Depression in neurological disorders: Parkinson disease and multiple sclerosis

Francesca Falzon Aquilina[1], Mark Agius[2,*]

[1] CT1 Psychiatry Trainee, Mount Carmel Hospital, Department of Psychiatry, University of Malta, Malta

[2] Clare College Cambridge Department of Psychiatry, University of Cambridge, Cambridge, UK

***Corresponding author email: ma393@cam.ac.uk**

Abstract

Depression is not only highly prevalent in the general population but also in neurological disorders such as Parkinson disease (PD) and multiple sclerosis (MS). The manifestations, diagnosis and treatment of depression in both PD and MS can be complex. There is limited scientific research related to current therapies. There is a need for further research with regard to treatment options in depression for both neurological disorders.

Keywords: depression, neurological disorder, multiple sclerosis, Parkinson disease, comorbid, diagnosis, treatment, research

Introduction

Depression is a heterogenous group of conditions that may contribute significantly to impairments in quality of life. The diagnosis of depression can be challenging in disorders that cause psychomotor disturbances and changes in vegetative states. It is important for clinicians to be able to recognize the signs and symptoms of depression in order to safeguard the wellbeing of the patient with a neurological illness.

The research and evidence base in this area remains very limited. The treatment of depression in neurological disorders rests mostly on clinical judgements made through general clinical consensus and from years of experience. More controlled trials of the treatment of depression within the context of neurological illness are needed.

Depression in Parkinson disease

Making a diagnosis of depression in a patient with Parkinson disease (PD) is important for a number of reasons. First, depression is common in PD and can directly influence morbidity and the quality of life. This can cause further disability and an increased strain on carers. These consequences are independent of the physical symptoms of the condition itself.

Epidemiology of depression in PD

The incidence of comorbid depression may vary between 4-75% in patients with PD (1). However, there are few prospective epidemiological studies. The available surveys have a number of methodological flaws which may result from inaccurate sampling methods and imprecise measures used to quantify depressive symptoms. One major source of variation is group selection. Research centres are found to diagnose depression in 40-50% of patients, whereas community studies may reveal rates lower than 10%. Rates of depression may also vary widely across different countries. The Global Parkinson Disease Survey, including 1000 patients, 200 clinicians and 187 carers in five countries, established that in the US almost half of patients with PD had clinical depressive symptoms while countries such as Norway and China produced estimates of 7.5% and 16.5%, respectively, for the rate of major depression in people with PD (1).

On the other hand, two well-conducted studies using case-control methodology have found that the odds ratio for a previous history of depression in PD cases was around 2 compared to controls. Moreover, the average time between the onset of depressive symptoms and motor symptoms was around six years,

which also correlated with PET studies, suggesting that the onset of the disease process may precede motor symptoms of PD by the same time frame (2).

Assessment of depression in PD

A diagnosis of depression may be challenging due to overlap between the symptoms of depression and PD. Patients with advanced PD may show alteration in their sleep cycle, fatigue, psychomotor slowness, difficulty concentrating and sexual dysfunction. Patients with PD may also exhibit withdrawal from social activities due to disabling dyskinesias, or feel uncomfortable with their appearance. Other hallmarks of depression include the following.

1. Low mood with diurnal variation for at least two weeks
2. Early-morning waking
3. Pessimistic thoughts about the world, themselves and a bleak vision of the future
4. Suicidal ideation

The table below highlights the criteria for diagnosing major depressive disorder according to DSM-5 criteria (3). Because many of the symptoms of depression in the DSM criteria are similar to those listed above for PD, it may be difficult to evaluate the degree to which a patient with PD is actually depressed.

DSM-5 criteria for major depressive disorder

1. Five or more of the following symptoms, present during the same two-week period and representing a change from previous functioning, and including depressed mood and/or loss of interest or pleasure • depressed mood most of the day, nearly every day • diminished interest or pleasure in activities most of the day, nearly every day • weight loss when not dieting, weight gain, or decrease or increase in appetite nearly every day • insomnia or hypersomnia • psychomotor agitation or retardation • fatigue or loss of energy nearly every day • feelings of worthlessness, excessive or inappropriate guilt • diminished ability to think or concentrate, or indecisiveness • recurrent thoughts of death, suicidal ideation without a specific plan, or suicide attempt or specific plan for committing suicide
2. The symptoms cause clinically significant distress or impairment in social, occupational and other important areas of functioning
3. The episode is not attributable to physiological effects of a substance or another medical condition
4. There has never been a manic or hypomanic episode
5. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specific or unspecific schizophrenia spectrum disorder or other psychotic disorder

Because symptoms of depression such as low mood can be ascribed to other psychiatric disorders, careful history taking is essential. For example, adjustment disorders manifest as brief changes in mood and function following a significant life event, such as being diagnosed with PD itself. As a result, directly after diagnosis, a patient may appear to be depressed while actually going through an adjustment disorder.

The adjustment disorder may resolve without active treatment. Low mood and reduction in daily function may also be a prodromal feature of dementia. Iatrogenic low mood should also be considered, as medication used to treat PD may precipitate such symptoms. Neurosurgical procedures have also been shown to cause transient dysphoria, especially when involving stimulation of the subthalamic nucleus (2).

Several rating scales can be used to diagnose depression in PD patients. These include the Beck Depression Inventory (BDI), the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale (HDRS). There are limited studies validating their use in this patient population (4). The cutoff score on a rating scale (eg: HDRS >18) may be used in treatment studies to diagnose depression in PD patients, however these scales may over-diagnose depression in PD as they do not distinguish physical and neurological symptoms of PD from depression. Nonetheless they can be useful in clinical and research work.

Treatment of depression in PD

Treating PD may be complicated by the difficulty in diagnosing and treating depression. Anti-Parkinson drugs (APDs) may increase the sensitivity to adverse effects of antidepressant medication and affect compliance to treatment. Tricyclic antidepressants (TCAs) may be difficult to tolerate because of the autonomic dysfunction that plays such an intrinsic role in PD. Moreover, TCAs may aggravate PD-associated orthostatic hypotension while anticholinergic adverse effects can exacerbate cognitive problems, constipation and dry mouth.

Selective serotonin reuptake inhibitors (SSRIs) are better tolerated but may still cause the adverse effects that commonly occur with these antidepressants. Such adverse effects can include insomnia, nausea and sexual dysfunction. Extrapyramidal symptoms may possibly be worsened by SSRIs, as shown by a survey carried out on members of the Parkinson's Study Group (PSG), where 49 of 71 investigators caring for a total of 23,000 PD patients completed a standardized written questionnaire about their use of antidepressants in PD (5). A total of 26% of patients were on an antidepressant, of which 51% were on an SSRI and 41% were on a TCA. While the majority of neurologists reported that SSRIs were more effective and had fewer adverse effects, 43% of investigators expressed concern that SSRIs might worsen motor function, with 37% of these having observed at least one case in which this problem occurred.

Electroconvulsive therapy (ECT) has been used in patients with PD and psychiatric disorder. There have been documented improvements in psychosis, depression and motor symptoms associated with PD when patients were treated with ECT (6-8). The levels of the dopamine metabolite, homovanillic acid were noted to be higher in the cerebrospinal fluid of patients receiving ECT (9). Animal models of ECT have demonstrated increased 5-hydroxytryptaminergic (5-HT) and dopaminergic neurotransmission (10).

Transcranial magnetic stimulation (TMS) has also shown potential for treatment of depression (11) and has been studied in PD as both a pathophysiologic probe of basal ganglia projections and as a potential treatment for motor symptoms (12).

Depression in multiple sclerosis

Depression is by far the most common psychiatric disorder in multiple sclerosis (MS). It is important to recognize it and treat it appropriately so as to diminish its burden on quality of life.

Epidemiology of depression in MS

Numerous studies have reported high rates of depression in patients with MS, revealing a lifetime prevalence of approximately 50% and an annual prevalence of 20% (13). Rates of depression in MS are usually higher in nursing home settings. Rickards (2) showed that younger people with MS are more likely to be depressed than their older counterparts with similar levels of physical disability.

Symptoms of depression in MS

As in PD, somatic symptoms might not be good discriminators of depression in MS as some of the symptoms may be related to fatigue rather than depression. Rickards showed that 'disinterest in sex' was

uniquely related to a depressive disorder in MS (rather than fatigue or physical disability). Important indicators of depression in MS are highlighted in the table below (2).

Indicators of depression in MS

1.	Pervasive mood change
2.	Diurnal variation in mood
3.	Beck's cognitive triad: • negative thoughts about self • negative thoughts about world or environment • negative thoughts about the future
4.	Mood-congruent psychotic symptoms
5.	Suicidal ideation
6.	A change in function not related to physical disability

Suicide and MS

With such a relatively high prevalence of depression in patients with MS, a higher risk of suicide might be anticipated. In an analysis by Sadovnick et al. (13) in Ontario, two Canadian MS clinics were used to establish the cause of death of approximately 3126 patients. The cause of death could be clearly established in the records of 119 patients, of whom 56 had died of a direct complication of the disorder, while out of the 63 patients who did not die of MS complications, 18 (28.6%) died by suicide. The authors concluded that death due to suicide was 7.5 times higher in MS patients than in the age-matched general population. Additional risk factors for suicide in MS include: male gender, young age of onset of illness, a past history of depression, social isolation and comorbid substance abuse (2).

Interferon and depression in MS

There has been concern about the possible association of depression with the use of interferon beta in the treatment of relapsing-remitting MS. Data from the Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) showed a significantly higher rate of depression (20%) amongst 193 patients treated with interferon than amongst the 190 controls who received placebo (13%) (14).

Treatment of depression in MS

The first and only double-blind controlled trial of antidepressant treatment in MS was with a TCA (desipramine), which was found to be more effective than placebo. Some patients had problems with anticholinergic adverse effects, which limited the dose that could be prescribed. Improvements were made according to clinical judgment and the Hamilton Rating Scale for Depression but not the Beck Depression Inventory (15).

Some evidence shows that SSRIs and the monoamine oxidase inhibitor moclobemide can be effective. However, Feinstein (16) has drawn attention to the SSRI adverse effect of impaired sexual functioning which is also a common symptom of MS.

Mild-to-moderate forms of depression could also be managed by cognitive behavioural therapy (CBT). However, drug treatment remains the first-line management for those with cognitive impairment.

There are few documented cases of the use of ECT in severe depression in MS. ECT can be effective in otherwise clinically refractory cases but MS symptoms may worsen in around 20% of patients (2).

Conclusion

Depression is a common and debilitating condition in neurological disorders such as PD and MS. The aetiology of depression in association with these conditions can be complex and multifactorial. Because of this, particular attention is required during history taking, physical examination and mental state examination. Despite the considerable additional disease burden, treatment and prevention of depression in both conditions has remained under-researched. However, diagnosing depression promptly in PD or MS and providing effective treatment can improve quality of life significantly.

References

1. McDonald WM, Richard IH, DeLong MR. Prevalence, etiology, and treatment of depression in Parkinson's disease. Biological Psychiatry. 2003 Aug 1;54(3):363-75.

2. Rickards H. Depression in neurological disorders: Parkinson's disease, multiple sclerosis, and stroke. Journal of Neurology, Neurosurgery & Psychiatry. 2005 Mar 1;76(suppl 1):i48-52.

3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

4. Leentjens AF, Verhey FR, Lousberg R, Spitsbergen H, Wilmink FW. The validity of the Hamilton and Montgomery-Åsberg depression rating scales as screening and diagnostic tools for depression in Parkinson's disease. International Journal of Geriatric Psychiatry. 2000 Jul;15(7):644-9.

5. Richard IH, Maughn A, Kurlan R. Do serotonin reuptake inhibitor antidepressants worsen Parkinson's disease? A retrospective case series. Movement Disorders: official journal of the Movement Disorder Society. 1999 Jan;14(1):155-7.

6. Aarsland D, Larsen JP, Waage O, Langeveld JH. Maintenance electroconvulsive therapy for Parkinson's disease. Convulsive Therapy. 1997 Dec;13(4):274-7.

7. Moellentine C, Rummans T, Ahlskog JE, Harmsen WS, Suman VJ, O'Connor MK, Black JL, Pileggi T. Effectiveness of ECT in patients with parkinsonism. The Journal of Neuropsychiatry and Clinical Neurosciences. 1998 May;10(2):187-93.

8. Wengel SP, Burke WJ, Pfeiffer RF, Roccaforte WH, Paige SR. Maintenance electroconvulsive therapy for intractable Parkinson's disease. The American Journal of Geriatric Psychiatry. 1998 Jun 1;6(3):263-9.

9. Fall PA, Ekman R, Granerus AK, Thorell LH, Wålinder J. ECT in Parkinson's disease. Changes in motor symptoms, monoamine metabolites and neuropeptides. Journal of Neural Transmission-Parkinson's Disease and Dementia Section. 1995 Jun 1;10(2-3):129-40.

10. Yoshida K, Higuchi H, Kamata M, Yoshimoto M, Shimizu T, Hishikawa Y. Single and repeated electroconvulsive shocks activate dopaminergic and 5-hydroxytryptaminergic neurotransmission in the frontal cortex of rats. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 1998 Feb 1;22(2):435-44.

11. George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in neuropsychiatry. Archives of General Psychiatry. 1999 Apr 1;56(4):300-11.

12. Cantello R. Applications of transcranial magnetic stimulation in movement disorders. Journal of Clinical Neurophysiology. 2002 Aug 1;19(4):272-93.

13. Siegert RJ, Abernethy DA. Depression in multiple sclerosis: a review. Journal of Neurology, Neurosurgery & Psychiatry. 2005 Apr 1;76(4):469-75.

14. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, Simonian NA, Slasor PJ, Sandrock AW, CHAMPS Study Group. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. New England Journal of Medicine. 2000 Sep 28;343(13):898-904.

15. Mohr DC, Boudewyn AC, Goodkin DE, Bostrom A, Epstein L. Comparative outcomes for individual cognitive-behavior therapy, supportive-expressive group psychotherapy, and sertraline for the treatment of depression in multiple sclerosis. Journal of Consulting and Clinical Psychology. 2001 Dec;69(6):942.

16. Feinstein A. The neuropsychiatry of multiple sclerosis. The Canadian Journal of Psychiatry. 2004 Mar;49(3):157-63.