial impairment, domains that are rather underrepresented in the MMSE, which may lead to false negative results. In studies examining this issue, patients with PD performed as well as normal control subjects on the MMSE. Therefore it is recommended to add more specific instruments designed for the assessment of frontal or subcortical dysfunction such as Mattis Dementia Rating Scale [187] . More recently, more specific cognitive batteries have been developed, including the Montreal cognitive assessment (MoCA) [188] and Parkinson’s disease – cognitive rating scale (PD-CRS) [189], which should be employed in future studies.

8.4.4 Findings in context

Study 1 is the first extensive review of prevalence studies of depression in PD taking the different settings and diagnostic approaches of the various studies into account. Two earlier reviews on the prevalence of depression in PD have been published, but

those did not perform a quality assessment before including studies. Studies which did not sufficiently describe patient selection or diagnostic criteria used for depression and PD were excluded. The average prevalence of major depressive disorder in PD is 17%, the prevalence of dysthymia is 13%, while minor depression occurs more frequently in 22% of PD patients. These prevalence numbers are somewhat lower than previously reported [24], but our review nevertheless confirms that depression is a common complication in patients with PD. As expected, in studies from the general population the numbers are lower, while they are higher in hospital outpatient and inpatient settings. A review is influenced by the limitations of the included studies themselves. One limitation is the fact that the relationship between psychopharmacological medication and the prevalence rate of depressive disorder was not examined in most reviewed studies. The fact that PD patients may be successfully treated with an antidepressant may therefore have lead to under-reporting the frequency in this review. Another issue is the limited declaration of the time interval the reported prevalence numbers refer to. Many studies failed to distinguish precisely between present MD and MD in remission, which made it difficult to determinewhether the reported numbers were prevalence ore lifetime prevalence rates.

In our study on the depressive symptom profile, the clinical phenotype of depression in PD differed from that in depressed patients without PD, with less experienced sadness and guilt, and more anxiety and concentration difficulties. This is consistent with previous studies of depressed PD patients [49 52 190], studies which did not include non-PD patients. This suggests that there are different etiological mechanisms underlying depression in people with and without PD, or that the symptoms of PD influence the depression phenomenology. Energy loss was more marked in non-PD than PD patients. We know that apathy is not identical to depression [191], but the clinical distinction between “loss of energy” as a depressive symptom and apathy is difficult. Apathy is particularly common in PD [26], and therefore, our finding was unexpected. Possibly, PD patients underreport their “loss of energy” (apathy) because

they may not suffer from it to the same extent, they may attribute this to PD, or may have become used to this change after many years of PD.

The proportion with sub threshold depression in PDD (study 3) was 21%, which is similar to the 18% with minor depression in overall PD found in Study 1. This finding underlines previous research showing that depression is an important clinical issue even if MD criteria are not fulfilled, particularly in elderly and somatically ill people. Furthermore, it suggests that minor depression is not more common in PDD than in PD, although this has not yet been studied specifically. On the other hand, an association between depression and cognitive impairment in PD has been frequently reported [25 66 115]. One possible explanation for this possible inconsistency is that major depression, but not minor depression, is associated with dementia in PD. Findings consistent with this hypothesis have been reported [55]. One potential explanation for this is that major depression in PD is more closely related to the brain changes associated with dementia in PD compared to minor depression. The association between depression and left-sided parkinsonism and young age at onset in males is consistent with previous studies [192]. The lack of such associations in female patients suggests potential gender differences in the underlying biology of depression.

Study 4 is the largest study to date showing an association between pain and depression in PD. Previously, only case reports [193 194] and two small studies without a control group [86 87] have been reported, showing comparable results. The proportion of subjects having a clinical depression score suggestive of major depression was three times higher among those with pain compared to those without pain. Since this was a cross-sectional study, the direction of causality cannot be determined, and the relative importance of psychological and biological contributing factors remains unknown. However, our results support the hypothesis that pain may cause or interfere with depression also in PD. The most interesting finding in Study 5 was that 5HT1a receptor density in temporal cortex was increased in depressed patients with PDD. Previous CSF and imaging studies have suggested that serotonergic mechanisms may contribute to depression in PD. This is the first autopsy study exploring the

serotonergic system in PD patients with depressive symptoms. One interpretation of the finding is that a secondary up-regulation due to serotonergic deficit has occurred. Taken together, based on the findings in studies 4 and 5, we propose that both brain changes and psychological factors interact in the aetiology of depression in PD.

Drugs with anticholinergic activity are frequently used by patients with PD. In Study 6 we observed for the first time, that the duration and dosage of the use of such drugs were associated with a more rapid cognitive decline in PD. Similar findings have been reported in clinical studies in elderly people and in patients with dementia [195]. The finding is also consistent with autopsy studies reporting more severe Alzheimer-type brain changes in PD patients [119] and DLB patients [196] who had used anticholinergic agents compared to patients who had not used such drugs, and vice versa, that cholinergic agents are associated with less severe senile plaques [197]. However, a recent report suggests that cholinergic drugs were associated with more severe tangle pathology in DLB [196]. Further studies of these important questions are needed.

8.4.5 Implications

Our systematic review of prevalence studies of depression in PD confirmed the high percentage of patients with this common neurodegenerative disorder, who additionally suffer from depression. As depression is one main contributor to impaired quality of life, our results underline how important it is to identify patients with this condition and to treat it.

We found a somewhat differing depression symptom profile in PD patients compared to depressed people without PD. This may have implications for diagnosis. Typical depressive symptoms like feelings of guilt may be less common than in patients with other depressive syndromes, especially endogenous depression. We also speculate that the depressive symptom profile in PD patients reflects a neurotransmitter deficiency differing from that in common depression. Thus, depression in PD might be more related to noradrenergic deficiency than depression in non-PD subjects. This

may have therapeutic implications. At present there is limited evidence available to guide the choice of antidepressive therapy in PD. The recently published study on nortriptyline against paroxetine and placebo support the hypothesis that drugs with affinity to different receptors are superior to drugs with just serotonergic mechanism [146].

The strong association between pain and depression in PD has several implications. We propose that pain assessment should be a regular component of care in PD, particularly in those with depression. Moreover, further research should examine, if active pain management can improve depression and thus quality of life in PD patients. This may include both pharmacological and physical treatment.

We discovered 60% higher 5-HT 1A receptor density in the temporal cortex (BA36) in DLB/PDD subjects in the presence of depressive behaviour relative to those patients who had never experienced depression. This finding should be replicated and examined further. The interactions between different neurotransmitters involved in depression in PD and their interdependent up- and down-regulation in different brain areas are not completely understood yet but may have important implications for developing effective treatments for depression. We speculate that drugs with 5HT1a activity may be particularly effective in PDD patients with depression, and clinical trials are warranted.

Drugs with anticholinergic properties are frequently prescribed to patients with PD and were associated with more rapid cognitive impairment. These findings have implications for the management of PD patients, since avoiding such drugs may avoid increasing progression of cognitive decline, and highlight the need for continued physician education to ensure avoidance of inadvertent prescription of such drugs. Clinicopathological studies should examine the association between morphological changes, cognitive impairment, and anticholinergic drug administration in PD.

Source of data

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