Eur Arch Psychiatry Clin Neurosci (2008) 258 [Suppl 5]:55–59 DOI 10.1007/s00406-008-5012-4

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Psychiatric symptoms in Parkinson's disease

Abstract Parkinson's disease (PD) is a neurodegenerative disorder which is often reduced to a mere dysfunction of motor performance. Non-motor symptoms, however, are frequent impairments in PD and result in a major impact on the patients and their caregivers. The major neuropsychiatric comorbidities depression, anxiety, and psychotic symptoms are briefly discussed. Additionally, a brief outlook on deep brain stimulation and its effect on psychiatric symptoms is provided. Several studies did show that neuropsychiatric symptoms are underdiagnosed and consecutively treated inadequately. All in all more attention should be directed to the detection and treatment of psychiatric symptoms in PD patients in routine clinical settings.

Key words Parkinson's disease · depression · anxiety · psychosis · hallucinations · quality of life · deep brain stimulation

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Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder that leads to the classic clinical features consisting of brady kinesia, tremor, rigidity and postural instability. Its prevalence in Europe is around 160 per 100,000, and is expected to rise with the increasing aging of the population [35]. In addition to the motor impairment, PD patients commonly suffer from neuropsychiatric symptoms. Depression, hallucinations, anxiety and psychoses are frequent psychiatric symptoms in PD patients [1, 10, 24] and in 64.7% [25] of PD patients at least one of these symptoms is present. They are associated with impairment in cognitive, functional, and social performance and may cause reduced quality of life. In more advanced PD stages, dementia occurs in up to one third of PD patients, with a major impact on patients and their families' quality of life. With regard to the limited space dementia will not be discussed in detail.

Depression in Parkinson's disease

Depression is the most common psychiatric disorder in PD. Estimates of the prevalence vary widely, from 2.7 to 76%, with an average prevalence of about 35% [24]. Although depression is common in PD and its major impact on the patients' quality of life is well known, depressive symptoms in PD are underrecognized and undertreated in clinical practice [2]. Factors consistently correlated with depression in PD include early-onset PD, advanced progression of PD, female gender, anxiety, cognitive impairment, and psychosis [26]. PD patients with depression tend to experience less guilt and self-blame, and greater rates of anxiety, cognitive deficits, irritability, and suicidal ideation without suicidal behavior than Major Depression patients without PD [30].

The underlying mechanism is still unclear; depression in PD is explained to be a combination of medical, neurochemical, and psychosocial phenomena. In the early stage of PD, depression might be a reaction to the diagnosis of a chronic and disabling disease. However, when compared to patients who suffer from other chronically disabling diseases, PD patients show more severe depressive symptoms [8]. Several studies reported that depression may precede PD onset. This supports the hypothesis that there is a biological risk factor for depression in these patients [19, 28]. Pathologic degeneration of mesolimbic dopamine, norepinephrine, and serotonine pathways in conjunction with degeneration of orbital–frontal circuits and subcortical structures, such as the locus coeruleus, dorsal raphe nuclei, and ventral tegmental area, are postulated to be associated with the development of depressive symptoms [6]. Interestingly, Kim et al. have found no correlation between serotonergic dysfunction and depressive symptoms in patients with PD, but evidence that the dysfunction of noradrenergic and limbic monoaminergic projections was associated with depression [17].

Estimations of the prevalence in PD vary widely from 2.7 to 76%. Possible reasons for this variability include the use of different diagnostic instruments, the criteria applied to define depression, and the diversity of the study populations assessed. Therefore, a recent workgroup proposed provisional diagnostic criteria for depression in PD [20]. Currently, the DSM-IV categories of major depression, minor depression, and dysthymic disorder as well as the category of subsyndromal depression have not been established as valid diagnoses in PD [19, 34]. The severity of depression in PD may range from mild dysthymia to a major affective disorder. Approximately 40% of the observed reduction in health status in PD can be explained by depression [29]. In the majority of cases, depressive symptoms persist or worsen when untreated and there is still uncertainty about how depressive symptoms in PD patients are treated best. Oral antidepressants, behavioral therapy or electroconvulsive therapy are currently used in the treatment of depression in Parkinson's disease [14]. In a recent meta-analysis, less than 30 studies evaluating the effectiveness of antidepressants in PD were identified [38]. Almost all studies failed to define what constituted a response to treatment. The main conclusion of this meta-analysis was that antidepressants have not been adequately evaluated for depression in PD. Therefore, evidence-based recommendations are scarce [23, 29]. One concern regarding the prescription of oral antidepressants in PD patients is the risk of deterioration of Parkinsonism as well as interactions between the medications used to treat PD and antidepressants [4]. Selective serotonine reuptake inhibitors (SSRI) are the most commonly prescribed antidepressants in PD. They are well tolerated in older patients and are characterized by their favorable side effect profile [34] and a low incidence of worsening of motor symptoms in PD [15]. The use of selegiline in combination with a SSRI is contraindicated due to possible adverse reactions [34]. Tricyclic antidepressants (TCA) inhibit the reuptake of serotonin and norepinephrine and produce long-term increases in sensitivity of these receptors. Their anticholinergic properties may be beneficial in the treatment of tremor, but may also worsen cognitive impairment. When patients are already taking anticholinergic medication, TCAs are contraindicated [34]. Nonselective monoamine oxidase (MAO) inhibitors should be avoided in levodopa-treated patients because of the risk for hypertensive crisis [6]. The precise mechanism of electroconvulsive therapy (ECT) on depression is not yet known, but it is hypothesized that the application of ECT stimulates various neurotransmitter systems including dopamine D_2-receptors [34]. Case studies have reported effectiveness of ECT in depressed PD patients, but there are no controlled trials available. Burn et al. state that drug treatment is often, but not always, necessary in depressed PD patients [4]. There is evidence that depression in PD may be partially amenable to psychosocial counselling and cognitive behavioral techniques [36]. Psychotherapeutic treatment options are especially worth considering since there is the possibility of adverse interactions between antidepressant and antiparkinsonian medications. Again, for the treatment of depression in PD patients no published psychotherapy trials are available.

Anxiety in Parkinson's Disease

Anxiety disorders frequently occur in PD patients. Estimations suggest that up to 40% of patients with PD experience substantial anxiety [36]. Anxiety and depression coexist in PD quite often. All types of anxiety disorders have been described in PD, but panic disorder, generalized anxiety disorder (GAD), and social phobia appear to be most commonly encountered in PD patients [22, 31, 33]. Anxiety may also cause a significant deterioration of parkinsonian symptoms.

Similar to depression in PD, anxiety disorders may be attributed to a combination of medical, neurochemical and psychosocial processes. Anxiety frequently develops before the motor features do, suggesting that anxiety may not only represent psychological and social difficulties as a result of PD [39]. Anxiety in PD may be related to the neurochemical changes of the neurodegenerative disease itself [36]. There is evidence for disturbances in central noradrenergic systems, but other neurotransmitters (e.g., serotonin, dopamine) may be involved as well [16]. Anxiety in PD could be due to interactions between dopaminergic deficits and the variable deficits in

norepinephrine and serotonin that are known to occur in PD. Both the ventral tegmental area and the locus coeruleus are characterized by significant neuronal loss in PD. Whether antiparkinsonian medication contributes to the pathogenesis of anxiety needs clarification.

Agents with anxiolytic properties include benzodiazepines, SSRIs, and TCAs. Currently, there is not enough evidence available for the efficacy and safety of anxiolytic agents in the treatment of anxiety in PD. Elderly patients are more sensitive to benzodiazepines due to their tendency towards falls and over-sedation, and concomitant medical conditions, so that these agents should be used with caution [36]. There is evidence of the effectiveness of SSRIs against anxiety in PD patients [6, 36]. So far, there has been no evidence from randomized, placebo-controlled trials as to the treatment of anxiety in patients with PD.

Psychotic symptoms in Parkinson's Disease

Psychotic symptoms rarely occur in untreated PD patients, patients with comorbid dementia, depression, or delirium bear the greatest risk of concomitant psychotic symptoms [10]. Estimates of the prevalence of illusions or hallucinations in treated PD patients vary from 15 to 52%. Delusions occur in 7–16% of patients who have PD, usually in addition to hallucinations [21, 40].

Unlike hallucinations in schizophrenia, hallucinations in PD are predominantly visual and less often auditory, gustatory, olfactory or tactile [6]. PD patients with psychotic symptoms can be divided into two phenomenological groups: one group experiences mild, primarily visual hallucinations (animal or human figures), retains insight into the hallucinations, and does not find them troubling ("benign hallucinosis") [3, 9]. The other group, typically PD patients with dementia, suffers from complex psychotic symptoms, including both hallucinations and delusions. These patients do not have insight into their psychosis, and often find their hallucinations frightening [21]. The latter is less common seen in daily practice.

Parkinson's disease patients manifest psychotic symptoms ≥10 years after the initial diagnosis. In its early stages, PD psychosis tends to occur within a context of a clear sensorium and retained insight. At this stage, assessment with appropriate scales [11], support and counseling may be sufficient in managing psychotic symptoms. However, these symptoms usually recur and worsen over time, and insight may be lost. Persistent psychosis in PD results in significant anxiety, increases the risk of long-term nursing home placement, has a strong impact on caretaker burden, and is strongly associated with social and functional impairment [40].

The underlying mechanism of psychosis in PD remains uncertain, but stimulation of mesolimbic and mesocortical dopamine receptors by dopaminergic agents has been implicated as a major cause of psychotic symptoms [41]. Psychosis occurs more commonly following treatment with dopamine agonists than with levodopa. Pharmacologic parameters, however, such as the dosage of dopaminergic medication, plasma concentrations, and duration of therapy are not correlated consistently with the development of hallucinations or psychosis [10]. The association between psychosis and cognitive impairment suggests more widespread brain involvement including diverse neurotransmitter systems and neural pathways [37].

The treatment of psychosis in PD is a challenge, since optimizing the management of motor symptoms with dopaminergic medication typically worsens psychosis, and treating psychosis with an antipsychotic can worsen Parkinsonism [37]. Usually, the management of psychosis in PD starts with a systematic and stepwise reduction of anti-parkinsonian drugs which are typically associated with a high risk of inducing psychosis and a relatively small beneficial effect on Parkinson symptoms. Furthermore, the short-acting formulation of levodopa may reduce the risk of accumulating adverse side effects. In addition, polypharmacy has been identified as an independent risk factor for psychosis in PD. Last but not least, medical causes, which bring on or aggravate psychosis, should always be considered and treated accordingly.

A reduction of psychotic symptoms may be achieved at the cost of modest deterioration in symptomatic motor benefit. If the worsening of motor symptoms is not tolerable, certain atypical antipsychotic drugs can be used without significantly worsening motor function [12]. A recent review and meta-analysis concluded clozapine to be the only atypical antipsychotic fully recommended for the treatment of Parkinson's disease psychosis due to its demonstrated efficacy and tolerability in two well-designed randomized controlled trials, and numerous open-label trials [13]. Clozapine, however, is often avoided because of the cumbersome monitoring related to agranulocytosis. Quetiapine, an atypical neuroleptic, was tested in numerous open-label studies and was shown to be well-tolerated and efficacious in the treatment of PD psychosis [12]. It appears to be slightly less effective than clozapine. It may also induce mild motor worsening, but not to the extent seen with risperidone and olanzapine. Furthermore, quetiapine does not carry an associated risk of agranulocytosis. Therefore, quetiapine is a common choice for treating PD psychosis.

While atypical antipsychotics continue to be the most commonly prescribed pharmacologic agents in the treatment of PD psychosis, it has been found that they are associated with an increased risk of mortality when used in elderly patients with dementia. This finding is particularly relevant for PD psychosis considering the age and frailty of the late-stage PD

patients who typically experience psychosis. Since the mechanisms by which atypical antipsychotics cause increased mortality have not been fully elucidated, alternative therapies are currently being evaluated. Recently, cholinesterase inhibitors have been described to have an effect on psychosis in PD but further research is necessary before cholinesterase inhibitors can be recommended as a first-line treatment for PD psychosis.

Deep brain stimulation in Parkinson's disease

In the last decade deep brain stimulation of the subthalamic nucleus (DBS) has become an accepted treatment option for the advanced stages of PD [7]. DBS is often assessed with regard to the improvement of PD motor symptoms, while psychological domains such as emotion or cognition have only recently come into the focus of interest.

An early study on psychiatric effects of DBS of the subthalamic nucleus was able to demonstrate selectively enhanced affective processing and subjective well being [27]. However, a 5-year follow-up study on bilateral DBS of the subthalamic nucleus did not report any changes or improvements in the Beck depression inventory-scores [18]. In a first review on effects of subthalamic stimulation on mood state, Takeshita et al. concluded that the majority of the studies could show antidepressant effects of DBS, but some studies even did show hints to pro-depressant effects including suicide attempts [32].

Few studies have directed their focus on effects of DBS other than depression or mood states. In a recent study by Castelli et al. cognition, anxiety states and personality traits have been examined. The authors conclude that DBS of the subthalamic nucleus is cognitively safe, and shows small improvements in depression, obsessive-compulsive and paranoid personality traits [5].

The picture becomes even more complicated when considering the heterogeneity of the chosen target points for DBS and the differences in unilateral or bilateral approaches.

Reconsidering the data dealing with effects of DBS on psychiatric symptoms, it seems only valid to conclude that effects on affective states such as depression are likely, and effects on other psychiatric comorbidities of PD are not yet understood. Future studies in DBS should involve thorough pre-, peri- and postoperative psychiatric assessment to provide reliable data on the effects of DBS on psychiatric symptoms.

Summary

Depression, anxiety and psychotic symptoms are frequent non-motor symptoms in PD patients with a significant impact on health-related quality of life and caregiver distress. Despite the high prevalence of anxiety and depression in PD, these conditions remain unrecognized and untreated in a large proportion of patients who have PD. Therefore, more attention needs to be paid to the detection and treatment of psychiatric symptoms in PD patients in routine clinical settings.

Conflict of interest statement F. Schneider received grants/research support from AstraZeneca and from Lundbeck in the recent years and is consultant for AstraZeneca, Otsuka and Janssen-Cilag. A. Althaus, V. Backes and R. Dodel have no financial conflicts of interests to declare.

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