

Treating depressed multiple sclerosis patients

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Approximately one in two multiple sclerosis patients will develop a major depression over the course of their lifetime. This is associated with a decreased quality of life and a high risk of completed suicide. A literature review suggests pharmacotherapy with a selective serotonin-reuptake inhibitor or tricyclic antidepressant is effective, the former likely better tolerated. Limited data show that psychotherapy, namely cognitive-behavioral and insight-oriented therapies, is effective, although cognitive-behavioral therapy is the only modality shown to rival medication in bringing about symptom response. Electroconvulsive therapy should be reserved for severe cases of depression as it may increase the risk of multiple sclerosis exacerbation. In treating the depressed multiple sclerosis patient, clinicians should always be on the lookout for comorbid anxiety.

Overview

Depression is a frequent and troubling symptom in patients with multiple sclerosis (MS). It is, however, frequently treatable. Before reviewing the literature pertaining to treatment, a summary of some relevant epidemiological and clinical findings will be given to better set the treatment data in context.

Prevalence

Depression is the most common psychiatric condition affecting people with a diagnosis of MS [1]. Lifetime prevalence rates range between 40 and 60% [2]. Population-based statistics indicate that at any given time, 19% of people with MS qualify for a strict diagnosis of major depressive disorder (MDD) [3]. A larger percentage who do not meet criteria for MDD fall into the categories of dysthymia or subsyndromal depression [4]. Depression occurs more commonly in MS than in other chronic neurological [5,6] or general medical [7] conditions, and is up to four-times as common as depression in the general population (5%) [8].

Assessment

A consensus expert opinion supports the use of the full Beck Depression Inventory (BDI) as a screening instrument in MS patients, with a cut-off score of 13 denoting clinically significant depression [9]. A shortened version of the BDI, the BDI-Fast Screen for depression in medically ill patients, has been validated for patients with MS [10]. Other widely used scales include the Center for Epidemiologic Studies Depression Scale [11] and the Chicago Multi-Scale Depression Inventory [12].

Characteristics

Whereas feelings of guilt and low self esteem are characteristic of depression in general psychiatry, irritability, discouragement and frustration are more commonly associated with low mood in MS [7]. Moreover, the neurovegetative symptoms of depression, such as fatigue, impaired sleep and difficulties of memory and concentration, may be symptoms of MS, not depression. These phenomenological differences present a diagnostic challenge and can, in part, explain why the diagnosis of depression is sometimes overlooked in the MS setting. Missed diagnosis and/or inadequate treatment [13] may be factors contributing to the elevated rates of suicidal thinking [14] and completed suicide [15,16] in MS patients.

Impact

In an illness characterized by disability and uncertainty, comorbid depression leads to further deterioration of an already compromised quality of life (QoL) [17,18]. MS patients with lifetime major depression, score lower than MS patients who have never been depressed on several QoL domains, including energy, cognitive function, mental health, general QoL, sexual function and role limitation due to emotional problems [17]. Depression also exerts deleterious cognitive effects, impairing working memory function and executive function [19], and likely exacerbating existing deficits due directly to demyelination. Furthermore, depressed MS patients can also inadvertently magnify their cognitive problems, adding further to their distress over a perceived loss of function [20]. Finally,

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depression adds to the strain on MS patients' relationships [21] and it may also impair compliance with disease-modifying treatments, such as β -interferons [22].

Treatment of depression

Medication

Double-blind, placebo-controlled trials

Despite the high prevalence of major depression in MS patients, there is only one double-blind, placebo-controlled treatment trial published and it is well over a decade old [23]. The trial describes 28 MS patients with a diagnosis of MDD who were randomized to receive either desipramine ($n = 14$) – a tricyclic antidepressant (TCA) – or placebo ($n = 14$) over a 30-day period. All patients were treated with concurrent psychotherapy during the trial. The aim of the treatment arm was to increase desipramine dose to reach a serum level of 125–200 ng/ml, unless prevented by side effects.

The results revealed that desipramine-treated patients improved significantly more than those receiving placebo, indicated by scores on the Hamilton Rating Scale for Depression (HRSD) (12/14 vs 6/14). Side effects prevented half the medication-treated patients from reaching a minimum serum desipramine level of 125 ng/ml. Common adverse reactions were postural hypotension, dry mouth and constipation, although dry mouth occurred just as commonly among placebo-treated patients. Of note, all but one patient whose serum level was subtherapeutic had improved significantly by the end of the trial. This matched the improvement percentage found in patients who had attained their target desipramine level. To explain this apparent anomaly, the authors suggested that the breakdown of the blood–brain barrier (BBB), frequently seen in MS patients, may have influenced the pharmacokinetics of desipramine metabolism. This in turn could explain the drug's efficacy in MS patients at dosages typically considered subtherapeutic. The study concluded that desipramine was a modestly effective treatment for MS-related depression, notwithstanding troublesome anticholinergic and α -adrenergic side effects.

Open-label trials

The remaining few antidepressant trials utilize an open-label design. Scott and colleagues treated 11 MS out-patients diagnosed with major depression [24]. All patients were given 100 mg of sertraline, a selective serotonin-reuptake inhibitor

(SSRI). Apart from one patient who dropped out in the first month due to subjective lack of efficacy, patients were treated for at least 3–6 months. Significant reductions in scores on the Carroll self-report measure of depression were obtained in all treated patients. Unwanted side effects were not reported. The results suggest that sertraline is effective and well tolerated in MS patients, although the open-label design introduces a cautionary note.

In a subsequent report, Scott and colleagues reviewed 238 patient charts from an out-patient MS clinic [25]. Just under half reported depressive symptoms, with 51 patients having symptoms severe enough to warrant antidepressant treatment. Either SSRIs or TCAs were used to treat the depression with promising results. Not only did all patients benefit from medication, but the response to treatment also came about quicker (within 2 weeks) and at lower doses than that seen in a general psychiatry setting. Patients treated with TCAs experienced problematic side effects (dry mouth, dizziness and urinary retention) necessitating discontinuation more commonly than patients treated with SSRIs. Nonetheless, SSRI treatment was accompanied by insomnia, nausea, sexual dysfunction, palpitations, tremor, anorexia and personality changes. Despite these difficulties, the effectiveness of treatment was reinforced by the observation that just over half of treated patients relapsed if their medication was ceased after approximately 5 months.

The findings from this study were limited by its retrospective design and reliance on case note material. Nevertheless, it offers some useful insights:

- It confirmed the high prevalence of depressive symptomatology in MS patients (46%)
- Both SSRI and TCA treatment were effective, with the former better tolerated
- Patients responded to lower doses of antidepressants and at a more rapid pace than that seen in the general population
- Relapse rate was high with early discontinuation of treatment

In a second open-label, SSRI study, 43 MS patients with diagnosed MDD based on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders IV (SCID-IV), were treated with fluvoxamine over a 12-week period [26]. Dosage began at 50 mg/day and was increased by 50 mg every 5 days until a daily target dose of 200 mg was

achieved. During this period, seven patients discontinued treatment due to gastrointestinal side effects. Of these, three patients had responded well prior to dropping out. Response was defined as a 50% reduction in scores on the Montgomery–Asberg Depression Rating Scale. Of the remaining patients, half responded to treatment by 1 month, and 86% by 3 months. Side effects such as nausea, vomiting and dyspepsia were a limiting factor. The authors recommend that future studies use slower titration rates and individualized dosing to improve patient compliance with treatment.

The antidepressant effect of moclobemide, a reversible inhibitor of monoamine oxidase type A, was studied in a 3-month, open-label trial of ten MS patients with comorbid depression [27]. Nine out of ten patients reached full remission according to the BDI, with side effects reported as moderate and transient.

Anecdotal reports

Anecdotal data complete the pharmacologic picture. There are two case reports of successful antidepressant treatment with fluoxetine (an SSRI) in MS patients causing minimal side effects [28,29]. A third report of MS exacerbation within 10 h of initiating fluoxetine treatment offset these data [30], although the likelihood that fluoxetine caused this relapse is low considering this medication is widely used without reported problems.

Finally, Russo and associates described a MS patient who developed depression while taking interferon β -1b [31]. The depression responded within 2 weeks to mirtazapine 15 mg/day.

In summary, the available literature indicates that a variety of antidepressant medications are useful in treating MS depression. There are, however, limitations inherent in the published data. Small sample size, the relative absence of double-blind, placebo-controlled trials and a paucity of relevant neurological data means results must be interpreted with some caution. Keeping this in mind, the following can be concluded: depressed MS patients do respond to TCAs, but side effects limit their usage. TCAs are widely used clinically in MS for the treatment of neuropathic pain and allodynia in addition to depression. The evidence suggests that, in depression, SSRIs such as fluvoxamine and sertraline appear equally effective and are probably better tolerated, although problematic side effects are still encountered. Of note, sexual dysfunction, occurring in 45–78% of MS patients [32], may be

induced or aggravated by SSRIs. Here, mirtazapine may prove helpful as its selective targeting of the 5-hydroxytryptamine (HT)₁ receptor with sparing of the 5HT₂ and 5HT₃ receptors translates into few sexual difficulties. Mirtazapine can, however, cause weight gain and sedation, the latter exacerbating fatigue, a symptom commonly reported by MS patients [33]. Given the possibility that MS patients may respond more quickly and to lower doses of antidepressants than general psychiatry patients, clinicians should not forget the old neuropsychiatry rule of thumb, ‘start low and go slow’ when initiating treatment (see Table 1 for a list of antidepressant medications [34]; see Table 2 for a summary of pharmacotherapy trials).

Psychotherapy

As in general psychiatry, there are data attesting to the effectiveness of psychotherapy [35], either as a stand-alone treatment or as an adjunct to medication for MS-related depression. Several small studies have reported successful results using cognitive–behavioral therapy (CBT) or skills-based therapy for MS patients with depressive symptoms. Lacombe and Wilson conducted six group CBT sessions with nine MS patients and found a significant reduction in depressive symptoms compared with a control group made up of patients on a waiting list [36]. Improved mood was noted on self report and objective indices of depression. These findings were replicated in a study with a similar methodology [37]. Teaching stress management skills to an MS group in ten weekly sessions was also found to be effective [38].

Further support for skills-based psychotherapy, known as ‘Coping with MS’ and modeled after CBT, comes from an innovative idea of delivering psychotherapy to patients via telephone-administered weekly sessions [39]. In an 8-week controlled trial, 32 MS patients with depressive symptoms were assigned to receive either Coping with MS psychotherapy or their usual care (in two patients this involved antidepressant treatment; one patient was receiving psychotherapy). Depression was rated using the Profile of Mood States, depression–dejection scale. Post-treatment depression ratings in the Coping with MS group were significantly lower than pretreatment ratings, whereas they did not change in the control group. Limitations in this study included the absence of a structured interview, which meant that a diagnosis of major depression could not be made, and the choice of

Table 1. Available treatments for depression.

Class	Therapeutic range (mg)	Adverse effects
TCA^s*		
Nortriptyline (Pamelor [®])	75–150	Anticholinergic (e.g., dry mouth, sedation, constipation, blurred vision and urinary retention)
Amitriptyline (Elavil [®])	50–150	Antihistamine (weight gain and sedation)
Imipramine (Tofranil [®])	100–200	α-adrenergic blockade (dizziness, sedation and hypotension)
Desipramine (Norpramin [®])	50–150	Cardiac arrhythmias [§] and seizures [§] , especially in overdose
Doxepin (Sinequan [®])	75–150	
MAOI^s†		
Phenelzine (Nardil [®])	45–75	Insomnia/sedation, tremor, headache, dizziness, constipation, dry mouth, weight gain, change in appetite, orthostatic hypotension, sexual dysfunction,
Tranlycypromine (Parnate [®])	30–60	hypertensive crisis [§] (when MAOIs are used with tyramine-containing food),
Isocarboxazid (Marplan [®])	40–60	seizures [§]
RIMA		
Moclobemide (Manerix [®])	300–600	Insomnia/sedation, tremor, headache, dizziness, constipation, dry mouth, weight gain, change in appetite, orthostatic hypotension, sexual dysfunction, hypertensive crisis [§] (when MAOIs are used with tyramine-containing food), seizures [§]
SSRI^s‡		
Fluoxetine (Prozac [®])	20–80	Sexual dysfunction, nausea, diarrhea, constipation, dry mouth, insomnia/sedation, tremor, headache, dizziness
Paroxetine (Paxil [®])	20–50	
Fluvoxamine (Luvox [®])	100–200	
Sertraline (Zoloft [®])	50–200	
Citalopram (Celexa [™])	20–60	
SNRI[‡]		
Venlafaxine (Effexor [®])	75–225	Headache, nervousness, insomnia, sedation, sexual dysfunction, nausea, diarrhea, SIADH, dose-dependant increase in blood pressure
Other		
Mirtazapine (Remeron [®])	15–45	Constipation, dry mouth, weight gain, change in appetite, sedation
Bupropion (Wellbutrin [™])	225–450	Constipation, dry mouth, weight loss, anorexia, insomnia, dizziness, headache, agitation, tremor, rare seizures ^{§#}

*Least expensive; †More expensive; ‡Most expensive; §Life threatening; #MS is rarely associated with seizures.

MAOI: Monoamine oxidase inhibitor; RIMA: Reversible inhibitor of monoamine oxidase type A; SIADH: Syndrome of inappropriate antidiuretic hormone secretion; SNRI: Serotonin–norepinephrine-reuptake inhibitor; SSRI: Selective serotonin-reuptake inhibitor;

TCA: Tricyclic antidepressant.

From [34].

the Profile of Mood States, a scale that has not been validated for MS patients. Nevertheless, the idea of telephone-administered psychotherapy offers the important advantage of making treatment accessible to a population that may be unable to attend frequent clinic appointments due to physical disability.

In a second trial exploring the utility of telephone-based treatment for MS, telephone administered CBT (T-CBT) was compared with telephone administered supportive-emotion focused therapy (T-SEFT) [40]. A total of

127 MS patients with a diagnosis of MDD or dysthymia based on the SCID-IV were included. Patients were randomized to receive either T-SEFT (n = 65) or T-CBT (n = 62) in weekly, 50-min sessions for a total of 16 weeks. Outcomes were assessed periodically over a 12-month period. Study measures included the SCID-IV to assess frequency of MDD, severity of depression was assessed using the HRSD and the second edition of the BDI(-II), and the Positive Affect Subscale of the Positive and Negative Affect Scale (PANAS-PA) estimated positive

Table 2. Summary of pharmacotherapy trials.

Study	Participants	Treatment arms	Measures	Side effects	Outcome	Ref.
Schiffer & Wineman (1990) RCT	28 MS, MDD	Desipramine (TCA) 125–200 ng/ml vs placebo	HRSD	Dry mouth, constipation, dizziness	Improved HRSD on desipramine over placebo	[23]
Scott <i>et al.</i> (1995) O-L (3–6 months)	10 MS, MDD	Sertraline (SSRI) 100 mg/day	Carroll Scale	None reported	Reductions on Carroll Scale on sertraline	[24]
Benedetti <i>et al.</i> (2004) O-L (3 months)	43 MS, MDD	Fluvoxamine (SSRI) 200 mg/day	MADRS	Dyspepsia, nausea, vomiting	Improved MADRS scores	[26]
Barak <i>et al.</i> (1999) O-L (3 months)	10 MS, MDD	Moclobemide (RIMA) 150–400 mg/day	BDI	Transient nausea, initial insomnia	9/10 full remission	[27]
Mohr <i>et al.</i> (2001) RT (16 weeks)	63 MS, MDD	SEG vs CBT vs sertraline (SSRI) 200 mg/day	BDI	None reported	CBT = sertraline; CBT, sertraline > SEG	[42]

BDI: Beck depression inventory; CBT: Cognitive-behavioral therapy; HRSD: Hamilton rating scale for depression; MADRS: Montgomery-Asperg depression rating scale; MDD: Major depressive disorder; MS: Multiple sclerosis; O-L: Open-label design; RCT: Randomized, controlled trial; RIMA: Reversible monoamine oxidase inhibitor type A; RT: Randomized trial; SEG: Supportive expressive group therapy; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressant.

affect. Evaluations were performed over the phone and researchers were blinded to treatment assignment. Therapists providing T-CBT treatment addressed cognitive distortions and maladaptive behaviors contributing to depression, whereas T-SEFT therapists worked to increase patients' emotional awareness.

Significant improvements on all outcome measures for all treated patients were found, suggesting that both T-CBT and T-SEFT are effective treatment options. Of note, outcomes for patients treated with T-CBT were significantly better than T-SEFT, as measured by the HRSD and PANAS-PA, although no significant difference was found in BDI-II scores. Treatment gains were maintained 12-months post-treatment when further improvement was noted on the HRSD and SCID-IV measures. However, the early advantages of T-CBT over T-SEFT were not evident at follow-up. The authors suggested a couple of explanations for this: either the need for T-CBT booster sessions to reinforce learned cognitive skills, or T-CBT may be more effective initially, but the benefits of T-SEFT catch up with time. In conclusion, this study provides further support for the usefulness of telephone-based psychotherapy in depressed MS patients. Furthermore, emotion-focused therapies were shown to rival CBT in alleviating low mood.

In summary, there are only a handful of trials to inform psychotherapeutic practice when managing the depressed MS patient. Cognitive-behavioral models seem to bring about an

earlier response than emotion-focused therapy, but may not prove more effective in the long term. The evidence here suggests that, for patients who are medication-sensitive or who shy away from psychotropic medication, psychotherapy appears to offer a reasonable alternative. Here, the biggest obstacle is often the lack of available therapists.

Rather than favoring one particular mode of psychotherapy as the gold standard for MS patients with depression, Minden encourages a more eclectic, integrative approach that embraces alternating supportive and psychodynamic techniques, depending on the particular needs of the patient at any given time [41]. In keeping with these principles, length of treatment and the need for adjunctive pharmacotherapy should also be individualized according to need.

Medication or psychotherapy: what to choose?

Empirical data also demonstrate that CBT is as affective as medication in treating depressed MS patients [42]. In a 16-week treatment trial, 63 MS patients with MDD of moderate severity were randomly assigned to one of three treatment groups: supportive expressive group therapy, individual CBT or sertraline (a SSRI) treatment. Sertraline treatment was initiated at a dose of 50 mg daily and increased by 50 mg every 4 weeks up to a target dose of 200 mg or until full remission in depression was seen. BDI scores indicated that sertraline and CBT were

equally effective, both proving superior to supportive expressive group therapy. Of note, all participating patients in this study continued to score in the mildly depressed range on outcome measures, suggesting that, although MS depression is responsive to treatment, full remission may be more difficult to achieve. At the 6-month follow-up, treatment gains were maintained across groups, although loss of between-group differences suggests medication, CBT and supportive expressive group treatments may be at par in the long term.

A meta-analysis of five treatment trials that were deemed methodologically sound confirmed that medication and psychotherapy were superior to placebo [43]. No significant therapeutic differences were found between antidepressant medication and psychotherapy. Psychotherapies that focused on teaching problem-solving skills were substantially more effective than insight-oriented approaches.

Recommendations

Given the frequency with which depression occurs in MS, coupled with the recognition that symptoms are sometimes overlooked [13], a group of MS behavioral researchers came up with a set of consensus guidelines with respect to the treatment of depression [9]. To begin with, the use of the BDI as a screening instrument was recommended as an adjunct to clinical practice. Should patients' scores exceed 13, or if they endorse suicidal thinking, a face-to-face interview was considered necessary. Thereafter, once a diagnosis of depression, be it major depression, dysthymia or subsyndromal depression, is made and found to affect QoL, treatment options should be discussed. For mild-to-moderate depression, either pharmacologic and/or psychotherapeutic modalities could be utilized depending on patients' preferences and therapists' availability. If medication was the chosen route, a choice of a TCA or SSRI was recommended. Psychotherapy utilizing a cognitive-behavioral orientation was preferred, although, insight-oriented therapy was also considered effective. For more severe cases of MS-related depression, an integrated approach using both pharmacologic and psychotherapeutic modalities was strongly recommended. Looking to the future, the Consensus Group advocated for the standardization of a tested treatment algorithm for MS depression to facilitate treatment decisions. In addition, the group called for ongoing research to understand the neurobiological and psychological

underpinnings of the mood change seen in MS, and to measure response to available and newly developing treatments.

Electroconvulsive therapy

Although rarely mentioned in the MS literature, electroconvulsive therapy (ECT) may be useful in depressed MS patients who do not respond to medications or psychotherapy or who cannot wait for less-invasive treatments to take effect due to the severity of their symptoms. There are 16 case reports in the literature of ECT used in MS [44]. They include three patients whose neurological status deteriorated after treatment with ECT, raising the question of whether ECT is a risk factor for disease exacerbation. Of note, an alternative explanation for this deterioration may be that depression in MS could represent a harbinger of MS relapse with symptom exacerbation following depression, regardless of treatment with ECT.

Nonetheless, a study of three patients with severe depression (one with psychotic features) who underwent contrast-enhancing (gadolinium) magnetic resonance imaging (MRI) prior to receiving ECT allows for inferences to be made about the connection between MS relapse and ECT [44]. One of the three patients displayed contrast-enhancing lesions on MRI: indicative of breakdown in the BBB. This patient's neurological status deteriorated after ECT treatment. From this, a recommendation emerged suggesting that patients requiring ECT have a gadolinium-enhanced MRI prior to ECT. Should a contrast-enhancing lesion be present, prophylactic glucocorticoids could be used to help reconstitute the BBB. ECT could then be reconsidered.

Anxiety

There is evidence showing that anxiety symptoms may occur often in MS patients with and without comorbid depression [45]. The lifetime prevalence of anxiety disorders among MS patients is 35.7%, with rates of some anxiety disorders elevated relative to the general population, including generalized anxiety disorder (18.6%), panic disorder (10%) and obsessive-compulsive disorder (8.6%) [46]. Anxiety is also often associated with excessive alcohol consumption and the presence of suicidal thoughts in MS patients [47]. Despite the high comorbidity, there are no treatment trials of anxiety in MS patients.

The situation is, however, different in relation to a more circumscribed type of anxiety, akin to a phobia, namely 'injection anxiety'. This symptom

has arisen as a consequence of the introduction of injectable disease-modifying treatments for MS, namely the interferons (β -1a and β -1b) and glatiramer acetate. It may affect up to one in two MS patients using injectable medications [48]. To assist with this maladaptive behavior, self-injection anxiety therapy has been developed. It is an intervention consisting of six, weekly, 50-min, individual sessions offering information regarding anxiety and self-injection, relaxation training, behavior-modification techniques and cognitive restructuring. Two studies found self-injection anxiety therapy brings about significant improvement in a patients' ability to self-inject [49,50].

Conclusion

The following conclusions can be drawn from this review. First, MS depression is extremely common, causing increased morbidity and mortality among those afflicted. Second, although depression detection rates may be better elsewhere, North American data suggest that MS depression is under-recognized and undertreated [13]. Third, although the literature is limited by few available treatment trials and study design, TCAs, SSRIs and psychotherapy are effective treatments of MS depression.

Future perspective

Looking to the future, research efforts should focus on the following pertinent areas. First, the rates of diagnoses should be optimized. Given that depression is closely linked to QoL [17] and

the potential for suicide [15,16,51], this point takes on added urgency. The effectiveness of introducing screening instruments, such as the BDI, into routine neurological practice should be evaluated as a first step.

Second, optimal detection must go hand in hand with providing effective treatments. Here, education for neurologists and nurses regarding the best available treatments for MS depression becomes imperative. Waiting for a psychiatrist to provide the remedy is often not the most effective way to approach this problem, given the waiting time involved in a referral and the fact that diagnosis of a mood disorder is most likely to occur in a neurologist's office. Similarly, while data have demonstrated the effectiveness of CBT in treating depression, trained therapists may not be readily available, which shifts the onus to treat back to the referring physician, who is most likely to be a neurologist or a family practitioner.

Third, a well-conducted, double-blinded, pharmacologic treatment trial is long overdue. A three-way comparison, such as SSRI versus TCA versus placebo, would be the most informative with respect to many unanswered questions, such as efficacy, side-effect profile and cost-effectiveness (SSRIs are expensive, TCAs are cheap). Whether such a trial will ever be industry funded, however, must be in doubt given the realities of healthcare politics and the introduction of generic substitutes for antidepressant drugs, such as fluoxetine (Prozac®) and citalopram (Celexa®).

Executive summary

Pharmacotherapy

- Tricyclic antidepressants (TCAs; i.e., desipramine) and selective serotonin-reuptake inhibitors (SSRIs; i.e., sertraline and fluvoxamine) are effective in treating multiple sclerosis (MS) depression, although SSRIs seem to be better tolerated.
- MS patients with major depressive disorder (MDD) may respond to lower doses of antidepressants than general psychiatry patients, medications should be titrated up according to symptom response.
- A randomized, control trial comparing a TCA versus a SSRI versus placebo would be helpful in clarifying whether SSRI treatment justifies the added expense.

Psychotherapy

- Individual, group or telephone-based cognitive-behavioral therapy (CBT) and insight-oriented therapies are effective treatments for MS depression, although CBT seems to bring about faster initial responses and may rival medication treatment.

Electroconvulsive therapy

- Electroconvulsive therapy may be used in severe cases of MS depression. In patients with active lesions on magnetic resonance imaging, prophylactic glucocorticoid treatment may reduce the risk of MS exacerbation.

Recommendations

- Screen all MS patients for depression using the Beck Depression Inventory with a cut-off score of 13.
- Assess patients who screen positive for depression or who endorse any suicidal symptoms.
- For mild-to-moderate MS depression, either medication or psychotherapy may be used.
- For moderate-to-severe MS depression, combined medication and psychotherapeutic treatment is recommended.

Fourth, newer and more innovative therapies for depression, such as transcranial magnetic stimulation (TMS), should be explored. Should they prove effective, many of the uncomfortable side effects linked to antidepressant medication may be avoided. TMS has been studied as a tool

to monitor disease progression in MS [52], so the precedent exists for its use in MS patients. While the procedure is not without risks, most notably seizures, exploring its effectiveness as an antidepressant in a population prone to high rates of depression appears warranted.

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