Chapter 8
Drug Management of Psychiatric Co-morbidity in Multiple Sclerosis

Pierre-Michel Llorca and Ludovic Samalin

Abstract Multiple sclerosis (MS) is associated with a higher risk of psychiatric comorbidities that have an impact on the evolution, prognosis, and quality of life of patients. Despite this observation, evidence-based data on the treatment of these psychiatric conditions are rather sparse. Selective serotonergic recapture inhibitors and serotonin norepinephrine reuptake inhibitors can be considered as the first-choice treatment for depression or anxiety disorder in MS patients. Second-generation antipsychotics are of interest in MS patients suffering of bipolar disorder, compared to lithium or anticonvulsants. They also have an efficacy on psychotic symptoms observed in MS patients. Adherence to treatment is also an important topic in these patients and needs to be evaluated and improved using psychoeducation programs. According to the consequences of psychiatric comorbidities, research on the efficacy of psychotropic drugs in MS patients must be developed.

Keywords Multiple sclerosis • Depression • Bipolar disorder • Anxiety • Psychotropics

Introduction

Multiple sclerosis (MS) is a relatively common chronic disabling central nervous system disease affecting 1 in 1,000 people in western countries [1]. Patients with MS appear to have higher lifetime prevalence rates of psychiatric symptoms and disorders compared with the general population (Table 8.1) [2–13].

Corticosteroids and beta interferon that are used to treat MS are also associated with an increased risk of neuropsychiatric side effects, from mood disorders to psychotic symptoms. Those side effects induce the need for patient education about psychiatric comorbidities and for regular psychiatric evaluation.

P.-M. Llorca, MD, Ph.D. (✉) • L. Samalin, MD
Department of Psychiatry B, CHU Clermont-Ferrand, University of Auvergne, EA 7280, 58 rue Montalembert, Clermont-Ferrand 63000, France
e-mail: pmllorca@chu-clermontferrand.fr; lsamalin@chu-clermontferrand.fr

B. Brochet (ed.), *Neuropsychiatric Symptoms of Inflammatory Demyelinating Diseases*, Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-3-319-18464-7_8

Table 8.1 Lifetime prevalence rates of psychiatric disorders in MS patients and the general population [2–13]

	Lifetime prevalence rates	
	Multiple sclerosis	General population
Major depressive disorder	36–54 %	16.2 %
Bipolar disorder	13 %	1–4.5 %
Anxiety disorder	35.7 %	28.8 %
Psychotic disorders	2–3 %	1.8 %

Psychiatric disorders in MS patients are associated with decreased adherence to treatment, impaired functional status, and quality of life. The reported rates of completed suicide in persons with MS are also high, and suicidality seems to be associated with psychiatric disorders [14].

This context highlights the importance of screening, diagnosing, and treating MS patients suffering from psychiatric comorbidities.

In this chapter, we will focus on the pharmacological treatments for each of the psychiatric conditions.

Drug Treatment of Depression in Multiple Sclerosis

Depression is the commonest psychiatric disorder in MS patients but remains underdiagnosed and undertreated. Major depressive disorder (MDD) in patients with MS does not relate directly to disability progression or to longer disease duration. The reported risk factors are female sex, age below 35 years, family history of major depression, and high stress levels. Multiple sclerosis patients also experience fatigue and cognitive dysfunction, both of which can worsen depression and be worsened by depression [14].

Despite the high prevalence of MDD in MS and although antidepressant (AD) use is common among patients with MS, the literature on the effectiveness of antidepressants in MS is limited.

Three double-blind controlled studies evaluated the impact of desipramine (a tricyclic antidepressant, TCA), sertraline, and paroxetine (two widely used selective serotonergic recapture inhibitors, SSRIs) in depressed MS patients [15–17]. Only the last one was placebo-controlled and the three samples were relatively small ($n=28$, $n=22$ and $n=42$, respectively). The antidepressant effect was moderate for sertraline (effect size: $d=0.46$, $p=0.047$) (findings presented in Minden et al. [2]), inconsistent for desipramine (according to the depression scales that were used), and comparable to the placebo for paroxetine. Desipramine is associated with a high level of side effects (postural hypotension, dry mouth, and constipation) that patients are not always able to tolerate.

A few open-label trials using SSRIs (sertraline, fluvoxamine, and fluoxetine), serotonin norepinephrine reuptake inhibitors (SNRIs) (duloxetine), reversible

inhibitors of monoamine oxidase A (RIMAs) (moclobemide), and mirtazapine were also published [18,19]. Those studies showed the effects on depressive symptoms, evaluated with specific depression scales, and demonstrated better tolerance of SSRIs compared to TCA among MS patients.

According to those studies, antidepressants seem to reduce depressive symptoms in MS patients and should be considered for treating MDD in this population. However in an evidence-based perspective, the available literature provides insufficient evidence to support or refute the efficacy and use of TCAs and SSRIs for depressive symptoms and MDD in MS patients [2]. In this specific population, the evaluation of the balance between efficacy and risks has to be very cautious.

In their guidelines for the management of patients with mood disorders and selected comorbid medical conditions [20], the Canadian Network for Mood and Anxiety Treatments (CANMAT) considered that the use of antidepressants in this population should be strongly considered (recommendation level 2). However, due to issues with fatigue, orthostatic hypotension, balance, cognitive issues, and bladder problems, antidepressants with significant sedating or anticholinergic side effects should be avoided (recommendation level 3).

Electroconvulsive therapy (ECT) is an option in the case of treatment-resistant depression. In depressed MS patients treated with ECT, the neurological status of those patients can deteriorate, raising the question of whether ECT is a risk factor for disease exacerbation [21].

Summary

- Antidepressants are largely used in MS patients with depressive symptoms or MDD, nevertheless empirical data are lacking.
- Selective serotonergic recapture inhibitors and SNRIs can be considered as a first-line option according to the efficacy/risk balance.
- In treatment-resistant patients, ECT should be considered with caution related to the risk of neurological deterioration in the presence of active disease.
- Antidepressants combined with cognitive behavioral therapy (CBT) is considered to be of interest to meet the particular needs of each individual patient whenever possible [22].

Drug Treatment of Bipolar Disorder in Multiple Sclerosis

In a study using standardized diagnostic tools and a case–control design, compared with controls, MS patients had a significantly higher lifetime prevalence of bipolar disorder type I ($p = 0.005$) and bipolar disorder type II ($p < 0.0001$) [23]. Because of this high prevalence, the CANMAT considered that people with MS should be

monitored for hypomanic and manic symptoms while they are being treated with antidepressant medications (recommendation level 4) [20].

Despite the impact of this co-morbidity, no specific clinical trials of pharmacologic interventions for these patients can be found in the literature. A few anecdotal reports underline interest in the various strategies for the treatment of bipolar disorder including benzodiazepines [24], second-generation antipsychotics [25], or lithium [26].

For most of the patients, the choice of treatment must be based on the recommendations used in general psychiatry. For the treatment of acute mania, risperidone, aripiprazole (two second-generation antipsychotics), and valproate (an anticonvulsant) are considered as a *grade 1 recommendation* (*Category A evidence and good risk–benefit ratio*) [27]. Lithium (formerly considered to be a "gold standard") is only a *grade 2 recommendation*. For the treatment of acute bipolar depression, quetiapine is the only drug considered to be a *grade 1 recommendation* [28]. Lithium, lamotrigine (an anticonvulsant), aripiprazole, and quetiapine are considered as a *grade 1 recommendation* for long-term treatment of bipolar disorder [29].

For Ameis and Feinstein [18], according to different case reports, anticonvulsants should be less effective on psychiatric symptoms in MS patients, compared with their usual efficacy. This has to be confirmed by specific studies.

In MS patients, the balance between efficacy and risk must be considered [18]:

- Lithium is not always well tolerated: the increase of diuresis induced by this compound, coupled with bladder dysfunction observed in MS, can make the patient incontinent.
- Second-generation antipsychotics are better tolerated than neuroleptics in terms of extrapyramidal side effects, but MS patients may be more sensitive to neurological side effects and must be regularly monitored.
- Anticonvulsants may induce sedation, dizziness, headaches, ataxia, tremors, nausea, constipation, and weight gain that may increase the disability associated with MS.

One of the specificities of MS patients is that some of them develop mania or hypomania secondary to treatment with steroids/ACTH prescribed for exacerbations of neurological symptoms [30]. Patients with a previous history of depression or a family history of depression must be considered to be at risk. Clinicians must consider using reduced doses of steroids/ACTH or adding lithium prophylaxis when treating high-risk patients.

Summary

- Multiple sclerosis patients are at high risk of developing bipolar disorder.
- Lithium, anticonvulsants, and second-generation antipsychotics must be considered for the treatment of acute phases (mania and depression) and for long-term maintenance treatment of bipolar disorder in MS patients.

- The specificity of the different side-effect profiles has to be taken into account.
- The iatrogenic effect of steroids/ACTH on mood has to be considered, high-risk patients have to be identified, and a prophylactic use of a mood stabilizer has to be considered.

Drug Treatment of Anxiety in Multiple Sclerosis

Generalized anxiety disorder appears to be the most common anxiety disorder in MS patients with 18 % of patients meeting the criteria for this disorder and more than half of these patients not receiving any treatment [31]. Panic disorder and obsessive–compulsive disorder may also be much more common. The advent of injectable disease-modifying treatments for MS induces an increase in "self-injection anxiety." If specific cognitive behavioral therapies have been developed for "self-injection anxiety," no studies on the pharmacological approach of anxiety have been published.

The main pharmacological agents that can be used for anxiety disorders in the general population [32] must be considered in MS patients. Selective serotonergic recapture inhibitors, SNRIs, noradrenergic and specific serotonergic antidepressants (NaSSAs), TCAs, monoamine oxidase inhibitors (MAOIs), and RIMAs have demonstrated their efficacy in the treatment of anxiety disorders. Selective serotonergic recapture inhibitors and SNRIs are usually preferred as initial treatments, since they are generally safer and better tolerated. Benzodiazepines may be useful as adjunctive therapy, particularly for acute anxiety or agitation or while waiting for the onset of adequate efficacy of SSRIs. Due to concerns about possible dependency, sedation, and cognitive impairment, those compounds should be restricted to short-term use. Several anticonvulsants and atypical antipsychotics have demonstrated efficacy in some anxiety and related disorders, but are generally recommended as second-line, third-line, or adjunctive therapies.

The choice of medication should take into consideration the evidence for efficacy and safety/tolerability specifically in MS patients. Selective serotonergic recapture inhibitors and SNRIs may induce sexual dysfunction, drowsiness, and fatigue that can be particularly disabling for these patients.

Summary

- Anxiety disorders are frequent in MS patients and have to be screened.
- Selective serotonergic recapture inhibitors and SNRIs can be considered as the cornerstone of the pharmacological treatment of anxiety disorders.
- The choice of the compound must rely on the efficacy and safety profile.

Drug Treatment of Psychosis in Multiple Sclerosis

The prevalence of psychotic disorders is higher in MS patients, with epidemiologic evidence of an association between MS and psychotic disorders in the general population [13].

There are only a few case reports describing the efficacy of neuroleptics or second-generation antipsychotics in the treatment of psychosis in MS [18]. Neuroleptics induced more neurological side effects and a higher risk for tardive dyskinesia in MS patients [33]. Consideration should be given to the fact that those patients may be more sensitive than general psychiatry patients to developing antipsychotic extrapyramidal symptoms or tardive dyskinesia.

Second-generation antipsychotics have a better risk–benefit balance with a specific interest of ziprasidone, risperidone, and aripiprazole [34]. They can be considered as a first-line treatment for MS patients with psychosis. There is no data suggesting that one second-generation antipsychotic is better than another. Clozapine is not a first-line treatment owing to the risk of agranulocytosis and the need for active blood monitoring.

Summary

- Psychotic symptoms are more prevalent in MS patients compared with the general population.
- Second-generation antipsychotics must be considered as a first-line treatment in MS patients with psychosis.
- MS patients may be more sensitive to extrapyramidal side effects that have to be monitored.

General Considerations

Adherence to Treatment

Multiple sclerosis patients with psychiatric comorbidities are more likely not to adhere to disease-modifying drug treatment and psychotropic treatment [14]. This can have a dramatic effect in terms of outcome and quality of life. There is a need to optimize adherence to psychotropic treatment:

- Clinicians must assess adherence at every consultation.
- Psychoeducation programs focusing on treatment adherence have to be developed and implemented.

Needs for Future Research

Despite the high prevalence of psychiatric disorders in MS patients and their consequences, there is a real lack of evidences to define precise pharmacological strategies. Large, methodologically rigorous, randomized, placebo-controlled studies must be conducted in this population to evaluate pharmacologic therapies with strong evidence of efficacy and widespread use for treating emotional disorders in individuals with MS [2]. This may include systematic examinations of combinations of pharmacologic and non-pharmacologic therapies.

Conclusion

Multiple sclerosis is frequently associated with psychiatric comorbidities. The drug management of these disorders is a challenge for clinicians because they can have an impact on the prognosis of MS, the adherence to treatment, and the quality of life of patients. The first step in the management of all patients with MS is the need to systematically assess and screen psychiatric comorbidities (especially MDD, bipolar disorder, general anxiety disorder, and psychotic disorder). The second step (pharmacological strategies) will select and introduce a compound as a first-line option according to the safety profile of the patient. Due to lack of evidence, most of the recommendations are based on guidelines for the treatment of psychiatric disorders in the general population. Specific studies and consequently clinical practice guidelines for patients with MS and psychiatric comorbidities are needed.

References

1. Hogancamp WE, Rodriguez M, Weinshenker BG. The epidemiology of multiple sclerosis. Mayo Clin Proc. 1997;72:871–8.
2. Minden SL, Feinstein A, Kalb RC, Miller D, Mohr DC, Patten SB, et al. Guideline Development Subcommittee of the American Academy of Neurology. Evidence-based guideline: assessment and management of psychiatric disorders in individuals with MS: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014;82(2):174–81.
3. Minden SL, Schiffer RB. Affective disorders in multiple sclerosis: review and recommendations for clinical research. Arch Neurol. 1990;47:98–104.
4. Sadovnick AD, Remick RA, Allen J, Swartz E, Yee IM, Eisen K, et al. Depression and multiple sclerosis. Neurology. 1996;46:628–32.
5. Minden SL, Orav J, Reich P. Depression in multiple sclerosis. Gen Hosp Psychiatry. 1987;9:426–34.
6. Joffe RT, Lippert GP, Gray TA, Sawa G, Horvath Z. Mood disorder and multiple sclerosis. Arch Neurol. 1987;44:376–8.
7. Schiffer RB, Caine ED, Bamford KA, Levy S. Depressive episodes in patients with multiple sclerosis. Am J Psychiatry. 1983;140:1498–500.

8. Patten SB, Beck CA, Williams JV, Barbui C, Metz LM. Major depression in multiple sclerosis: a population-based perspective. Neurology. 2003;61:1524–7.
9. Schiffer RB, Wineman NM, Weitkamp LR. Association between bipolar affective disorder and multiple sclerosis. Am J Psychiatry. 1986;143:94–5.
10. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld M, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2007;64:543–52.
11. Korostil M, Feinstein A. Anxiety disorders and their clinical correlates in multiple sclerosis patients. Mult Scler. 2007;13:67–72.
12. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593–602.
13. Patten SB, Svenson LW, Metz LM. Psychotic disorders in MS: population-based evidence of an association. Neurology. 2005;65(7):1123–5.
14. Fragoso YD, Adoni T, Anacleto A, da Gama PD, Goncalves MV, Matta AP, et al. Recommendations on diagnosis and treatment of depression in patients with multiple sclerosis. Pract Neurol. 2014;14(4):206–9.
15. Schiffer RB, Wineman NM. Antidepressant pharmacotherapy of depression associated with multiple sclerosis. Am J Psychiatry. 1990;147:1493–7.
16. 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. J Consult Clin Psychol. 2001;69:942–9.
17. Ehde DM, Kraft GH, Chwastiak L, Sullivan MD, Gibbons LE, Bombardier CH, et al. Efficacy of paroxetine in treating major depressive disorder in persons with multiple sclerosis. Gen Hosp Psychiatry. 2008;30(1):40–8.
18. Ameis SH, Feinstein A. Treatment of neuropsychiatric conditions associated with multiple sclerosis. Expert Rev Neurother. 2006;6(10):1555–67.
19. Solaro C, Bergamaschi R, Rezzani C, Mueller M, Trabucco E, Bargiggia V, et al. Duloxetine is effective in treating depression in multiple sclerosis patients: an open-label multicenter study. Clin Neuropharmacol. 2013;36(4):114–6.
20. Ramasubbu R, Taylor VH, Samaan Z, Sockalingham S, Li M, Patten S, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and select comorbid medical conditions. Ann Clin Psychiatry. 2012;24(1):91–109.
21. Mattingly G, Baker K, Zorumski CF, Figiel GS. Multiple sclerosis and ECT: possible value of gadolinium-enhanced magnetic resonance scans for identifying high-risk patients. J Neuropsychiatry Clin Neurosci. 1992;4(2):145–51.
22. Goldman Consensus Group. The Goldman Consensus statement on depression in multiple sclerosis. Mult Scler. 2005;11(3):328–37.
23. Carta MG, Moro MF, Lorefice L, Trincas G, Cocco E, Giudice ED, et al. The risk of bipolar disorders in multiple sclerosis. J Affect Disord. 2014;155:255–60.
24. Blanc F, Berna F, Fleury M, Lita L, Ruppert E, Ferriby D, et al. Inaugural psychotic events in multiple sclerosis? Rev Neurol (Paris). 2010;166(1):39–48.
25. Sidhom Y, Ben Djebara M, Hizem Y, Abdelkefi I, Kacem I, Gargouri A, et al. Bipolar disorder and multiple sclerosis: a case series. Behav Neurol. 2014. doi:10.1155/2014/536503.
26. Kemp K, Lion JR, Magram G. Lithium in the treatment of a manic patient with multiple sclerosis: a case report. Dis Nerv Syst. 1977;38(3):210–1.
27. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. World J Biol Psychiatry. 2009;10(2):85–116. Erratum in: World J Biol Psychiatry. 2009;10(3):255.

28. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression. World J Biol Psychiatry. 2010;11(2):81–109.
29. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. World J Biol Psychiatry. 2013;14(3):154–219.
30. Minden SL, Orav J, Schildkraut JJ. Hypomanic reactions to ACTH and prednisone treatment for multiple sclerosis. Neurology. 1988;38(10):1631–4.
31. Chwastiak LA, Ehde DM. Psychiatric issues in multiple sclerosis. Psychiatry Clin North Am. 2007;30(4):803–17.
32. Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14 Suppl 1:S1.
33. Pine DS, Douglas CJ, Charles E, Davies M, Kahn D. Patients with multiple sclerosis presenting to psychiatric hospitals. J Clin Psychiatry. 1995;56(7):297–306.
34. Davids E, Hartwig U, Gastpar M. Antipsychotic treatment of psychosis associated with multiple sclerosis. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28(4):743–4.