What a neurologist should know about depression in Parkinson's disease

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ABSTRACT

Depression is a frequent non-motor symptom of Parkinson's disease. Its prevalence varies widely across studies (between 2.7% and 90%); around 35% have clinically significant depressive symptoms. Although depression can have an immense impact on the quality of life of affected patients and their caregivers, depressive symptoms in Parkinson's disease frequently remain unrecognised and, as a result, remain untreated. Here we overview the diagnostic challenges and pitfalls, including the factors contributing to the underdiagnosis of depression. We also discuss current ideas on the underlying pathophysiology. Finally, we offer a treatment approach based on currently available evidence.

INTRODUCTION

James Parkinson first acknowledged an association between Parkinson's disease (PD) and depressed mood. In his 'Essay on the Shaking Palsy', he cited his colleague Dr Maty, who referred a patient with the following words: 'A more melancholy object I never beheld'. We now realise that depression is one of the most frequently observed non-motor symptoms of PD, with a place in the new clinical diagnostic criteria for PD.[1] Depression has an immense impact on the quality of life of patients and their caregivers, even early in the disease.[2] Even though depressive symptoms are associated with more severe cognitive and motor problems, an increased mortality risk and earlier withdrawal from the workforce, depression in PD frequently remains unrecognised.[3 4]

To improve the quality of life of PD patients and their caregivers and to reduce the impact on society, we need better diagnosis and treatment of depression in PD. In this review, we discuss the diagnostic challenges and pitfalls of depression in PD, its pathophysiological background and we recommend a treatment approach.

DIAGNOSING DEPRESSION

Epidemiology and diagnostic criteria

Diagnostic criteria for a major or minor depressive episode, dysthymic disorder and adjustment disorder with depressed mood have been formulated within the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) (box 1). The prevalence of depression in PD varies widely across studies (between 2.7% and 90%). The prevalence of clinically significant depressive symptoms is around 35%.[5] Most patients have mild symptoms that can be classified as a mild depressive episode, dysthymic disorder or adjustment disorder with depressed mood. The prevalence of major depression in PD ranges from 2.3% to 55.6% (estimated average 19%).[5] A subgroup of patients experience clinically relevant depressive symptoms restricted to off periods (ie, during episodes of the day when the dopaminergic drug effects have worn off). This subgroup of depression does not meet the criteria of a mild or major depressive episode, dysthymic disorder or adjustment disorder with depressed mood, as in these cases depressive symptoms are often of shorter duration (ie, restricted to off periods). These depressive symptoms are classified as subsyndromal depression.[6]

There are subtle differences between depression in the general population and depression in PD. For instance, patients with PD less often report feelings of guilt and worthlessness but more often

Box 1 DSM-IV criteria for diagnosing a depressive disorder

A: The following symptoms are present during two consecutive weeks and represent a change from baseline: at least five in case of a major depressive episode and at least two in case of a minor depressive episode. At least criteria 1 or criteria 2 should be met. Each criterion should be present nearly every day.

1. Depressed mood most of the day.
2. Decreased interest or pleasure in most activities, most of each day.
3. Significant weight change (5%) or change in 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 more indecisiveness.
9. Recurrent thoughts of death or suicide or has a suicide plan.

B: The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
C: The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse and a medication) or a general medical condition (eg, hypothyroidism).
D: The major depressive episode is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder or psychotic disorder not otherwise specified.
E: There has never been a manic episode, a mixed episode or a hypomanic episode.

Box 2 How to improve the diagnosis of depression

Proactive approach by the treating physician/nurse (including routinely conducting a careful hetero-anamnesis in an immediate caregiver).
Consider depression in patients with (unexplained) motor or cognitive deterioration and/or sleep disturbances.
Be aware of overlap between Parkinson's disease (PD) symptoms and depressive symptoms

- Motor symptoms (lack of facial expression, stooped posture and slowing of movements)
- Somatic symptoms (fatigue and lack of energy)
- Cognitive features (diminished attention and mental slowing)

Use an inclusive approach to diagnose depression (no distinction between symptoms attributable to PD or to depression).
Distinguish depression (high degree of subjective suffering) from apathy (low to absent subjective suffering).
Distinguish psychotic features accompanying depression (mood-congruent) from psychotic features related to dopaminergic treatment and/or cognitive decline (more common, not mood-congruent).
Screening questionnaires can help; using adjusted cut-off scores is recommended.

experience indecisiveness.[7] In addition, the risk of suicide in patients with PD is lower than that in the general population: 0.08% in patients with PD compared with 0.8% in the general population.[8] Case reports suggested an increased suicide risk in patients with PD after deep brain stimulation, but more recent evidence does not confirm this.[9] Note that the strongest predictor of suicide after deep brain stimulation is the existence of depressive symptoms; such patients therefore require careful monitoring for depression.

Diagnostic challenges and pitfalls

Depressive symptoms in patients with PD frequently remain unrecognised. Of the 44% of patients attending a routine appointment that actually had depression, their neurologist identified this in only 21%.[10] Several factors lead to this underdiagnosis (box 2).

First, treating physicians frequently do not recognise depressive symptoms in patients with PD or at least not in time. This is actually quite understandable, because depressive symptoms grossly overlap with PD symptoms.[6] For example, psychomotor retardation with slowing of movements, a stooped posture and lack of facial expression can occur during a depressive episode and also resemble the motor features characterising PD. Physicians therefore need to search literally 'behind the mask' (the poker face) to identify the depressed mood. Also, cognitive changes that typically accompany a depressive episode, such as diminished attention and mental slowing, can occur in patients with PD irrespective of depression. Moreover, sleep disturbances and fatigue are well known features of both depression and PD itself. Therefore, depression should be considered in patients with depressed mood or anhedonia (ie, decreased interest or pleasure) and in patients with (unexplained) motor impairment, cognitive deterioration or sleep disturbances. To prevent underdiagnosis of depression in PD, we advocate an inclusive approach that does not distinguish between symptoms putatively attributable to PD or attributable to depression. This approach has been validated for diagnosing a major or mild depressive episode or dysthymic disorder in patients with PD.[11]

Second, it can be difficult to distinguish depression from other non-motor symptoms of PD, such as apathy, anxiety or psychotic features. Patients with PD may show apathy, anxiety and psychosis in isolation and separately from depression. However, these also commonly accompany depression. About 20%–60% of patients with PD have apathy, the prevalence increasing with greater disease severity. It is important to distinguish apathy from depression, because apathy

Table 1 Questionnaires validated to assess depression in PD

	Number of somatic items	Recommended cut-off score
Questionnaires suited for screening purposes		
Hamilton Depression Rating Scale (HAM-D)	***	<10
Beck Depression Inventory (BDI)	**	<14
Hospital Anxiety and Depression Scale (HADS)	*	<11
Montgomery Asberg Depression Rating Scale (MADRS)	**	<15
Geriatric Depression Scale (GDS)	*	<5
Questionnaires suited to assess depression severity and changes over time		
Hospital Anxiety and Depression Scale (HAM-D)		
Beck Depression Inventory (BDI)		
Montgomery Asberg Depression Rating Scale (MADRS)		
Zung Self-Rating Depression Scale (SDS)		

Number of somatic items: *25%; **25%–50%; ***50%.

requires a different treatment approach. Apathy is defined by reduced goal-directed behaviour resulting from a lack of motivation, enthusiasm and blunted emotion. Note that anhedonia—a decreased ability to experience pleasure—can be a core feature of both apathy and depression. The key clinical difference between depression and apathy is the lack of subjective suffering in apathetic patients (low or absent) compared with patients that have a depression (high degree of subjective suffering). For a comprehensive review on apathy in PD, see ref.[12]

About 30% of people with PD have anxiety disorders, the most common being generalised anxiety disorder, social phobia, anxiety not otherwise specified, specific phobia and panic disorder. About 20% of all patients with PD have depression and comorbid anxiety.[13] Note that both apathy and anxiety, as with depression, can occur during off periods in patients with motor fluctuations. This suggests that the neurobiological substrates that underly depression, anxiety and apathy in PD partly overlap.[14] A depressive episode in PD can be accompanied by psychotic symptoms, but these are mainly mood-congruent (eg, nihilistic delusions and delusions of guilt). Psychotic features (like paranoia) in PD more often relate to cognitive decline and to (dopaminergic) medication than to a depressive episode.

Finally, another important factor contributing to underdiagnosis is the patients themselves under-reporting depressive symptoms. In a large study, incorporating data of over 1000 patients, about half had clinically relevant depressive symptoms as measured with the Beck Depression Inventory, yet only 1% volunteered depressive symptoms—a striking degree of under-reporting.[15] Why there is such under-reporting is not clear. This study highlights the importance of a proactive approach by the treating physician or nurse in diagnosing depression in PD and particularly emphasises the need to conduct a careful hetero-anamnesis (interviewing a close carer).

Diagnostic tools

Although a formal diagnosis should be made based on DSM criteria, in clinical practice, screening tools might be useful for first detecting a depression. A taskforce from the *Movement Disorders Society* investigated which questionnaires are most suitable to assess depression in PD.[16] Several questionnaires were compared, and recommendations were made (differentiating screening purposes from severity assessments) (table 1). Note that while the Montgomery Asberg Depression Rating Scale and Hamilton Depression Rating Scale were originally developed to assess depression severity, they have also been validated for screening purposes in PD. All these questionnaires incorporate somatic items that overlap with symptoms related to PD; therefore, it is recommended to use adjusted cut-off scores (table 1).

We acknowledge that administrating self-rated questionnaires in a busy clinical practice is not always possible. A potentially useful approach when screening for depression (though not formally evaluated) might be to pose the question related to the depression item of the new Unified Parkinson Disease Rating Scale.[17] Specifically, clinicians could ask: 'Over the past week have you felt low, sad, hopeless or unable to enjoy things?' If yes, determine the duration and impact by asking: 'Was this feeling for longer than one day at a time?' And: 'Did it make it difficult for you to carry out your usual activities or to be with people?' If the patient experiences depressive symptoms, always determine if there is a relationship with their dopaminergic medication schedule and/or motor symptoms.

PATHOPHYSIOLOGY

The underlying mechanisms of depression in PD are incompletely understood, but a multifactorial model appears to be most appropriate. Contributory factors

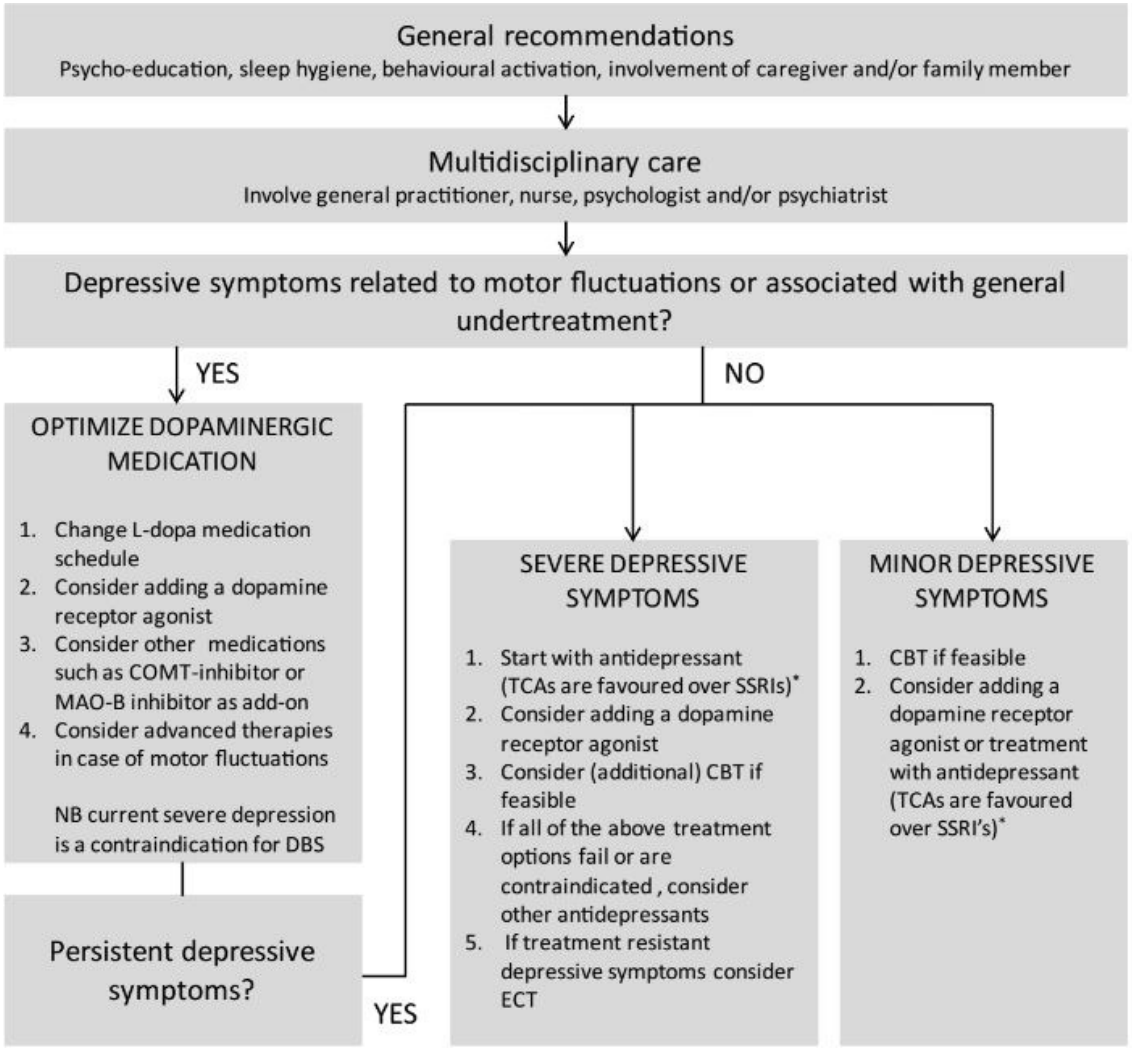

Figure 1 Flow chart treatment recommendations. When prescribing antidepressants, always take possible adverse effects into account and be aware of drug interactions (see table 2). CBT, cognitive–behavioural therapy; ECT, electroconvulsive therapy; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; DBS, deep brain stimulation; NB, nota bene.

include: the individual underlying (genetic) vulnerability to depression, the occurrence of life events, individual coping abilities, psychosocial factors and disease-specific factors. As in the general population, a positive family history of depression, a personal history of depression and lower education levels contribute to an enhanced depression risk. Moreover, a diagnosis of PD can lead to reactive depression and to anxieties about the disease course, possible future disabilities and concerns about future perspectives. Many patients with PD already experience depressive symptoms in the years before being diagnosed with PD,[18] and depression is considered one of the premotor symptoms.[19]

Several studies support the idea that changes in the dopamine system contribute to PD-related depression. For example, clinical studies revealed that approximately 75% of patients with motor fluctuations also experience prominent off period-related depressive symptoms.[20] Moreover, pharmacological trials show that dopaminergic medication has an antidepressant effect (see below). Nuclear neuroimaging studies have confirmed involvement of the dopamine system in PD-related depression. Depressed patients with PD have lower striatal dopamine transporter (DAT) binding compared with non-depressed patients.[21] Lower DAT binding is thought to reflect more severe neurodegeneration of striatal dopaminergic neurones resulting in lower striatal dopamine levels.

In addition to dopamine, other neurotransmitters may also contribute, and these include noradrenalin, acetylcholine and serotonin. Although evidence is scarce, neuropathological and neuroimaging studies have shown that noradrenergic neurones in the locus coeruleus and serotonergic neurones in the raphe nucleus degenerate in patients with PD, with more severe degeneration in those patients with PD who suffer(ed) from depression.[14] The exact contribution

Table 2 Antidepressant medications, contraindications and adverse effects

Type of medication	Contraindications	Potential adverse effects
Dopamine receptor agonists	Take care in older patients with PD (>70 years of age), PD patients with cognitive impairment and/or psychotic symptoms and orthostatic hypotension	Impulse control disorder, cognitive dysfunction, hallucinations, orthostatic hypotension, gastric complaints and excessive daytime sleepiness
TCAs	Take care in PD patients with urinary retention, orthostatic hypotension, (angle-closure) glaucoma and cardiovascular disorders (especially tachycardia)	Cognitive dysfunction, excessive daytime sleepiness, orthostatic hypotension, tachycardia, gastric complaints, dry mouth, urinary retention and headache
SSRIs	Take care in patients with PD who use MAO-B inhibitors (selegeline or rasagiline) due to the risk of developing a serotonin syndrome	Sleep disturbances, gastric complaints, dry mouth, erectile dysfunction, dizziness, headache, musculoskeletal pain, pharyngitis and less often cognitive dysfunction

MAO-B, monoamine oxidase B; PD, Parkinson's disease; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

of each of these neurotransmitter systems to depression in PD needs to be elucidated in future research.

TREATMENT

We propose a flowchart with recommended treatment steps for depression in patients with PD. This is based on meta-analyses of randomised placebo-controlled trials or just randomised (placebo)-controlled studies. Lower class evidence studies were only included if no other evidence was available.

General recommendations

Before starting treatment, evaluate the severity of depressive symptoms and assess if there are any suicidal ideation or concrete plans for suicide. A multidisciplinary team approach is particularly important for all PD patients with depression (figure 1). Depending on the severity, this could mean involving an experienced nurse, general practitioner, psychologist and/or psychiatrist. In cases with severe depressive symptoms, especially when there is an enhanced suicide risk, we strongly recommend psychiatric consultation. Our recommendation for a multidisciplinary team approach is largely based on our experience but is also partially supported by clinical studies (acknowledging the challenge that there are multiple models and that it is difficult to evaluate multidisciplinary care). Recent work suggests that some forms of multidisciplinary care may contribute to better quality of life and a greater reduction of depressive symptoms.[22]

General interventions for treating depression include verbal and written psychoeducation, information about self-help, support groups, sleep hygiene, the need for behavioural activation and involvement and support of family members/carers.[23] Involving family members and carers is even more important when depression develops in the setting of another chronic disease (such as PD): a recent meta-analysis showed that involving family members in treating depression is effective (although effects were small) in reducing depression in patients with chronic disease.[24] Only few studies have specifically examined the effect of psychosocial interventions in depression in PD; most had small sample sizes and so did not reach firm conclusions.

Below we discuss several possible clinical interventions for depression in PD. The treatment choice in general should be guided by various factors, including the severity and duration of the depressive episode, previous response to treatment, potential adverse effects, the likelihood of adherence to treatment and the patient's own preferences.[23]

Depression related to motor fluctuations or general undertreatment

The next step in our treatment algorithm is to decide if the depression relates to motor fluctuations or is associated with general undertreatment: if it is, the first step is to optimise dopaminergic treatment. Although clinical experience suggests that levodopa plausibly has an antidepressant effect, this has never been investigated in randomised placebo-controlled trials. One small sample size (n=8) placebo-controlled study showed a short-term effect of levodopa infusion on mood and anxiety.[25] The antidepressant effect of dopamine receptor agonists, especially pramipexole, has been shown in a few randomised clinical trials.[26 27] Dopamine receptor agonists and levodopa have not been compared directly for antidepressant effect.

Optimising dopaminergic treatment mainly depends on the (dopaminergic) medication that the patient already uses and on other individual patient characteristics (see table 2). In general, clinicians can follow established strategies to treat motor symptoms. Note that the dopamine receptor agonists (and maybe also levodopa) have relatively small antidepressant effects,[26 27] so patients with severe depressive

Table 3 Randomised placebo-controlled clinical trials

Study	Inclusion criteria	Design	Results	Meta-analyses
Cognitive–behavioural therapy (CBT)				
Dobkin *et al*[39]	PD + major depression, dysthymia or depression not otherwise specified according to the DSM-IV criteria	Randomised-controlled trial of 10 weekly CBT sessions (n=41) versus clinical monitoring (n=39) Primary outcome: change in HAM-D score	CBT versus clinical monitoring (p<0.001) CBT: HAM-D baseline 20.9; endpoint 13.6 Clinical monitoring: HAM-D baseline 19.4; endpoint 19.3	
Antidepressants				
Devos *et al*[33]	PD + major depression according to the DSM-IV + MADRS ≥20	Double-blind randomised-controlled trial of 30 days treatment with desipramine (n=17), citalopram (n=15) or placebo (n=16) Primary outcome: change in MADRS score	Desipramine versus placebo (p<0.05) Citalopram versus placebo (p<0.05) Desipramine versus citalopram (ns) Desipramine: MADRS baseline 29; endpoint 9 Citalopram: MADRS baseline 25; endpoint 11 Placebo: MADRS baseline 27; endpoint 18	Rocha *et al*[31] Antidepressants versus placebo (CI 0.98 to 1.87, ns) TCAs versus placebo (CI 0.57 to 2.52, ns) SSRIs versus placebo (CI 0.57 to 2.52, ns) TCAs versus SSRIs (CI 1.06 to 2.99, significant)
Leentjens *et al*[34]	PD + major depression according to the DSM-IV	Double-blind randomised-controlled trial of 10 weeks treatment with sertraline (n=6) or placebo (n=6) Primary outcome: change in MADRS score	Sertraline versus placebo (ns) Sertraline: MADRS baseline 20; endpoint 11 Placebo: MADRS baseline 19; endpoint 8	
Menza *et al*[37]	PD + major depression or dysthymia according to the DSM-IV	Double-blind randomised-controlled trial of 8 weeks' treatment with paroxetine (n=18), nortriptyline (n=17) or placebo (n=17) Primary outcome: change in HAM-D score	Paroxetine versus placebo (ns) Nortriptyline versus placebo (p<0.01) Paroxetine versus nortriptyline (p=0.08) Paroxetine: HAM-D baseline 18.8; endpoint 12.5 Nortriptyline: HAM-D baseline 21.1; endpoint 10.8 Placebo: HAM-D baseline 19.3; endpoint 15.9	Troeung *et al*[32] Antidepressants versus placebo (CI −1.33 to 3.08, ns) TCAs versus placebo (*d*=1.35, CI 0.19 to 2.52, significant) SSRIs versus placebo (*d*=0.57, CI −1.33 to 2.47, ns)

Continued

Table 3 Continued

Study	Inclusion criteria	Design	Results	Meta-analyses
Richard *et al*[36]	PD + major depression, minor depression or dysthymia according to the DSM-IV or subsyndromal depression	Double-blind randomised-controlled trial of 12 weeks' treatment with paroxetine (n=42), venlafaxine (n=34) or placebo (n=39) Primary outcome: change in HAM-D score	Paroxetine versus placebo ($p<0.001$) Venlafaxine versus placebo ($p<0.05$) Paroxetine versus venlafaxine (ns) Paroxetine: HAM-D baseline 22.2; endpoint 9.2 Venlafaxine: HAM-D baseline 21.2; endpoint 10.2 Placebo: HAM-D baseline 21.4; endpoint 14.6	
Wermuth *et al*[35]	PD + major depression according to the DSM-III	Double-blind randomised-controlled trial of 52 weeks' treatment with citalopram (n=18) or placebo (n=19) Primary outcome: change in HAM-D score	Citalopram versus placebo (ns) Citalopram: HAM-D baseline 16.6; endpoint 3.5 Placebo: HAM-D baseline 16.2; endpoint 9.8	
Dopamine receptor agonists				
Barone *et al*[26]	PD + GDS $\geq$5 and UPDRS part 1 depression item score $\geq$2	Double-blind randomised-controlled trial of 12 weeks' treatment with pramipexole (n=139) or placebo (n=148) Primary outcome: change in BDI score	Pramipexole versus placebo ($p<0.05$) Pramipexole: baseline BDI 18.7, endpoint 13.1 Placebo: BDI baseline 19.2, endpoint 15.0	

DSM, Diagnostic and Statistical Manual of Mental Disorders; GDS, Geriatric Depression Scale; ns, non-significant; UPDRS, Unified Parkinson's Disease Rating Scale.

symptoms require a different treatment approach (see below).

PD patients with depression seem more vulnerable to develop impulse control disorders,[28] such as hypersexuality, binge eating, compulsive shopping and pathological gambling, so they need close monitoring.

Advanced treatments, such as continuous jejunal levodopa infusion or deep brain stimulation, can also be considered in patients with motor fluctuations who have accompanying non-severe mood fluctuations. Although, no clinical trials have assessed depressive symptoms as a primary outcome in patients that received advanced treatments, indirect evidence suggests that depressive symptoms are likely to improve.[29 30] However, these patients definitely need extra careful psychiatric (preintervention and postintervention) evaluation as well as strict follow-up monitoring. Moreover, current severe depression is a contraindication for deep brain stimulation. Depression on its own is not an indication for advanced treatment.

Depression unrelated to motor fluctuations or motor symptom deterioration

The choice of treatment for depressive symptoms that are unrelated to motor fluctuations or motor symptom deterioration depends mainly on depression severity. This approach can also be used in PD patients with depressive symptoms that are (or initially were) related to motor fluctuations or motor symptom deterioration, but persist despite optimising dopaminergic treatment.

Severe depressive symptoms

If depressive symptoms are severe, we suggest considering antidepressant medication. Although evidence is still scarce, two recent meta-analyses suggest that antidepressant medication might help depression in patients with PD (table 3).[31 32] These meta-analyses included randomised placebo-controlled clinical trials that assessed treatment effects in patients with PD and a clinical diagnosis of depression (mostly major depression).[33–37] Table 3 gives the inclusion criteria, sample sizes, interventions and outcome measures. Note that there were methodological difficulties with both meta-analyses, the number of included studies was limited and sample sizes were small. Troeung *et al*'s meta-analyses found a non-significant pooled effect of treatment with antidepressants over placebo. However, the pooled effect of treatment with tricyclic antidepressants (TCA) (desipramine and nortriptyline) identified a significant antidepressant effect (with medium effect size). There was no such effect for selective serotonin reuptake inhibitors (SSRIs) (citalopram, sertraline and paroxetine). In the meta-analyses by Rocha *et al*, both SSRIs and TCAs were not superior to placebo, but TCAs were superior to SSRIs.[31] Therefore, treatment with TCAs (nortriptyline and desipramine) is favoured slightly over treatment with SSRIs.

There was no significant difference in antidepressant effect between an SSRI (sertraline) and a dopamine receptor agonist (pramipexole).[27] There has been no direct comparison of dopamine receptor agonists and TCAs. Based on the effect sizes of the separate studies (see also table 3), the antidepressant effect of TCAs is seemingly larger than that of dopamine receptor agonists.[26 31 32] Therefore, in a case of severe depression, we prefer antidepressants (especially TCAs) over dopamine receptor agonists. If treatment fails and the patient has not yet received a dopamine receptor agonist, clinicians should consider adding a dopamine receptor agonist. When prescribing antidepressants or dopamine receptor agonists, it is important to take contraindications and possible adverse effects into account and to monitor patients closely (table 2). Both dopamine receptor agonists and antidepressants frequently cause sleep disturbances. While dopamine receptor agonists and TCAs most often cause excessive (daytime) sleepiness, SSRIs can induce increased sleepiness as well as insomnia. For a patient with depression and comorbid sleeping difficulties, sleepiness can be a potentially positive side effect: they may benefit from taking a dopamine receptor agonist or TCA before bedtime.

In practice, we suggest taking a dopamine receptor agonist and/or TCA at night and an SSRI in the morning. If the SSRI causes excessive daytime sleepiness, it can be taken instead at night. Other frequent side effects of both dopamine receptor agonists and antidepressants, specifically TCAs, are cognitive disturbances and psychotic symptoms. These are less common with SSRIs. Therefore, SSRIs are preferred when treating depression in patients with comorbid cognitive impairment.

With respect to other antidepressants: venlafaxine, a combined serotonin and noradrenalin reuptake inhibitor, was no more effective than treatment with SSRIs; atomoxetine—a noradrenalin reuptake inhibitor—was not superior to placebo.[36 38] Thus far, no randomised placebo-controlled trials have investigated the effect of newer antidepressants such as buproprion—a combined reuptake inhibitor of dopamine, serotonin and noradrenalin. As such, there is little evidence to support the efficacy of these antidepressants in PD.

When starting treatment, we recommend the motto: start slow, then go. At first, carefully monitor for potential side effects. If the medication is well tolerated, then start to increase the dose. For dopamine receptor agonists, we suggest increasing the dose

every 1–2 weeks until there is a response. If the patient does not respond to pramipexole 3 mg/day or ropinirole 15 mg/day, we suggest not increasing the dose further.[26] The dose of TCAs should be increased gradually, every other week, until reaching the therapeutic range (monitor serum drug concentrations). The start dose of SSRIs is usually the therapeutic dose. Both TCAs and SSRIs should be continued for 6 weeks after reaching the therapeutic dose to assess its efficacy.[23]

Besides medication treatments, clinicians should always consider additional cognitive–behavioural therapy (CBT). In one large randomised controlled trial, CBT was compared with clinical monitoring.[39] In this study with 1 month follow-up, CBT was more effective in treating depressive symptoms than clinical monitoring (table 3). There has been no direct comparison in PD between treating depressive symptoms with CBT or medication (antidepressants or dopaminergic medication). One advantage of CBT is that it has no adverse effects. Moreover, CBT's mechanism of action differs from that of medication. Thus, combining CBT with medication potentially has a greater effect. Note, however, that CBT requires sufficient cognitive capacity and no language barriers.

If all these treatment options fail and the patient still has severe depressive symptoms, it is worth considering electroconvulsive therapy (ECT). There are no randomised controlled trials studying the efficacy of ECT for treating depression in PD. However, data from one retrospective study, analysing 25 PD patients with depression who underwent ECT, found a significant reduction in depressive symptoms after treatment.[40] Interestingly, ECT might also help PD motor symptoms. It is regarded as safe in patients with PD (without deep brain stimulation) and as such clinicians should consider it in patients with severe and treatment-resistant depression.

Mild depressive symptoms

In patients with mild depressive symptoms, we suggest starting with CBT. We advocate CBT over medication mainly because it has no potential adverse effects. If CBT is not feasible or ineffective, one could consider adding a dopamine receptor agonist or antidepressant (TCAs are favoured slightly over SSRIs) to the medication regimen. (See text above and table 3 for available evidence, and table 2 for contraindications and most common side effects.)

CONCLUSION

Depression in PD can greatly influence the quality of life of both affected patients and their caregivers, yet is frequently underdiagnosed and often undertreated. We have reviewed the diagnosis, diagnostic pitfalls and diagnostic clues, pathophysiology and a broad spectrum of treatment options, thus providing clinicians with tools to improve the quality of life patients and their caregivers.

Key points

- Depression is a frequent, debilitating and often unrecognised non-motor symptom of Parkinson's disease.
- Neurologists should be aware of the overlap between depressive symptoms and Parkinson's disease symptoms.
- Consider depression in patients with (unexplained) motor or cognitive deterioration and/or sleep disturbances.
- We advocate a proactive approach, with regular careful anamnesis and hetero-anamnesis to improve depression diagnosis.
- Treating depression requires a multidisciplinary team approach and depends on associated motor function and depression severity.

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