

Antidepressant Treatment for Major Depression in Multiple Sclerosis

The Evolving Efficacy Literature

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*Major depressive disorder (MDD) is widely acknowledged to be an important clinical issue in multiple sclerosis (MS). Although antidepressant medications are generally regarded as efficacious, few studies have been conducted on their use in MS patients. Recently a randomized controlled trial reported negative results, raising new questions about the efficacy of these medications in this population. The objective of this review was to revisit the question of the efficacy of antidepressant medications in the treatment of MDD in MS. A literature search uncovered only three randomized controlled trials on this topic. These studies differed in their methodology, including the specific antidepressants used (desipramine, sertraline, paroxetine), the approach to the analysis (two of the three used intention-to-treat analyses), measures of depression (two defined response as a 50% reduction in the Hamilton Depression Rating Scale, and two included the Beck Depression Inventory), methodological features (two used blinding, and one included cases of dysthymia), and duration of follow-up (ranging from 1 to 4 months). Nevertheless, all of the results suggested modest therapeutic benefits for the medications evaluated. Although the current literature in this field is inadequate, the best available evidence points toward a modest positive effect of certain medications in the treatment of depression in people with MS. *Int J MS Care*. 2009;11:174–179.*

Clinicians and researchers agree that major depressive disorder (MDD) is an important clinical issue in MS.¹ This consensus is based in part on a succession of epidemiological studies showing that MDD occurs commonly in clinical and community populations with MS. The annual prevalence of the disorder is approximately 16%,² and the lifetime prevalence may be around 50%.³⁻⁵ Depression has a dramatic impact on health-related quality of life, particularly its mental health dimensions.⁶⁻¹⁰ Impaired functioning is an intrinsic component of depressive disorders as they are currently defined.¹¹ Functional impairment due to depression is likely to be especially important for people with MS, who are faced with the functional demands of coping with a chronic illness in addition to other life stressors. The occurrence of depression in MS may also partially explain the high suicide rates that have been

reported in this population.¹²⁻¹⁵ According to the most recent study, approximately 1% of men and 0.5% of women die by suicide during the 10 years following diagnosis.¹³ Treatment of depression may improve adherence to MS medication regimens¹⁶ and may even be associated with favorable immunologic changes.¹⁷

The clinical importance of MDD is predicated largely on the expectation that it is a modifiable determinant of negative outcomes in MS—in other words, that it is treatable. Both nonpharmacologic and pharmacologic treatments have been investigated. Pharmacologic management centers on the use of antidepressant medications, which have generally been regarded as effective.¹ In 1999 Mohr and Goodkin¹⁸ conducted a meta-analysis of the five randomized treatment studies that had been reported in the literature at that time, only one of which was an antidepressant trial. The meta-analysis found evidence of efficacy for all of the treatments evaluated, including insight-oriented therapy, cognitive-behavioral therapy, and stress management.

Recent developments, however, have raised questions about the efficacy of antidepressant medications in the

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MS population. Specifically, a recent randomized controlled trial (RTC) reported no statistically significant impact of antidepressant treatment with paroxetine in its primary intention-to-treat (ITT) analysis.¹⁹ This finding may discourage treatment of depression in people with MS. In statistical terms, however, a mixture of significant and nonsignificant results does not necessarily indicate inconsistency of the available efficacy data. Small trials often lack statistical power to detect modest effects, so that negative results may result from a type II error.

The primary objective of this study was to examine published trials of antidepressant treatment in people with MS in order to identify possible reasons for the inconsistency of their results. A second objective was to pool the results of these trials in order to determine whether, as a whole, these studies provide convincing evidence of efficacy.

Methods

Criteria for Study Consideration

The studies considered in this review were restricted to RCTs. Such studies have unique methodological strengths, because randomization can control for the effects of both measured and unmeasured confounding variables. For this reason, they have become the standard for assessing the efficacy of therapeutic interventions.

Types of Participants

Participants in eligible studies were required to have MS, but no distinction was made among MS subtypes in the selection of studies. Likewise, no restrictions were applied to the age and sex of study participants. None of the RCTs in the literature focused on children or the elderly.

Types of Interventions

Only pharmacologic treatments were considered in this review. This should not be interpreted as an implicit assertion that antidepressant medications are the sole or preferred treatment for MDD. For example, positive outcomes have been reported for cognitive-behavioral and other types of therapies.^{18,20}

Types of Outcome Measures

Outcomes of antidepressant clinical trials can be categorized in several ways. One distinction is between self-rated and observer-rated instruments. Observer-rated instruments are generally preferred in the psychiatric literature. However, the most commonly used observer-rated scale, the Hamilton Depression Rating Scale

(HAM-D), places a strong emphasis on physical symptoms, which is potentially problematic in MS because some symptoms of MS can resemble those of depression (eg, fatigue, cognitive deficits). HAM-D ratings are often categorized using a 50% reduction as an indication of treatment response. Several self-rated scales, notably the Center for Epidemiologic Studies Depression Scale (CESD)²¹ and the Beck Depression Inventory (BDI),²² place less emphasis on physical symptoms and have been frequently employed in MS research for this reason. Self-rated outcomes were considered eligible for inclusion in the review as well. Another distinction is between categorical and continuous measures of outcome. Both categories were considered eligible for inclusion in the review.

Primary Outcomes

Primary and secondary outcomes were not determined *a priori*. The expectation was that only a small number of RCTs would be identified by the literature search, and the intention was to describe the available data.

Search Methods for Identification of Studies

PubMed (www.pubmed.gov) was the search engine used in the literature search. The following search strategy was used: (drug therapy) AND ((depressive disorder) AND (multiple sclerosis)). An initial review of the abstracts uncovered in the literature search was sufficient to determine that only three of these studies were RCTs. As the inclusion criterion was a fully distinct methodological feature rather than a less-concrete standard such as a methodological quality rating, the selection of individual studies was not considered vulnerable to bias. Therefore, the review of studies was not blinded: all studies were reviewed by the author of this article.

Assessment of Risk of Bias in Included Studies

The RCTs were reviewed in detail, and "RevMan"²³ risk-of-bias tables were completed for each of the studies. An important issue concerning units of analysis arose with self-reported scales. Two of the studies used the BDI as an outcome measure, whereas the other used the CESD. These scales are often considered to be alternatives for case-finding in MS populations, and they tend to yield roughly similar scores. As all of the studies uncovered in the review were small (and therefore likely to be subject to imprecision), an advantage to statistical pooling was anticipated, and a decision was made to pool the results of the self-rated scales unless evidence of

statistical heterogeneity was found. Evidence of heterogeneity (ie, rejection of the “null” hypothesis of homogeneity) at the 5% level of significance was regarded as the deciding point. When data were pooled, random-effects models were used. Forest plots generated with the “RevMan” software were used to provide a visual impression comparing the pooled results to the results of individual studies.

It should be emphasized that statistical pooling of study results runs the risk of providing a false sense of precision based on pooling of heterogeneous results. In most meta-analyses, statistical pooling is restricted to methodologically *and* statistically homogeneous studies.

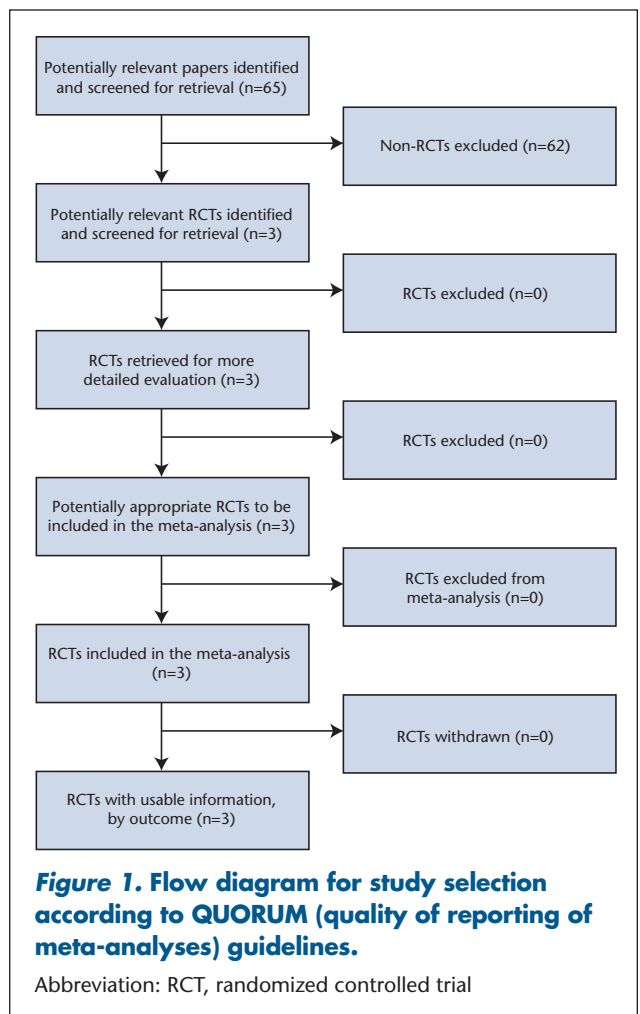
Results

Description of Studies

The search was carried out on May 25, 2009, and uncovered 65 articles. This group included three RCTs of antidepressant medications for the treatment of depressive disorders in MS, by Schiffer and Wineman,²⁴ Mohr et al.,²⁰ and Ehde et al.¹⁹ These studies evaluated desipramine, sertraline, and paroxetine, respectively. The results of the literature search and the reason for exclusion of 62 of the 65 articles are shown in Figure 1. There were three uncontrolled studies,²⁵⁻²⁷ all of which were excluded.

The three eligible studies all had methodological features that created vulnerabilities to bias. One area of methodological heterogeneity involved randomization procedures. The Ehde et al.¹⁹ study reported the use of a computer-generated random sequence for allocation. Because of the needs of the group therapy intervention, the Mohr et al.²⁰ study used a method of allocation that was not strictly random. Schiffer and Wineman²⁴ reported random assignment but did not provide details of the allocation method.

Blinding was another area of methodological heterogeneity. In the Schiffer and Wineman²⁴ study, the comparison was between psychotherapy alone and psychotherapy plus desipramine. All of the psychotherapy was carried out by one therapist, also the lead author, who was blinded to allocation at the time. The Mohr et al.²⁰ study compared sertraline treatment with two types of psychotherapy and was therefore not blinded. The Ehde et al.¹⁹ study used identical placebo capsules in the control condition, and the assessment of outcome was carried out by an assessor who was blinded at the time of that assessment.



Intention-to-treat analysis was used in the Ehde et al.¹⁹ and Mohr et al.²⁰ studies, but not the Schiffer and Wineman²⁴ study. The Ehde et al. study, which reported a nonsignificant primary outcome assessment, also carried out an analysis restricted to those who completed the study protocol in which a statistically significant improvement in the paroxetine-treated group was seen. The Ehde et al. study used last observation carried forward imputation in its ITT analysis. The imputed data were those abstracted for the review. In the Ehde et al. study, 47.6% of the treated patients achieved remission, defined as a post-treatment score of ≤ 7 on the HAM-D. In the Schiffer and Wineman study, only 4 of 14 treated (and 3 of 14 control) subjects achieved full remission.

Two studies, that by Schiffer and Wineman²⁴ and that by Ehde et al.,¹⁹ reported treatment response defined as 50% reduction in HAM-D ratings. In the Schiffer and Wineman study, the relevant data derived from a table reporting week 0 and week 5 HAM-D scores. The two studies were both consistent either with no effect or with

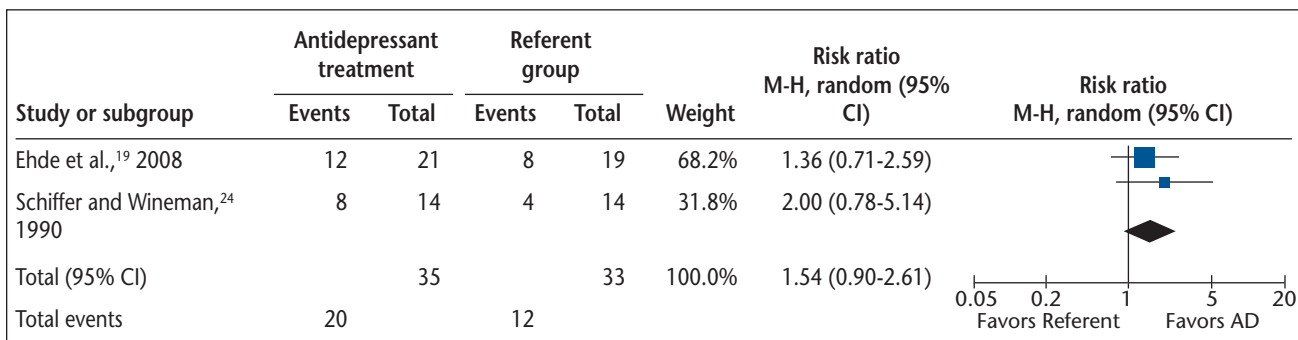


Figure 2. Forest plot for treatment response.

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.45$; $df = 1$ ($P = .50$); $I^2 = 0\%$

Test for overall effect: $Z = 1.58$ ($P = .11$)

Abbreviations: AD, antidepressant; CI, confidence interval; M-H, Mantel-Haenszel

a clinical effect according to the “RevMan” software, but even the pooled estimate was imprecise (Fig. 2). All three studies reported mean HAM-D scores after treatment along with associated dispersion statistics. The results were more heterogeneous, although not significantly so (Fig. 3). The pooled estimate is of questionable validity given the size of the difference in the estimates, with the Schiffer and Wineman study reporting a larger difference than the other two studies. The inclusion of respondents with dysthymia in the Ehde et al. analysis is a possible explanation for this difference, as dysthymic symptoms are typically less responsive to antidepressant treatment than major depressive episodes. Nevertheless, in a qualitative sense, the direction of effect is in each case toward a positive outcome from treatment. A forest plot for the self-reported depressive symptom scores is shown in Figure 4. Although two of the three studies used the BDI and the other (Ehde et al.) used the CESD, the mean post-treatment ratings in the treatment and control groups are similar. Each of the estimates is imprecise, but all indicate a similar direction of effect. When the data

were pooled, the difference in mean scores was statistically significant (Fig. 4).

Discussion

Only a few clinical trials of antidepressant treatment in people with MS have been published, and none can be regarded as definitive. Although methodological problems can be identified in each study, no clear pattern of impact on the results is evident. The randomization, analysis, and blinding procedures used in the Ehde et al.¹⁹ study (computer-generated random number sequence, ITT analysis, blinding with identical-appearing capsules) may have made this study less vulnerable to bias than the others. Thus the fact that this study is also the one that reported the most negative results may give rise to concern. However, all three studies were underpowered, and nonsignificant results would have been expected in the face of a modest effect of treatment. In fact, all three studies are similar in reporting weak positive effects; when assessed with self-rated scales, the outcomes were nearly identical.

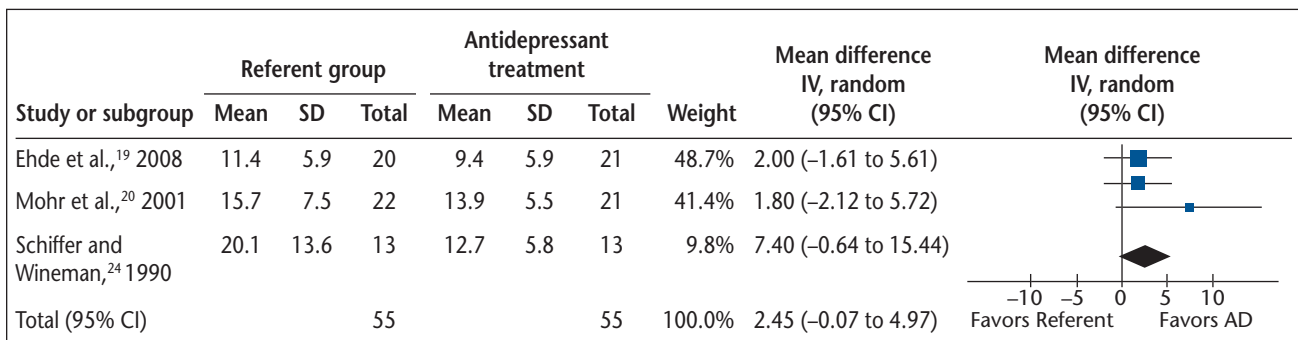
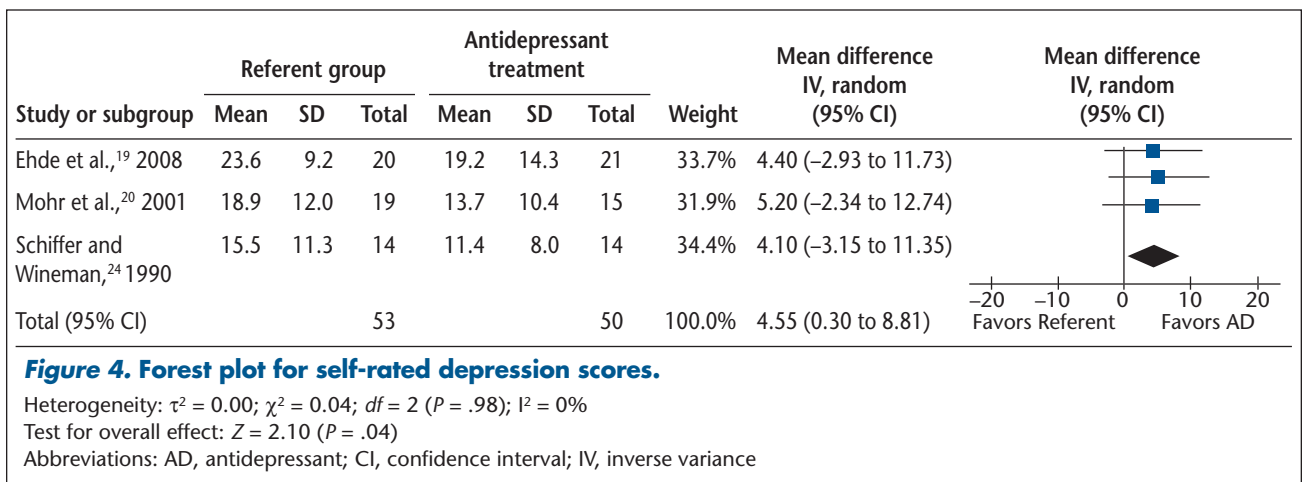


Figure 3. Forest plot for mean Hamilton Depression Rating Scale scores.

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.62$; $df = 2$ ($P = .44$); $I^2 = 0\%$

Test for overall effect: $Z = 1.90$ ($P = .06$)

Abbreviations: AD, antidepressant; CI, confidence interval; IV, inverse variance



Although this literature does not provide conclusive evidence of antidepressant efficacy in the MS population, the results are actually quite consistent, despite the apparently stark differences in results (two positive and one negative). The literature as a whole indicates a modest positive impact of the antidepressant treatments evaluated: desipramine, sertraline, and paroxetine.

Interpretation of these results depends to some extent on one's interpretive stance. If one begins with an assumption of the general effectiveness of antidepressant medications, this literature provides no evidence to suggest that this efficacy cannot be generalized to the MS population. A corollary to this interpretation is the suggestion that although only three specific antidepressants have been evaluated in randomized studies, the efficacy of these antidepressant medications is generalizable to other medications. This is the perspective adopted by the Goldman Consensus Group,¹ and the negative results of the Ehde et al.¹⁹ trial do not provide a strong challenge

to this perspective. On the other hand, if one considers *a priori* that evidence of antidepressant efficacy in MS must derive from RCTs conducted specifically in samples with MS, then the literature can be regarded as inconclusive, as none of the published studies are free of methodological concerns and the reported results are mixed. A similar statement could be made about the use of antidepressant medications in the treatment of MDD in many clinical populations in which only a few small controlled trials have been conducted.

In the psychiatric community, antidepressant medications have generally been considered practically equivalent in terms of efficacy, so that the choice of a specific agent in clinical practice depends largely on other considerations such as history of previous response, safety, and side-effect profiles. Recent meta-analyses have placed more emphasis on differential efficacy and tolerability. For example, a recent meta-analysis by Cipriani et al.²⁸ favored sertraline as a first-line treatment choice based on efficacy, tolerability, and cost considerations. It is unclear whether the RCT results for the three specific antidepressants evaluated in MS can be generalized to other medications. Similarly, this review cannot answer the question of whether clinicians should favor one of the three medications evaluated in MS-specific trials, especially when they feel that other clinical considerations support the choice of another medication.

The most important result of this review is that the apparently discordant results of the Ehde et al.¹⁹ study should not prompt a re-evaluation of the current consensus that the medications are effective: although the results of the primary analysis in this study were negative, the results are consistent with those of prior studies and with modest efficacy. Nevertheless, the question of

Practice Points

- Overall, the results of reported clinical trials of antidepressant medications for the treatment of major depression in MS show modest beneficial effects, albeit with a small number of medications (desipramine, sertraline, and paroxetine).
- Even with antidepressant treatment, many patients have residual depressive symptoms.
- Combining nonpharmacologic treatment modalities, especially cognitive-behavioral therapy, with antidepressant medication is likely to be a valuable strategy in clinical practice, although it has not been well studied.

antidepressant efficacy in this population should not be closed prematurely. Additional data are needed. Also, the finding that few treated patients achieve full remission (HAM-D score ≤ 7) indicates that clinicians should have modest expectations for the outcome of antidepressant treatment. The literature documenting the effectiveness of nonpharmacologic approaches^{18,20} suggests an important role for multimodal intervention. □

Additional Information: A set of appendices containing supplementary information on the studies reviewed ("Data Extraction and Risk of Bias Tables from Eligible Studies," "Characteristics of Excluded Studies," and "References to Studies") is available at the University of Calgary Institutional Repository at <http://hdl.handle.net/1880/47450>.

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References

- Goldman Consensus Group. The Goldman Consensus statement on depression in multiple sclerosis. *Mult Scler*. 2005;11:328–337.
- Patten SB, Beck CA, Williams JVA, Barbui C, Metz L. Major depression in multiple sclerosis: a population-based perspective. *Neurology*. 2003;61:1524–1527.
- Minden SL, Orav J, Reich P. Depression in multiple sclerosis. *Gen Hosp Psychiatry*. 1987;9:426–434.
- Sadovnick AD, Remick RA, Allen J, et al. Depression and multiple sclerosis. *Neurology*. 1996;46:628–632.
- Joffe RT, Lippert GP, Gray TA, Sawa G, Horvath Z. Mood disorders and multiple sclerosis. *Arch Neurol*. 1987;44:376–378.
- D'Alisa S, Miscio G, Baudo S, Simone A, Tesio L, Mauro A. Depression is the main determinant of quality of life in multiple sclerosis: a classification-regression analysis. *Disabil Rehabil*. 2006;28:307–314.
- Frühwald S, Löffler-Statka H, Eher R, Saletu B, Baumhackl U. Relationship between symptoms of depression and anxiety and the quality of life in multiple sclerosis [in German]. *Wien Klin Wochenschr*. 2001;113:333–338.
- Janssens AC, van Doorn PA, de Boer JB, et al. Anxiety and depression influence the relation between disability status and quality of life in multiple sclerosis. *Mult Scler*. 2003;9:397–403.
- Lobentanz IS, Asenbaum S, Vass K, et al. Factors influencing quality of life in multiple sclerosis: disability, depressive mood, fatigue and sleep quality. *Acta Neurol Scand*. 2004;110:6–13.
- Wang JL, Reimer MA, Metz LM, Patten SB. Major depression and quality of life in individuals with multiple sclerosis. *Int J Psychiatry Med*. 2000;30:309–317.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed., text rev. Washington, DC: American Psychiatric Association; 2000.
- Sadovnick AD, Eisen K, Ebers GC, Paty DW. Cause of death in patients attending multiple sclerosis clinics. *Neurology*. 1991;41:1193–1196.
- Brønnum-Hansen H, Stenager E, Stenager EN, Koch-Henriksen N. Suicide among Danes with multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2005;76:1457–1459.
- Koch-Henriksen N, Brønnum-Hansen H, Stenager E. Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis Registry. *J Neurol Neurosurg Psychiatry*. 1998;65:56–59.
- Stenager EN, Stenager E, Koch-Henriksen N, et al. Suicide and multiple sclerosis: an epidemiological investigation. *J Neurol Neurosurg Psychiatry*. 1992;55:542–545.
- Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA. Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Arch Neurol*. 1997;54:531–533.
- Mohr DC, Goodkin DE, Islar J, Hauser SL, Genain CP. Treatment of depression is associated with suppression of nonspecific and antigen-specific TH1 responses in multiple sclerosis. *Arch Neurol*. 2001;58:1081–1086.
- Mohr DC, Goodkin DE. Treatment of depression in multiple sclerosis: review and meta-analysis. *Clin Psychol Sci Pract*. 1999;6:1–9.
- Ehde DM, Kraft GH, Chwastiak L, et al. Efficacy of paroxetine in treating major depressive disorder in persons with multiple sclerosis. *Gen Hosp Psychiatry*. 2008;30:40–48.
- 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;69:942–949.
- Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Measurement*. 1977;1:385–401.
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:53–63.
- Review Manager (RevMan)* [computer program]. Version 5.0.20. Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.
- Schiffer RB, Wineman NM. Antidepressant pharmacotherapy of depression associated with multiple sclerosis. *Am J Psychiatry*. 1990;147:1493–1497.
- Barak Y, Ur E, Achiron A. Moclobemide treatment in multiple sclerosis patients with comorbid depression: an open-label safety trial. *J Neuropsychiatry Clin Neurosci*. 1999;11:271–273.
- Benedetti F, Campori E, Colombo C, Smeraldi E. Fluvoxamine treatment of major depression associated with multiple sclerosis. *J Neuropsychiatry Clin Neurosci*. 2004;16:364–366.
- Scott TF, Nussbaum P, McConnell H, Brill P. Measurement of treatment response to sertraline in depressed multiple sclerosis patients using the Carrol scale. *Neurol Res*. 1995;17:421–422.
- Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373:746–758.