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Cognitive and Psychiatric Aspects of Parkinson's Disease

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder affecting a variety of brain structures. Its prevalence in the general population is around 0.3% and increases considerably with age (de Lau & Breteler, 2006). The median age of onset is 60 years and the incidence is equal in both sexes (Katzenschlager et al., 2008). While initially symptoms are subtle severe disability often requiring permanent care is present in many patients within a time-frame of about ten years. On the other hand, there are patients who do not show relevant progression of PD over up to ten years (Hoehn & Yahr, 1967). Indeed, the most severe state of PD with regard to the Hoehn and Yahr (H&Y) scale may be reached after 6 to 40 years according to a variety of epidemiological studies (Poewe, 2006). Yet, overall the mortality rate of patients with PD is increased by a factor of 1.5-2.5 compared to the general population (Poewe, 2006).

The existence of at least two of the criteria resting tremor, bradykinesia and rigidity in an asymmetrical distribution leads the way to the diagnosis of this movement disorder. Accordingly, the pentamerous unified Parkinson's disease rating scale (UPDRS) mainly reflects the state of the motor symptoms of PD. Only the first item of the UPDRS takes into account psychiatric symptoms of the disease. However, cognitive decline as well as psychiatric disturbances are common in patients with PD and pose major problems. While the non-motor aspects of PD have been less well studied for a long time, they have received more attention in recent years. Nevertheless, therapy of these symptoms is less advanced compared to the numerous therapeutic options for the motor symptoms of PD. And not infrequently, treatment of motor symptoms and treatment of psychiatric and cognitive aspects of PD interfere with each other. For this chapter the literature on some factors of non-motor aspects of PD has been reviewed and is summarized here.

2. Cognitive and psychiatric comorbidities of Parkinson's disease

2.1 Dementia in PD

Epidemiology: Parkinson's disease is the second most common neurodegenerative disease and dementia is one of the main manifestations of PD. A large epidemiological study of 1449 patients with PD conducted in Germany found a point prevalence of dementia of 28.6% in this population (Von Reichmann et al., 2010). Accordingly, meta-analyses of prevalence

studies on Parkinson's disease dementia (PDD) report point prevalence rates of 24.5% (Aarsland et al., 2005) or 30% (Marder, 2010). Hence, 30% may be an accurate estimate of the point prevalence of PDD. Additionally, it affects probably more than 50% of patients with PD in the course of the disease and cumulative prevalence rates reach 80% in some studies (Aarsland & Kurz, 2010). Indeed, compared to a control population the risk of developing dementia in PD is increased 6-fold (Buter et al., 2008). On the other hand, 3-4% of dementias in general are attributed to PD (Marder, 2010).

The most significant risk factors for developing PDD are a higher age of onset of PD as well as a higher degree of severity of parkinsonism. Also, the development of PDD often is preceded by the diagnosis of mild cognitive impairment (MCI). It has been suggested that deficits in semantic fluency and visuoconstruction indicate a higher risk for developing PDD compared to frontal executive dysfunctions (Aarsland & Kurz, 2010). An association between dementia and visual hallucinations in PD is established as well.

Pathophysiology: The pathophysiological mechanisms of PDD are not fully understood. As opposed to the motor symptoms cognitive deficits in PD normally do not improve with dopaminergic therapy. Therefore other pathology than the cerebral dopamine deficit is relevant in the pathophysiology of PDD. Postmortal analysis of brain of patients who had clinical symptoms of PDD shows a heterogeneous histological and immunochemical profile. Abundant cortical and nuclear Lewy bodies resembling the histopathological profile of Lewy body dementia (LBD) may be present. On the other hand, the pattern of post-mortem analysis may resemble that of Alzheimer's disease (AD). Lack of cortical amyloid, tau, or synuclein pathology in the presence of Lewy bodies in the substantia nigra was associated with less significant dementia underlining the importance of cortical pathology regarding PDD (Galvin et al., 2006). More knowledge on biomarkers of dementia has evolved in the last years with several studies that demonstrated specific findings in the cerebrospinal fluid of patients with PDD (CSF). Amyloid-beta (Aβ) peptides are the main components of amyloid-plaques which are found abundantly in patients with AD but also form part of the pathological changes in the brains of patients with PDD. Presence of the most prominent form of amyloid-beta - the Aβ-42 - in the CSF has been shown to be a reliable marker for dementias and particularly for AD. But discrimination between AD and PDD or LBD is not possible with this marker. However, the ratio between the subforms 42 and 37 of the Aβ protein have been proposed as biomarker for a differentiation between AD from PDD and LBD whereas the latter two forms of dementia may be differentiable by new subforms of the Aβ-protein that have been found in the CSF of patients with dementia (Bibl et al., 2006). Other proteins that can be detected in the CSF and whose concentration may indicate dementia are phospho-tau and alpha-synuclein. Regarding neurophysiological techniques a study analyzing the EEG of 50 patients with AD, 50 patients with LBD and 40 patients with PDD showed that patients with PDD or LBD had significantly slower posterior rhythms (5.6-7.9 Hertz) than patients with AD even in early stages of the disease (Bonanni et al., 2008). Neuroimaging studies demonstrate whole brain atrophy in PDD lacking confirmed specific changes that would differentiate between patients with PD and those with PDD. The co-occurrence of visual hallucinations and PDD has prompted pathoanatomical explanations relating both symptoms to Lewy body pathology in the temporal lobes (Harding et al., 2002). Another common mechanism of these manifestations of PD may be a cholinergic deficit supported by the therapeutic

success that can be achieved by application of inhibitors of the acetylcholinesterase (Emre et al., 2004). A relation to the known protective effect of cigarette smoking on the incidence of PD may exist (Alves et al., 2004). Association of PDD with particular familial forms of PD have been demonstrated. But genetic risk factors for PDD exceeding these relatively rare forms of PD have not yet been found.

Phenomenology: Typically, patients with PDD exhibit deficits in different aspects of memory. A recent study showed that impaired attentional filtering as well as a reduced storage capacity is present in patients with PD even in the absence of dementia (Lee et al., 2010). However, no specific pattern of cognitive decline is characteristic for PDD and all major cognitive domains including memory, attention, constructional function, visuospatial function and execution are affected. Differentiation from AD and especially LBD is not reliably available based on the neuropsychological testing. Still, many studies suggest executive dysfunction as the predominating cognitive pattern in patients with PDD (Emre et al., 2007). Importantly, patients with dementia and PD show similar clinical signs compared to LBD even though postural instability is more common in PDD. Nevertheless, the frequency of falls does not differ between patients with PDD, LBD and AD. Visual and auditory hallucinations, as well as depression, sleep disturbances and cognitive fluctuation characterize PDD as well as LBD. Importantly, aside from the presence of extrapyramidal motor symptoms these criteria common in PDD and LBD are very useful in distinguishing PDD from AD (Galvin et al., 2006). The most significant predictor of developing PDD compared to patients with PD without dementia are visual hallucinations the occurrence of which at any point in the progress of PD increases the risk for developing dementia by a factor of twenty (Galvin et al., 2006). Typical clinical features that establish the diagnosis of PDD are found in table 1.

Diagnosis: Recently, a task force of 23 experts in the field of PD developed clinical diagnostic criteria for PDD. Features of this disorder were defined as well as the likelihood of its diagnosis based on the combination of symptoms (Emre et al., 2007; Goetz et al., 2008). According to the criteria in table 1 and 2 diagnosis of PDD is probable if 1) both core features are present, 2) at least two cognitive features and at least one behavioral feature are present, 3) none of the group III or group IV features are found. Diagnosis of PDD is possible if 1) both core features are present, 2) there is an atypical profile of cognitive impairment in one or more of the cognitive features like prominent or receptive-type aphasia, pure storage-failure type amnesia with preserved attention while behavioral symptoms may or may not be present. Possible PDD can be diagnosed also with one or more features of category II present in the absence of category IV features (Emre et al., 2007; Goetz et al., 2008).

Therapy: Currently, there are four relevant drugs with approval for the treatment of the symptoms of dementias. Donepezil, rivastigmine and galantamine are inhibitors of the acetylcholinesterase whereas memantine is an antagonist of the glutamatergic N-methyl-d-aspartate (NMDA)-receptor. These drugs are approved for the treatment of AD in the United States and/or within the European Union. Their indication for treatment of PDD has been established or is currently under approval. 20 studies regarding the treatment of PDD with inhibitors of the acetylcholinesterase were identified by a review published in 2010. The effects of donepezil were investigated in 12 studies, those of rivastigmine in 6 and galantamine was tested in 2 studies. 11 of these studies were open-label studies and 2 reported case series and all of these smaller studies with less than 40 patients showed

I. Core features	1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria	2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as: 1. Impairment in more than one cognitive domain 2. Representing a decline from premorbid level 3. Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms
II. Associated clinical features	**1. Cognitive features** **Attention:** Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day Executive functions: Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia) Visuo-spatial functions: Impairment in tasks requiring visual-spatial orientation, perception, or construction **Memory:** Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall **Language:** Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present	**2. Behavioral features** **Apathy:** Decreased spontaneity; loss of motivation, interest, and effortful behavior **Personality:** Changes in personality and mood including depressive features and anxiety **Hallucinations:** Mostly visual, usually complex, formed visions of people, animals or objects **Delusions:** Usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions **Excessive daytime sleepiness**

Table 1. Features favoring the diagnosis of dementia associated with Parkinson's disease (according to Emre et al., 2007 and Goetz et al., 2008)

III. Features which do not exclude PD-D, but make the diagnosis uncertain	• Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging	• Time interval between the development of motor and cognitive symptoms not known
IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D	• Cognitive and behavioral symptoms appearing solely in the context of other conditions such as: **Acute confusion due to** - Systemic diseases or abnormalities - Drug intoxication **Major Depression according to DSM IV**	• Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN = dementia in the context of cerebrovascular disease as indicated by 1. focal signs in neurological exam such as hemiparesis, sensory deficits, and 2. evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: 1. onset of dementia within 3 months after a recognized stroke 2. abrupt deterioration in cognitive functions 3. fluctuating, stepwise progression of cognitive deficits

Table 2. Features not favoring the diagnosis of dementia associated with Parkinson's disease (according to Emre et al., 2007 and Goetz et al., 2008)

improvement in selected clinical outcome measures to some degree. Nevertheless, by nature the limitations of these studies' designs affect their representative value. Still, it may be an important clinical observation that improvement of hallucinations was observed among patients treated with rivastigmine, donepezil or galantamine in several of these studies while their were generally no changes in motor symptoms. 5 of the studies as of 2010 were randomized controlled trials of which only two had included more than 40 patients (van Laar et al., 2010). One of these studies investigated the effects of rivastigmine while the other investigated the effects of donepezil in patients with PDD. The latter study has not been published in a peer-reviewed journal as of April 2011 and results of the review are based on a poster presentation at an international conference in 2007 (van Laar et al., 2010). According to this preliminary review, this study included 550 patient with PDD who were randomized to one of three treatment arms receiving either 5 mg donepezil, 10 mg donepezil or placebo. A trend towards improvement but no significant effect on the primary cognitive outcome

scales was the main result of this report. Nonetheless, significant improvement was present in several secondary outcome measures like the mini-mental state examination (MMSE), the brief test of attention (BTA) or the verbal fluency test from the Delis-Kaplan executive function system test battery (D-KEFS). Nausea and parkinsonian side effects were reported as most common adverse events. In the other placebo-controlled, randomized trial with 541 patients a moderate effect of 3-12 mg rivastigmine per day on cognitive outcome measures in patients with PD and mild to moderate dementia has been demonstrated. Primary efficacy variables were the scores for the cognitive part of the Alzheimer's disease assessment scale (ADAS-cog) and the scores for the Alzheimer's disease cooperative study-clinician's global impression of change (ADCS-CGIC) which both showed improvement in the group of patients treated with rivastigmine compared to the placebo-group. Importantly, both scales which originally are derived from use in patients with AD are regarded as valid and reliable for use in patients with PDD as well (Harvey et al., 2010). A decrease of 2.1 points in the ADAS-cog was found in the verum group while the score of this scale increased by 0.7 after 24 weeks of application of the placebo. This decline in cognitive performance has been attributed to the natural course of PDD. Significant but only weak improvement was found in several other scales of cognitive performance and activity level. The rate of side-effects like nausea (29%), vomiting (16.6%), tremor (10.2%) and dizziness (5.8%) was significantly increased in patients who had received rivastigmine compared to those who had received placebo leading to a drop out rate due to adverse effects of 17% in the treated group compared to 8% in the placebo group (Emre et al., 2004). In line with the cited observations of previous reports and open studies the rate of hallucinations in the group receiving rivastigmine was significantly lower than in the placebo group. In fact, presence of hallucinations tended to be a predictor of favorable cognitive outcome. An open-label extension study with a daily dose of 3-12 mg rivastigmine for another 24 weeks in 334 patients with PDD who previously had received rivastigmine or placebo largely confirmed the results of the original study. Hence, the efficacy as well as the profile of side effects of rivastigmine were reproduced in the group that had received placebo during the first part of the study (Poewe et al., 2005). Additionally, in a large meta-analysis on therapy of dementia in patients with PD it was concluded that rivastigmine could improve cognition and activities of daily living (Maidment et al., 2006). Memantine has been tested in several clinical trials in patients with PDD. In a first pilot study of this drug in PDD there was no beneficial effect on cognitive outcome measures while a good tolerability compared to application of inhibitors of the acetylcholinesterase was shown (Leroi et al., 2009). An early double-blind placebo controlled trial showed a positive effect in the clinical global impression of change scale as well as an improved speed on attentional tasks under treatment with memantine (Aarsland et al., 2009). But more recent evidence from a randomized, double-blind, placebo-controlled trial with 199 participants with PDD or LBD showed no clinical benefit in patients with PDD in any of the cognitive tests applied after 24 weeks of therapy whereas those with LBD improved moderately (Emre et al., 2010). Therefore, memantine may not be regarded as choice for the pharmacotherapy of PDD. Use of galantamine has been tested in one clinical trial which reported overall beneficial effects on several scales of cognitive performance as well as improvement of hallucinations, anxiety, apathy and sleep disturbances (Litvinenko et al., 2008). However, this was an open controlled trial. Still, not unlike in other forms of dementia the current therapeutic options to treat PD dementia are purely symptomatic. And unfortunately, the effect size of antidementive drugs tends to be small in the therapy of dementias may they be related to

PD or not. Finally it can be concluded that rivastigmine is currently the only FDA-approved drug to treat dementia associated with PD while donepezil can be considered as a treatment choice. When applying rivastigmine in patients with PDD slow titration should be adhered to in order to reduce the incidence of side effects like tremor or nausea. A transdermal patch of rivastigmine now available for treatment has been shown to be more tolerable compared to the capsule applied normally (Winbald et al., 2007). This may enable more frequent use and use of higher doses of rivastigmine in patients sensitive to side-effects of this drug. Whether rivastigmine or other inhibitors of the acetylcholinesterase is applicable for the primary treatment of hallucinations may be subject of future studies.

2.2 Depression in PD

Epidemiology: Depression is one of the most common diseases of humans and up to 21 million people in Europe are affected by uni- or bipolar depression (Olesen et al., 2006). In the western world it is among the most common causes of incapacity to work among employees under the age of 50 years. Depression may also be the most common psychiatric comorbidity in patients with PD. Reported prevalence rates of depression in PD vary between 3 and 90% depending on the population studied. Whereas earlier reports suggested prevalence rates of 40-50% (Zesiewicz & Hauser, 2002) more recent studies tend to report a lower prevalence of moderate to severe depression of 5-20% (Tandberg et al., 1996; Schrag et al., 2001). In fact, these figures are in line with a recent meta-analysis which calculated an average prevalence of depression in PD of 17%. Regarding prevalence rates the population under investigation needs to be exactly defined. In exemplum prevalence rates tend to be smaller in population studies as compared to inpatient or outpatient cohorts (Reijnders et al., 2008). Minor depression was found in 22% of the patients within this meta-analysis. Finally, a recent large nationwide study in Germany with 315 participating neurological settings recruited a random sample of 1,449 outpatients with PD who performed a standardized clinical assessment in order to evaluate the frequency of dementia, depression, and other neuropsychiatric symptoms in PD on a selected study day. Depression as defined by a score of ≥14 in the Montgomery Asberg depression rating scale (MADRS) was diagnosed in 23.8% of all patients. Though not directly related to age prevalence of depression increased from 14.7% in patients with PD in HY stage I-II to 44.9% in patients with HY status IV-V (Riedel et al., 2010). Given that there are about 1.2 million patients suffering from PD in Europe 250.000 to 600.000 of these patients may be affected by any type of depression.

Pathophysiology: The major mechanism that underlies the antidepressant effect of most antidepressant drugs is an increase of the concentration of neurotransmitters in the synaptic cleft by inhibition of axonal reuptake mechanisms or inhibition of intrasynaptic fermentation. The most relevant neurotransmitters targeted by antidepressants are the monoamines dopamine, noradrenaline and serotonine. The discovery of the mechanisms of action of these antidepressants has considerably influenced the pathophysiologic theory of transmitter deficiency in depression still valid today (Kalia, 2005; Schildkraut, 1965). However, as opposed to the pathophysiologic models of PD there is no specific neuropathoanatomical correlate for depression. Several systems of transmitters and cortical areas are thought to be altered in patients with depression. Hypometabolism in a FDG-PET has been demonstrated in the dorsal and ventral prefrontal cortex, as well as in the anterior cingulate cortex and the inferior parietal region in patients with depression (Mayberg, 2002). Increased cerebral blood-flow was found in the orbital cortex, the medial thalamus and the

amygdala (Drevets, 2000). Studies with post-mortal cerebral tissue of patients who had suffered from depression indeed have shown cell atrophy in the dorsolateral prefrontal cortex and the orbitofrontal cortex as well as cell loss in the subgenual prefrontal cortex (Rajkowska, 2000). Other studies report on hippocampal volume loss in patients with major depression being related to the duration of the disease suggesting a possible link between the pathophysiology of neurodegenerative disorders and depression (Bremner et al., 2000). Cell loss or cell atrophy in depressed patients have been partially attributed to elevated cellular "stress" particularly mediated by corticosteroids. Reduced neuronal plasticity substantiated by decreased levels of the brain derived neurotrophic factor (BDNF) which plays an important for neuronal plasticity has been suggested to be causative for neuronal cell atrophy or cell loss. Interestingly, antidepressant treatment was found to upregulate the neuronal expression of the BDNF among others. Therefore, a neuroprotective effect of antidepressants on neuroanatomical structures which are affected by depression has been proposed (Duman et al., 2000). Regarding another neurotransmitter system, loss in cortical cholinergic function has been shown in a PET-study in patients with PD dementia and depression (Bohnen et al., 2007). Also there is a degeneration of several subcortical nuclei in PD a finding that resembles results from patients with depression only (Lisanby et al., 1993). Twin studies indicate hereditarity of major depression of 30-40 %. Still, there is no single genetic locus with a high association to depression whereas several polymorphisms of serotonine-transport genes or genes of the mono-amino-oxidase (MAO) have been linked to depression. Generally, depression is regarded as a polygenetic disease (Ebmaier et al., 2006; Hamet & Tremblay, 2005). These mechanisms have been recognized in the pathogenesis of major depression in the absence of PD but probably represent the most relevant mechanisms that lead to depression in patients with PD as well (Lemke et al., 2004).

Phenomenology: Not unlike other patients with depression patients with PD and depression present loss of interests, depressed mood, anhedonia, hopelessness, pessimism, feeling of worthlessness, loss of weight, insomnia, less often hypersomnia, suicidal ideas. Symptoms like hypomimia, bradyphrenia, disturbance of libido or sleep which are common in depression are common symptoms of PD without coexisting depression as well and may pose problems regarding their differentiation. Importantly, depression is thought to precede the occurrence of motor symptoms in PD not infrequently.

Apathy has been proposed as a symptom or syndrome distinct from depression in PD. Apathy is a condition which is characterized by a primary lack of motivation and involves behavioral, cognitive and affective deficits while there is no relevant affective component i.e. no feelings of sadness, depressed mood or feelings of worthlessness. Problems with the initiation and sustaining of activities have been described as being characteristic for apathy (Pluck & Brown, 2002). Even though symptoms of apathy and depression overlap apathy can occur in the absence of depression as has been demonstrated particularly in patients with progressive supranuclear palsy (PSP) (Litvan et al., 1996).

Diagnosis: The most common diagnostic manuals which define criteria for diagnosing a major depressive episode are the diagnostic and statistical manual of mental disorders (DSM-IV) as well as the tenth edition of the classification of diseases and related health problems (ICD-10). In the DSM-IV five or more of nine defined depressive symptoms of which one has to be either depressed mood or loss of interest/pleasure have to be present for at least 2 weeks and must represent a change from previous states. Besides 1) depressed mood most of the day (indicated by feeling or expression of sadness) and 2) reduced interest or pleasure in activities the other predefined symptoms which should

each be present nearly every day are 3) significant weight loss or weight gain (change >5% of the body weight within one month), 4) insomnia or hypersomnia most of the day, 5) psychomotoric retardation or agitation, 6) fatigue/loss of energy, 7) the feeling of worthlessness or inappropriate guilt, 8) reduced concentration or ability to think, 9) recurrent thoughts of death/suicidal ideation/a plan for committing suicide or a suicide attempt. Significant clinical distress and impairment in the absence of a recognized medical condition accounting for the depressive symptoms are further criteria that need to be checked in order to diagnose a major depressive episode (American Psychiatric Association, 2010a). In the ICD-10 the depressive episodes can be categorized into mild, moderate or severe forms. While using a catalogue of criteria comparable with that of the DSM-IV diagnosis of a mild depressive episode requires 2 to 3 of the criteria, while a moderate depressive episode is diagnosed when 4 or more criteria are fulfilled. In contrast to a moderate depressive episode, presence of suicidal thoughts or plans as well as presence of several somatic symptoms indicate a severe depressive episode (World Health Organization, 2007a). Depressions often are classified based on depression scales like the Hamilton depression scale (HAM-DS) or Beck's depression inventory or the Montgomery Asberg depression rating scale (Gotham et al., 1986). These scales differ regarding the significance of somatic and psychic symptoms and the HAM-DS is probably the most frequently used inventory in patients with PD and depression (Dissanayaka et al., 2007; Schrag et al., 2007).

Therapy: Despite the existence of a broad spectrum of antidepressants there is scarce evidence for the efficacy of antidepressants in patients with PD. Studies utilizing selective serotonin reuptake inhibitors (SSRIs) like citalopram, sertraline and paroxetine or tricyclic antidepressants imipramine, desipramine, amitriptyline and nortriptyline or bupropion have been conducted. In a large literature review effect sizes between antidepressant and placebo treatment did not differ in patients with PD and depression being in line with previous meta-analyses (Weintraub et al., 2005). Within this review only 11 studies performed between 1965 and 2003 with a treatment duration of about 12 weeks on average utilizing SSRIs in the majority were found suitable for meta-analysis. Only two of these studies were placebo-controlled trials. Sample size was 30 patients on average. Generally, the effect size of antidepressant as well as placebo treatment was regarded as considerable. Therefore, nonspecific treatment effects were suggested as likely reason for the positive effects reported in several open-label studies. In accordance, the effect size found was similar to that of placebo arms of randomized, placebo-controlled trials in elderly patients with depression and without PD. Finally, the completion rates of open-label studies with antidepressants were about 87% in general and 86% in patients receiving SSRIs thus deeming poor tolerance of antidepressants in patients with PD an unlikely cause of the ineffective antidepressive action (Weintraub et al., 2005). In the meantime two rather small placebo controlled trials with each about 50 participants have demonstrated superiority of selected antidepressants. In one study citalopram as well as desipramine proofed to be more affective than placebo 30 days after initializing treatment as demonstrated by significant improvement in the Montgomery Asberg depression rating scale (MADRS). Additionally, treatment with desipramine resulted in a significant antidepressant effect after 14 days as well. On the other hand, side-effects were reported twice as often in patients with desipramine compared to patients who received citalopram being often in accordance with the anticholinergic profile of tricyclic drugs. Still, with 15 or less patients in each group sample sizes were low (Devos et al., 2008). In another recent placebo controlled trial

application of 48.5 mg of nortriptyline on average and 28.4 mg of paroxetine on average each was compared to placebo in 52 patients with PD and depression. The primary outcome variable in this study was change in the Hamilton depression rating scale (HAM-D). While nortriptyline was superior to placebo 2 and 8 weeks after initializing treatment paroxetine was not. Also the responder rate defined as a change of ≥50% in the HAM-D was significantly higher in the group treated with nortriptyline (Menza et al., 2009). Other studies have evaluated the antidepressant effect of antiparkinsonian medication. Most recently it has been shown that depressive symptoms in PD can be treated with the dopamine agonist pramipexole (Barone et al., 2010). Of 287 patients with mild to moderate PD on stable antiparkinsonian therapy 139 received 0.125 – 1.0 mg pramipexole three times a day and 148 received placebo each over 12 weeks. Significant therapeutic effects of pramipexole on Beck's depression inventory as well as in the UPDRS motor scores were found. Therefore, pramipexole may be a favorable primary choice for patients with PD and depression.

2.3 Psychoses in PD

Epidemiology: Hallucinations, illusions and delusions are the main psychotic symptoms in PD. Among these hallucinations are the most common with visual hallucinations being much more frequent than acoustic hallucinations. Tactile hallucinations are less frequent and prevalence rates are not well-established. Olfactory hallucinations should be regarded as unusual in PD and there are occasional reports on this type of phenomenon. Hallucinations occur in up to 40% of patients with PD if minor visual hallucinations like sensation of the presence of another person are included (Fénelon et al., 2000). Within the parkinsonian disorders visual hallucinations occur predominantly in PD and dementia with Lewy bodies. They are much less likely to occur in patients with progressive supranuclear palsy (PSP), multiple system atrophy (MSA) or vascular Parkinsonism and in fact this symptom has been proposed as a useful predictor for the differential diagnosis of these groups of parkinsonian syndromes (Williams et al., 2008).

Pathophysiology: In a post-mortem study of 788 brains of patients with history of parkinsonism a history of visual hallucinations predicted the existence of Lewy body pathology with 93%. On the other hand visual hallucinations were present in 50% of patients with PD and 73% of patients with LBD (Williams et al., 2008). Visual hallucinations were identified as a symptom of advanced stages of Lewy body parkinsonism and occurred in the second half of the duration of PD from onset to death in almost every patient in this study. In a longitudinal study with 5-year clinical follow up patients were divided into two groups: those who experienced hallucinations within 3 months after initiating levodopa therapy and those who experienced such hallucinations after 1 year or later. In everyone of the 12 patients who had experienced hallucinations during the first 3 months of levodopa treatment the primarily made diagnosis of PD had to be revised either due to a newly diagnosed underlying psychiatric illness or due to existence of LBD or AD with extrapyramidal signs (Goetz et al., 1998a). Therefore, very early occurrence of hallucinations should prompt a control of a diagnosis of PD. With regard to the dopamine hypothesis of schizophrenia and the fact that antipsychotic drugs all include an antidopaminergic effect it may be reasoned that the occurrence of psychosis in PD is due to the dopaminergic treatment. Indeed, it has been suggested that treatment with levodopa may "kindle" psychotic symptoms in PD (Moskovitz et al., 1978). Still, other diseases which are treated with dopaminergic agents like hyperprolactinemia do not carry an increased risk for

hallucinations (Williams & Lees, 2005). Additionally, intravenous infusion of levodopa was not able to induce hallucinations in patients who experienced spontaneous hallucinations on a daily basis rendering a simple association of hallucinations to levodopa serum-levels unlikely (Goetz et al., 1998b). And importantly, hallucinations have been described in patients with PD before introduction of levodopa into therapy of PD (Diederich et al., 2009). Probably, the pathophysiology of PD itself is mainly responsible for the increased risk of hallucinations in patients with PD. Similarly, other neurodegenerative disorders like AD or LBD harbor a higher risk for the occurrence of hallucinations in the absence of dopaminergic treatments. Additionally, there appears to be a difference between the levodopa-equivalent dose between patients with hallucinations and those without hallucinations (Diederich et al., 2009). Pathophysiologically, the existence of Lewy bodies in the basolateral nucleus of the amygdala as well as in the parahippocampus and other inferior temporal regions has been identified as possible correlate of visual hallucinations (Harding et al., 2002). A correlation between cholinergic dysfunction and visual hallucinations has been recently established when the short-latency afferent inhibition - a neurophysiologic measure of inhibitory intracortical mechanisms depending on cholinergic function - was shown to be significantly reduced compared to patients with PD and compared to healthy controls without visual hallucinations (Manganelli et al., 2009).

Phenomenology: In accordance with previous statements early presence of visual hallucinations is a predictor for early mortality (Williams & Lees, 2005). Additionally, there is a correlation between visual hallucinations and cognitive dysfunction which may reflect its association with advanced disease state. Nevertheless, cognitive function of patients without visual hallucinations appears not to differ from those with minor hallucinations whereas patients with major visual hallucinations show deficits in verbal fluency tasks which are not found in patients without visual hallucinations (Llebaria et al., 2010).

In one study with 216 patients hallucinations were divided into three groups. First, minor forms of hallucinations including the feeling of the presence of somebody or something, which was also the most frequent hallucination, were grouped together. With regard to this type of hallucination, patients perceived the presence of a living or deceased relative, another person, an animal or an unidentified sensation. Within the group of the minor symptoms hallucinations of passage were identified as distinctive phenomena and were described as a brief impression of a person or animal (frequently a cat or a dog) passing by. Illusions were a second group of symptoms and were described as impression of a transformation of an object e.g. into an animal (Fénelon et al., 2000). Formed visual hallucinations and auditory hallucinations formed the other major groups of hallucinations in PD in this study. With a prevalence of approximately 10% auditory hallucinations in PD are less common than visual hallucinations and frequently do not occur alone but in association with visual hallucinations (Inzelberg et al., 1998; Fénelon et al., 2000). Auditory hallucinations are perceived as externally generated human voices. They may be incomprehensible or may be commenting familiar voices. In contrast to auditory hallucinations in schizophrenia they predominantly do not have an affective component, are not imperative and are not paranoid in character in PD (Inzelberg et al., 1998). Tactile hallucinations have been rarely reported. One study described eight patients with PD and tactile hallucinations which were always associated with simultaneously or non-simultaneously occurring visual or auditory hallucinations. Those tactile hallucinations predominantly included the sensation of contact with animals like spiders, cockroaches, grubs, mites, ants or rats. Often sensation of contact with these

small animals were also subject of simultaneous visual hallucinations. They occurred predominantly in the evening or at night and were perceived as unpleasant. Interestingly and in accordance with the descriptions of visual hallucinations insight into the non-realistic nature of the phenomena was maintained or recovered within a few seconds (Fénelon et al., 2002).

Diagnosis: Only 20% percent of patients with PD spontaneously report the occurrence of hallucinations or other psychotic symptoms (Fénelon & Alves, 2010). Therefore, these symptoms should be actively asked for when examining patients and/or persons associated with the patient's care. There is no generally accepted scale for evaluation of psychotic symptoms in PD. An expert group recently suggested criteria for the diagnosis of PD associated with psychosis. First, at least one of the symptoms of hallucinations, illusions, delusions or false sense of presence has to be present. Second, the primary diagnosis of PD has to be established according to the UK Brain Bank criteria for PD. Third, the onset of PD has to precede the onset of the psychotic symptoms mentioned first. Fourth, the symptoms occur recurrently or continuously for at least one month. Fifth, other possible causes of parkinsonism and psychiatric disorders have to be excluded. Sixth, it should be specified if symptoms occurred a)with or without insight, b)with or without preexisting dementia and c) if they were associated with a specific treatment for PD (Ravina et al., 2007).

Therapy: Upon occurrence of psychotic symptoms in PD possible reversible causes have to be excluded. First, any association to changes of the patients antiparkinsonian treatment has to be reviewed. If there is no recent change in medication which could explain the onset of psychotic symptoms modification of the patients' medication should follow a distinct sequence which ranks the psychotic potential of different classes of drugs used in the treatment of patients with PD. According to the guidelines of the German Neurological Association 1) anticholinergic substances and tricyclic antidepressants which carry anticholinergic side-effects should be discontinued. 2) budipine, amantadine and inhibitors of the mono-amino-oxidase-B (MAO-B) should be reduced or discontinued, 3) dopamine-agonists should be reduced or discontinued, 4) inhibitors of the catechyl-O-methyl-transferase (COMT) should be reduced or discontinued, 5) therapy with levodopa may be reduced to its lowest effective dose if reduction/discontinuation of one or more of the previously listed substances did not to lead to relief from psychotic symptoms (Eggert et al., 2008). Secondary, a relation to the treatment with other drugs e.g. antibiotics that can increase the likelihood of psychotic symptoms should be assessed. Third, acute infection or imbalance of serum electrolytes should be excluded. Restitution of the dopaminergic deficit caused by cell loss of the neurons of the pars compacta of the substantia nigra is the leading mechanisms of most antiparkinsonian drugs. On the other hand antipsychotic drugs all act antidopaminergic based on the dopamine-hypothesis of psychosis. Most of the classic antipsychotic drugs especially of the butyrophenon group exhibit a high affinity to several D (=dopamine)-receptors especially the D2-receptors. Therefore most antipsychotic drugs can not be used in PD. However, for therapy of psychosis or hallucinations in PD the group of atypical antipsychotics is much better tolerated from patients with PD due to a more favorable mechanism of action. A fast dissociation of atypical neuroleptics from the D2-receptor has been proposed as possible explanation for the comparatively good tolerability in patients with PD therefore being first-line therapeutics in Parkinson patients with psychotic symptoms (Kapur & Seeman, 2001). Notably, quetiapine or clozapine are the preferred antipsychotic drugs in patients with PD. Clozapine is the drug of choice for the treatment of psychosis in patients with PD and is used in a low-dose range of 25-100 mg/d.

It acts predominantly on the D4-dopaminergic receptor and therefore has less impact on the striatonigral dopaminergic system which exhibits predominantly D1- and D2-receptors. Several studies have proven the effectiveness of clozapine in treating psychotic symptoms in PD. One rater-blinded study compared quetiapine and clozapine use in 27 patients with PD and psychosis. Both drugs were effective in treating psychosis based on the clinical global impression of change scale (CGIC). Whereas clozapine was more efficient in treating delusions it induced leucopenia in one case (Merims et al., 2006). Clozapine has proven its efficacy in a randomized, double-blind, placebo-controlled trial with 60 patients who received either placebo or clozapine in a dose of 50 mg or less for 4 weeks while the antiparkinsonian medication was left stable. A significant improvement in all clinical rating scales was demonstrated and importantly there was no deterioration of motor symptoms. But one case of leucopenia occurred (The Parkinson Study Group, 1999). Side-effects of clozapine are sleepiness, dysarthria, weight gain which are dose-dependent and less common in patients with PD psychosis as compared to patients with schizophrenia where much higher doses of up to 1000 mg per day are used. However, the risk of agranulocytosis of clozapine requires regular blood counts and depending on individual legislations the patient needs to be carefully instructed regarding benefits and risks and informed consent may be obtained before starting a treatment with clozapine. Quetiapine is the second atypical antipsychotic used in patients with PD. Its effect is probably mainly mediated by antagonistic effects on 5HT2-, D1- and D2-receptors with a higher selectivity for 5HT2-receptors. Common side effects of quetiapine include sedation, hypotension, increase in weight and change of blood sugar and lipids. Moreover, there have been case reports of agranulocytosis, prolactin elevation and rhabdomyolysis under therapy with quetiapine (Stephani & Trenkwalder, 2010). Whereas the efficacy of clozapine has been proven by blinded studies a double-blind study which compared quetiapine use to placebo in patients with PD and psychosis over a three-month interval found no significant effect in any clinical scale evaluated (Rabey et al., 2006). The number of patients in this study was rather small due to a significant drop-out rate which may have influenced the results. Indeed, the result of this trial contrasts with the clinical experience which favors a beneficial role of quetiapine for treatment of psychosis in PD. And currently the use of quetiapine for the treatment of psychotic symptoms in patients with PD is widely accepted despite the inconclusive evidence on the topic. It has been proposed that this discrepancy of negative studies and positive clinical evaluation may be due to the sedative (side-)effect of quetiapine rather than a direct anti-hallucinatory effect (Diederich et al., 2009). Doses of up to 300 mg quetiapine a day are currently applied in patients with PD. Aside from pharmacotherapy, patients experiencing visual hallucinations naturally often use coping strategies. These have been categorized into visual techniques, cognitive techniques and interactive techniques (Diederich et al., 2003). Visual techniques include focusing on the hallucination or defocusing. With cognitive techniques the patient should try to actively remain conscious about the hallucinatory or illusionary nature of the psychotic symptom. Interactive techniques would describe any technique that requires participation of others. Patients may be asked for application of such techniques and may be instructed on if required. However, there are no controlled studies on the effectiveness of this kind of therapeutic approach.

2.4 Impulse control disorders

The chapter on mental and behavioral disorders of the 10th revision of the international statistical classification of diseases and related health problems (ICD-10) lists 4 specific

habit and impulse control disorders which are pathological gambling (F63.0), pyromania (F63.1), kleptomania (F63.2) and trichotillomania (F63.3). Whereas pathological gambling is a well-known impulse control disorder in patients with PD there is no report of pyromania in patients with PD available. Anecdotal reports of kleptomania and trichotillomania in PD exist but there is no study on their frequency in patients with PD compared to controls. In addition to pathologic gambling there are other specific psychiatric disorders that have been found to exist in patients with PD and that are not listed in the group of impulse control disorders in the ICD-10 but share characteristics with disorders of the impulse control. Hypersexuality is currently neither directly classified in the DSM-IV of the American psychiatric association nor in the ICD-10. Excessive sexual drive (F52.7) is classified in the latter within the subsection of sexual dysfunctions and comprises those deviations classically named satyriasis and nymphomania. Similarly, binge-eating can be a impulse control disorder-like psychiatric comorbidity in patients with PD. Binge-eating most closely corresponds to the symptom of overeating (F50.4) among the non-organic eating disorders classified in the ICD-10. Oniomania which is compulsive shopping again is not a specified symptom in the current psychiatric classifications and therefore may be ranked within the category of "other impulse control disorders" (F63.8) of the ICD-10. These disorders have been also described as repetitive and reward-seeking behaviors or behavioral addictions concepts that considerably overlap with that of compulsive or impulsive control disorders. These disorders are regarded as dopamine replacement related-disorders therefore being extrinsically generated and not directly depending on PD itself (Wolters et al., 2008).

2.4.1 Pathological gambling

According to the ICD-10 of the World Health Organization (WHO) pathological gambling consists of "frequent, repeated episodes of gambling that dominate the patient's life to the detriment of social, occupational, material, and family values and commitments" (World Health Organization, 2007b). Pathological gambling was found to have a lifetime prevalence of 0.42% in a large US cohort (Petry et al., 2005). In patients with PD this trait was reported in more than 7% of those who were on a dopamine agonist (Voon et al., 2006a). The overall lifetime prevalence of pathologic gambling in PD has been reported to be 3.4% and the point prevalence was reported with 1.7% (Voon et al., 2006b). Similarly, in a prospective study of 388 consecutive PD clinic patients a prevalence of pathological gambling of 4.4% in general. and of 8% in patients treated with dopamine agonists was demonstrated (Grosset et al., 2006). Pathological gambling as a psychiatric comorbidity of PD can be largely attributed to therapy with dopamine agonists or levodopa and has been recognized in patients with restless legs syndrome treated with dopamine agonists as well (Pourcher et al., 2010). Confirmatory, there is no evidence for an increased prevalence of this trait in untreated patients with PD (O'Sullivan & Lees, 2007). A younger age of onset of PD, a higher novelty seeking personality profile and an impaired planning capacity each compared to patients with PD but without impulse control or compulsive behaviors have been recognized as factors associated with the occurrence of pathological gambling in PD. A positive personal or immediate family history of alcohol use disorders is a risk factor for developing pathological gambling indicating a genetic predisposition (Voon et al., 2007). Pathophysiologically, a functional magnetic resonance imaging (fMRI) study with 12 female patients with restless legs syndrome without pathological gambling who were under chronic therapy with dopamine agonists showed that the ventral striatal activation upon

receipt or omission of rewards in a gambling task during dopaminergic treatment differed significantly from that while off treatment with dopamine agonists (Abler et al., 2009). The diagnosis of pathological gambling currently is often based on the criteria of the DSM-IV. These indicate persistent and recurrent maladaptive gambling behavior as indicated by five (or more) of the following: the patient 1) "is preoccupied with gambling", 2) "needs to gamble with increasing amounts of money in order to achieve the desired excitement", 3) "has repeated unsuccessful efforts to control, cut back, or stop gambling", 4) "is restless or irritable when attempting to cut down or stop gambling", 5) "gambles as a way of escaping from problems or of relieving a dysphoric mood", 6) "after losing money gambling, often returns another day to get even", 7) "lies to family members, therapist, or others to conceal the extent of involvement with gambling", 8) "has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling", 9) "relies in other to provide money to relieve a desperate financial situation caused by gambling". Additionally, a manic episode as possible underlying cause needs to be excluded (American Psychiatric Association, 2010b). A history of illegal acts like forgery, fraud theft, embezzlement to finance gambling is currently a 10th possible criterion for the diagnosis of pathological gambling but is not included in the proposed revision for the DSM-5 which is scheduled to be released 2013. Importantly, the work group for this revision also proposes to reclassify the diagnosis from an impulse-control disorder into a substance-related disorder (American Psychiatric Association, 2010b). The therapy of choice of pathological gambling in PD is the discontinuation of the dopamine agonist and replacement by an adequate dose of levodopa. In fact, 15 patients with PD and pathological gambling were followed up for 21 months on average. In all of them the treatment with dopamine agonists had been discontinued and was replaced by levodopa. All of them reported cessation of the pathological gambling even though one patient reported to have a continuing urge to gamble (Macphee et al., 2009). If levodopa itself is the suspected cause of pathological gambling dose reduction will be necessary.

2.4.2 Hypersexuality

In a large multicentre study the prevalence of compulsive sexual behavior in patients with PD was 3.5% (Weintraub et al., 2010). Others found lifetime prevalence rates of 2.4% in patients with PD with a point prevalence of 2.0%. The lifetime prevalence increased to 7.2% in patients on therapy with dopamine agonist (Voon et al., 2006b). Importantly, hypersexuality occurs nearly exclusively in male patients according to most reports. However, this symptom has been also recognized in women with PD (Cooper et al., 2009). There is a proposal for operational diagnostic criteria of symptoms defining hypersexuality. 1) maladaptive preoccupation with sexual thoughts, 2) inappropriately or excessively requesting sex from spouse or partner, 3) habitual promiscuity, 4) compulsive masturbation, 5) use of telephone sex lines or pornography, 6) paraphilias are symptoms that can define hypersexuality if one or more of them persist for at least one month and if symptoms are not exclusively due to a period of hypomania or mania. Additionally, this must cause at least one of the following 1) marked distress, 2) unsuccessful attempts to control thoughts or behavior or marked anxiety or distress due to such attempts, 3) significant time consuming 4) interference with social or occupational functioning (Voon et al., 2006b). If none of the last 4 symptoms are found while the other symptoms of hypersexuality are present subsyndromal hypersexuality may be diagnosed. Dopaminergic drugs are a significant risk factor for the occurrence of hypersexuality in

PD. They are present in 90% of those patients with PD developing the disorder. Additionally, symptoms may resolve as soon as dopamine agonists are discontinued while continuing treatment with levodopa. Also association with other obsessive or addictive symptoms is frequent (Klos et al., 2005). An association to depression has been described and it is not clear whether there is any functional dependency between both symptoms. Therapeutically, the medical history of the patients needs to be controlled for any temporal relation of the occurrence of pathological gambling to installation of a dopamine agonist therapy. If applicable a treatment with such a dopamine agonist should be reduced or replaced by an equivalent dose of levodopa. Persisting symptoms may then even warrant other therapeutic options like general reduction of the dopaminergic treatment. There is no evidence for specific pharmacologic treatments of hypersexuality in PD.

2.4.3 Obsessive eating

The prevalence of obsessive eating or binge-eating among patients with PD was 1% in a recent analysis while subthreshold binge eating was diagnosed in about 8% (Zahodne et al., 2011). However, in a cross-sectional study with 3000 patients with PD binge eating was diagnosed in 5.6% (Antonini & Cilia, 2009). The weight gain often is significant and an average gain of 13 ± 7 kg has been found in 7 patients with this disorder (Nirenberg & Waters, 2005). As in other impulse control disorders in PD the major risk factor is the use of a dopamine agonist of which pramipexole based on the existing literature has been most often associated with obsessive eating. Other risk factors include a young age of onset of PD, a personal or direct family history of addictive behavior as well as a novelty seeking and impulsive personality profile. A mechanism based on stimulation of the mesolimbic dopaminergic reward system which is probably common to the impulse control disorders recognized in PD has been proposed as being causative for obsessive eating. Again, discontinuation of dopamine agonists is effective based on evidence from case reports (Nirenberg & Waters, 2005; Khan & Rana, 2010).

2.4.4 Oniomania

This symptom also known as compulsive shopping is characteristic of manic episodes of psychiatric patients. In the absence of uni- or bipolar disorders it is currently not further specified in the classification systems of mental diseases. Still, its prevalence in a large study of patients with PD was described with 7.2% (Antonini & Cilia, 2009). A current prevalence of oniomania of 0.7% was reported in another study demonstrating the tentativeness of the current data (Voon et al., 2006b). Still, in general the prevalence of oniomania appears to be lower than that of pathologic gambling or hypersexuality (Ceravolo et al., 2010). Due to a scarcity of data specific risk factors for oniomania are not established. Most studies report general risk factors for developing impulse control disorders in PD with oniomania among them. Most significant risks for developing an oniomania are the younger age of onset of PD and a personal or family history of addictive behavior (Ceravolo et al., 2010; Voon et al., 2006b). Diagnosis of oniomania in PD requires exclusion of a general hypomanic or manic episode. Oniomania is time-consuming and distressing and results in financial, family-related or social problems (McElroy et al., 1994). The therapy again relies on the adjustment of the patients antiparkinsonian medication especially in the withdrawal from dopamine agonists. Additionally, the patients access to money or shopping opportunities may be regulated if possible.

3. Conclusion

Cognitive and psychiatric consequences of Parkinson's disease have a major impact on patients as well as caregivers. They affect the majority of patients with Parkinson's disease to some extent. Dementia, depression and psychotic symptoms are very common traits of advanced parkinsonism and especially affect elderly patients. Still they remain untreated not infrequently. Impulse control disorders are less common in Parkinson's disease and are related to the medical treatment and early onset parkinsonism. Their possibly devastating implications require awareness of the treating physician. Therapeutic options for the cognitive and psychiatric aspects of Parkinson's disease will benefit from future research efforts.

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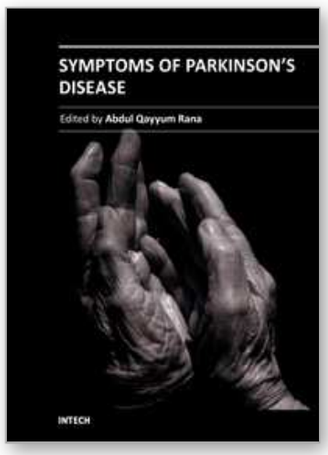

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This book about Parkinsonâ€™s disease provides a detailed account of various aspects of this complicated neurological condition. Although most of the important motor and non-motor symptoms of Parkinsonâ€™s disease have been discussed in this book, but in particular a detailed account has been provided about the most disabling symptoms such as dementia, depression, and other psychiatric as well as gastrointestinal symptoms. The mechanisms responsible for the development of these symptoms have also been discussed. Not only the clinicians may benefit from this book but also basic scientists can get enough information from the various chapters which have been written by well known faculty.

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