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## Appendix I. Data Extraction and Risk of Bias Tables from Eligible Studies

### Ehde et al. 2008

Methods	Parallel group randomized controlled trial.
Participants	42 volunteer participants recruited from a variety of sources Neurologist-confirmed MS. Diagnosis of MDD or Dysthymia based on SCID. Age range was 24 to 63.
Interventions	12 weeks of treatment with paroxetine (10-40 mg.) or placebo.
Outcomes	The primary outcome measure was a 50% reduction in HAM-D score.
Notes	20 of the respondents had either Dysthymia alone (n=7) or double depression (n=13).

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Computer generated random number sequence.
Allocation concealment?	Yes	Identical capsules.
Blinding?	Yes	Outcome assessors were blind to treatment "at the time of assessment."
Incomplete outcome data addressed?	Yes	ITT analysis reported, 8 of 20 placebo responders (40%), the analogous response rate in treated subjects was 57.1%, approximately 13 of 22 responders.
Free of selective reporting?	Yes	Clearly identified primary and secondary endpoints.
Free of other bias?	Yes	Main issue is one of generalizability, as 1/3 of the screened population was on antidepressants. The study sample was a residual group.

**Mohr et al. 2001**

Methods	Randomized controlled trial.
Participants	63 MS patients, Neurologist-confirmed. Major Depressive Disorder, confirmed by the SCID. Exceeded HAM-D and BDI severity thresholds.
Interventions	16 weeks of treatment with sertraline (50-200 mg.) or CBT or SEG.
Outcomes	BDI, DSM diagnosis and HAM-D were all used as outcome measures.
Notes	The SEG groups was treated as a referent for sertraline in this analysis, rather than CBT.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	No	The randomization procedure was linked to operational needs for the group therapy intervention.
Allocation concealment?	No	Not possible with these treatments.
Blinding?	No	The raters were not blind to treatment group.
Incomplete outcome data addressed?	Yes	ITT analysis was reported.
Free of selective reporting?	Yes	Difficult to because of complexity of modelling.
Free of other bias?	Yes	Generalizability may be an issue due to eligibility screening.

## Schiffer et al. 1990

Methods	Randomized controlled trial.
Participants	28 patients with definite MS and SADS-confirmed major depressive disorder.
Interventions	Desipramine or short-term psychotherapy. Desipramine dosage was titrated to 150 mg. per day if tolerated, and guided by serum levels.
Outcomes	Hamilton and BDI scales after 30 days.
Notes	It is reported that it was difficult to achieve standard therapeutic serum levels in this population. Nevertheless, significant improvement on the Ham-D scores and blinded global ratings were significant.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Allocation was randomized, details not reported.
Allocation concealment?	Yes	Identical appearing placebo.
Blinding?	Yes	Psychotherapy to all patients, therapist not aware of treatment allocation, but this is a situation in which blinding could be compromised.
Incomplete outcome data addressed?	Yes	ITT not carried out, but Table 1 reports detailed data on n=28 completers.
Free of selective reporting?	Yes	Pre-specified primary outcome (global judgment).
Free of other bias?	No	One patient was removed from the protocol because of severe depression and several did not finish the protocol, therefore, this is best considered a "completer" analysis rather than an ITT analysis, in essence, it is vulnerable to selection bias.

## **Appendix II. Characteristics of Excluded Studies**

Andersson 1996

Reason for exclusion	This is a review article.
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Antonijevic 2003

Reason for exclusion	This is not a therapeutic study.
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Appel 1971

Reason for exclusion	Pharmaceutical development report. Not a therapeutic study.
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Bagert 2002

Reason for exclusion	Not a therapeutic study.
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Barak 1999

Reason for exclusion	Uncontrolled study.
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Benedetti 2004

Reason for exclusion	Uncontrolled trial.
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Browning 1990

Reason for exclusion	Case-report of toxicity. Not a therapeutic trial.
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Bykova 2006

Reason for exclusion	This is an interferon trial.
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Cetin 2007

Reason for exclusion	Epidemiologic study: not a therapeutic trial.
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De Broucker 2000

Reason for exclusion	Interferon study, not a depression trial.
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Defer 2001

Reason for exclusion	Review article.
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El 2008

Reason for exclusion	Not a therapeutic trial.
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Falcone 2005

Reason for exclusion	Interferon trial, not a depression trial.
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Feinstein 2002

Reason for exclusion	Study of interferon side effects - especially depression, but not a depression trial.
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Fitzsimons 2007

Reason for exclusion	Concerned with ECT, not antidepressants. Case report.
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Flax 1991

Reason for exclusion	Not a study, just "comment."
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Folkerts 1995

Reason for exclusion	Not English. Could not review. Seems to be about ECT.
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Galeazzi 2005

Reason for exclusion	Epidemiologic study, not a therapeutic trial.
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Gaughan 1984

Reason for exclusion	About the DST. Not a therapeutic trial.
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Gill 2000

Reason for exclusion	A withdrawn Cochrane review. Topic ADs in pregnancy.
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Goeb 2003

Reason for exclusion	Case report of delirium.
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Goeb 2006

Reason for exclusion	Paper about interferon side effects.
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Gusev 2003

Reason for exclusion	Report about interferon side effects.
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Haase 2004

Reason for exclusion	Not a depression study.
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Huber 1999

Reason for exclusion	Review of data relevant to the idea that amantadine might be a treatment for depression - not a therapeutic trial.
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Jaussaud 1999

Reason for exclusion	About Crohn's disease.
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Julian 2006

Reason for exclusion	Another report from the Mohr study.
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Kraft 2005

Reason for exclusion	Study of modafanil for fatigue.
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Kulmatycki 2006

Reason for exclusion	A review article about antidepressants and inflammation. Not a therapeutic trial.
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Kumar 2008

Reason for exclusion	Review of modafanil.
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Lebrun 2001

Reason for exclusion	French language. Not a therapeutic study.
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Levine 1986

Reason for exclusion	Not an MS study.
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Loftis 2004

Reason for exclusion	Phenomenologic study about interferon side effects.
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Mendez 1999

Reason for exclusion	Case report only. Catonia in MS.
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Mendez 2000

Reason for exclusion	About mania.
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Mikova 2001

Reason for exclusion	Epidemiologic study about TNF in depression in MS.
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Mohr 2001a

Reason for exclusion	Another report from the Mohr study.
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Mohr 2003

Reason for exclusion	Another report from the Mohr study.
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Mohr 2006

Reason for exclusion	This was an epidemiologic study of depression treatment frequency in a clinic setting.
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Notcutt 2004

Reason for exclusion	Cannabis for pain.
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Pandya 2002

Reason for exclusion	Case report.
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Pandya 2005

Reason for exclusion	About predictive value not a therapeutic trial.
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Pariante 1995

Reason for exclusion	Case report.
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Patten 1997

Reason for exclusion	This is a review.
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Patten 2005

Reason for exclusion	Interferon trial data, not a depression trial.
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Pittion-Vouyovitch 2006

Reason for exclusion	A fatigue study.
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Pollak 2002

Reason for exclusion	Animal study.
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Porcel 2006

Reason for exclusion	Study of depression as interferon outcome. Not a therapeutic trial.
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Rickards 2005

Reason for exclusion	Review.
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Rickards 2006

Reason for exclusion	Review.
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Rodgers 1996

Reason for exclusion	Review.
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Russo 2003

Reason for exclusion	Case report.
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Sandyk 1993

Reason for exclusion	About melatonin secretion in MS and affective disorder. Not a therapeutic trial.
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Scott 1995

Reason for exclusion	Uncontrolled retrospective study.
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Scott 1996

Reason for exclusion	Uncontrolled retrospective study.
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Shafey 1992

Reason for exclusion	Case Report.
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Silver 1990

Reason for exclusion	Case Report.
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Solomon 1978

Reason for exclusion	Case Report.
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Tsai 2007

Reason for exclusion	Review article about Copaxone as an antidepressant.
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Tsivgoulis 2007

Reason for exclusion	Not a therapeutic trial. It is about the depression/fatigue interaction.
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Wallin 2006

Reason for exclusion	Review article.
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Wilken 2007

Reason for exclusion	Review article.
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## **Appendix III. References to Studies**

### Included studies

Ehde 2008

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. General hospital psychiatry 2008;30(1):40-8. [PubMed: 18164939]

Mohr 2001

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;69(6):942-9. [PubMed: 11777121]

Schiffer 1990

Schiffer RB, Wineman NM. Antidepressant pharmacotherapy of depression associated with multiple sclerosis. The American journal of psychiatry 1990;147(11):1493-7. [PubMed: 2221162]

### Excluded studies

Andersson 1996

Andersson PB, Goodkin DE. Current pharmacologic treatment of multiple sclerosis symptoms.

The Western journal of medicine 1996;165(5):313-7. [PubMed: 8993211]

Antonijevic 2003

Antonijevic IA, Steiger A. Depression-like changes of the sleep-EEG during high dose corticosteroid treatment in patients with multiple sclerosis. Psychoneuroendocrinology 2003;28(6):780-95. [PubMed: 12812864]

Appel 1971

Appel P, Berger I, Harrer G. Experiences with Wy 4036, a new tranquilizing agent from the benzodiazepine group [Erfahrungen mit Wy 4036, einem neuen Tranquilizer aus der Benzodiazepin-Reihe.]. Arzneimittel-Forschung 1971;21(7):1083-6. [PubMed: 4935400]

Bagert 2002

Bagert B, Camplair P, Bourdette D. Cognitive dysfunction in multiple sclerosis: natural history, pathophysiology and management. CNS drugs 2002;16(7):445-55. [PubMed: 12056920]

Barak 1999

Barak Y, Ur E, Achiron A. Moclobemide treatment in multiple sclerosis patients with comorbid depression: an open-label safety trial. The Journal of neuropsychiatry and clinical neurosciences 1999;11(2):271-3. [PubMed: 10334000]

Benedetti 2004

Benedetti F, Campori E, Colombo C, Smeraldi E. Fluvoxamine treatment of major depression associated with multiple sclerosis. *The Journal of neuropsychiatry and clinical neurosciences* 2004;16(3):364-6. [PubMed: 15377746]

Browning 1990

Browning WN. Exacerbation of symptoms of multiple sclerosis in a patient taking fluoxetine. *The American journal of psychiatry* 1990;147(8):1089. [PubMed: 2375445]

Bykova 2006

Bykova OV, Kuzenkova LM, Maslova OI. The use of beta-interferon-1b in children and adolescents with multiple sclerosis. *Zhurnal nevrologii i psichiatrii imeni S.S. Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psichiatrov* 2006;106(9):29-33. [PubMed: 17069059]

Cetin 2007

Cetin K, Johnson KL, Ehde DM, Kuehn CM, Amtmann D, Kraft GH. Antidepressant use in multiple sclerosis: epidemiologic study of a large community sample. *Multiple sclerosis* (Hounds Mills, Basingstoke, England) 2007;13(8):1046-53. [PubMed: 17623732]

De Broucker 2000

De Broucker T, Lhote F. Severe Raynaud's phenomenon associated with interferon-beta 1a and fluoxetine [Phénomène de Raynaud sévère associé à un traitement par interféron bêta-1a et fluoxetine.]. Annales de médecine interne 2000;151(5):424-5. [PubMed: 11033481]

Defer 2001

Defer G. Neuropsychological evaluation and psychopathology of multiple sclerosis [Evaluation neuropsychologique et psychopathologique dans la sclérose en plaques.]. Revue neurologique 2001;157(8-9 Pt 2):1128-34. [PubMed: 11787345]

El 2008

El Moutawakil B, Sibai M, Bourezgui M, Boulaajaj FZ, Rafai MA, Gam I, et al. Manic-depressive psychosis as prevalent manifestation of multiple sclerosis [La psychose maniaque dépressive comme manifestation prévalente d'une sclérose en plaques.]. Revue neurologique 2008;164(5):472-6. [PubMed: 18555881]

Falcone 2005

Falcone NP, Nappo A, Neuteboom B. Interferon beta-1a overdose in a multiple sclerosis patient. The Annals of pharmacotherapy 2005;39(11):1950-2. [PubMed: 16204396]

Feinstein 2002

Feinstein A, O'Connor P, Feinstein K. Multiple sclerosis, interferon beta-1b and depression A prospective investigation. Journal of neurology 2002;249(7):815-20. [PubMed: 12140662]

Fitzsimons 2007

Fitzsimons MG, Welch CA, Haspel KL, Gorman JM. The safety and efficacy of ECT and anesthesia in the setting of multiple sclerosis. *Journal of psychiatric practice* 2007;13(3):195-8.  
[PubMed: 17522564]

Flax 1991

Flax JW, Gray J, Herbert J. Effect of fluoxetine on patients with multiple sclerosis. *The American journal of psychiatry* 1991;148(11):1603. [PubMed: 1928482]

Folkerts 1995

Folkerts H. Electroconvulsive therapy in neurologic diseases [Elektrokrampftherapie bei neurologischen Krankheiten.]. *Der Nervenarzt* 1995;66(4):241-51. [PubMed: 7783810]

Galeazzi 2005

Galeazzi GM, Ferrari S, Giaroli G, Mackinnon A, Merelli E, Motti L, et al. Psychiatric disorders and depression in multiple sclerosis outpatients: impact of disability and interferon beta therapy. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 2005;26(4):255-62. [PubMed: 16193252]

Gaughan 1984

Gaughan TJ, Popkin MK. The utility of the dexamethasone suppression test in affective disorder associated with multiple sclerosis. *Psychiatric medicine* 1984;2(4):323-7. [PubMed: 6599904]

Gill 2000

Gill D, Hatcher S. WITHDRAWN: Antidepressants for depression in medical illness. Cochrane database of systematic reviews (Online) 2000;(4):CD001312. [PubMed: 17636666]

Goeb 2003

Goeb JL, Cailleau A, Laine P, Etcharry-Bouyx F, Maugin D, Duverger P, et al. Acute delirium, delusion, and depression during IFN-beta-1a therapy for multiple sclerosis: a case report. Clinical neuropharmacology 2003;26(1):5-7. [PubMed: 12567157]

Goeb 2006

Goeb JL, Even C, Nicolas G, Gohier B, Dubas F, Garre JB. Psychiatric side effects of interferon-beta in multiple sclerosis. European psychiatry : the journal of the Association of European Psychiatrists 2006;21(3):186-93. [PubMed: 16386408]

Gusev 2003

Gusev EI, Demina TL, Boiko AN, Khachanova NV. Certain problems of therapy with beta-interferon preparations [Nekotorye voprosy terapii preparatami beta-interferona.]. Zhurnal nevrologii i psichiatrii imeni S.S. Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psichiatrov 2003;(Spec No 2):98-102. [PubMed: 12938643]

Haase 2004

Haase CG, Tinnefeld M, Faustmann PM. The influence of immunomodulation on psycho-neuroimmunological functions in benign multiple sclerosis. Neuroimmunomodulation 2004;11(6):365-72. [PubMed: 15467351]

Huber 1999

Huber TJ, Dietrich DE, Emrich HM. Possible use of amantadine in depression. Pharmacopsychiatry 1999;32(2):47-55. [PubMed: 10333162]

Jaussaud 1999

Jaussaud R, Deville JF. Central neurologic manifestations of Crohn disease [Les manifestations neurologiques centrales de la maladie de Crohn.]. La Revue de medecine interne / fondee ... par la Societe nationale francaise de medecine interne 1999;20(6):527-30. [PubMed: 10422146]

Julian 2006

Julian LJ, Mohr DC. Cognitive predictors of response to treatment for depression in multiple sclerosis. The Journal of neuropsychiatry and clinical neurosciences 2006;18(3):356-63. [PubMed: 16963585]

Kraft 2005

Kraft GH, Bowen J. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. Neurology 2005;65(12):1995-7; author reply 1995-7. [PubMed: 16380634]

Kulmatycki 2006

Kulmatycki KM, Jamali F. Drug disease interactions: role of inflammatory mediators in depression and variability in antidepressant drug response. *Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques* 2006;9(3):292-306. [PubMed: 17207413]

Kumar 2008

Kumar R. Approved and investigational uses of modafinil: an evidence-based review. *Drugs* 2008;68(13):1803-39. [PubMed: 18729534]

Lebrun 2001

Lebrun C. Therapeutic indications in symptomatic cognitive and psychopathological disorders in multiple sclerosis [Indications therapeutiques a visee symptomatique des troubles cognitifs et psychopathologiques dans la sclerose en plaques.]. *Revue neurologique* 2001;157(8-9 Pt 2):1085-90. [PubMed: 11787341]

Levine 1986

Levine S. The management of resistant depression. *Acta psychiatrica Belgica* 1986;86(2):141-51. [PubMed: 3088916]

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Loftis JM, Hauser P. The phenomenology and treatment of interferon-induced depression. *Journal of affective disorders* 2004;82(2):175-90. [PubMed: 15488246]

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Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. *Anaesthesia* 2004;59(5):440-52. [PubMed: 15096238]

Pandya 2002

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Pandya 2005

Pandya R, Metz L, Patten SB. Predictive value of the CES-D in detecting depression among candidates for disease-modifying multiple sclerosis treatment. *Psychosomatics* 2005;46(2):131-4. [PubMed: 15774951]

Pariante 1995

Pariante CM, Orru MG, Carpiello B, Rudas N. Multiple sclerosis and major depression resistant to treatment. Case of a patient with antidepressive therapy-induced mood disorder, associated with manic features [Sclerosi multipla e depressione maggiore resistente al trattamento. Il caso di una paziente con disturbo dell'umore indotto dalla terapia antidepressiva, con caratteristiche maniacali.]. *La Clinica terapeutica* 1995;146(6-7):449-52. [PubMed: 7586996]

Patten 1997

Patten SB, Metz LM. Depression in multiple sclerosis. *Psychotherapy and psychosomatics* 1997;66(6):286-92. [PubMed: 9403917]

Patten 2005

Patten SB, Francis G, Metz LM, Lopez-Bresnahan M, Chang P, Curtin F. The relationship between depression and interferon beta-1a therapy in patients with multiple sclerosis. *Multiple sclerosis* (Hounds Mills, Basingstoke, England) 2005;11(2):175-81. [PubMed: 15794391]

Pittion-Vouyouitch 2006

Pittion-Vouyouitch S, Debouverie M, Guillemin F, Vandenberghe N, Anxionnat R, Vespignani H. Fatigue in multiple sclerosis is related to disability, depression and quality of life. *Journal of the neurological sciences* 2006;243(1-2):39-45. [PubMed: 16434057]

Pollak 2002

Pollak Y, Orion E, Goshen I, Ovadia H, Yirmiya R. Experimental autoimmune encephalomyelitis-associated behavioral syndrome as a model of 'depression due to multiple sclerosis'. *Brain, behavior, and immunity* 2002;16(5):533-43. [PubMed: 12401467]

Porcel 2006

Porcel J, Rio J, Sanchez-Betancourt A, Arevalo MJ, Tintore M, Tellez N, et al. Long-term emotional state of multiple sclerosis patients treated with interferon beta. *Multiple sclerosis* (Hounds Mills, Basingstoke, England) 2006;12(6):802-7. [PubMed: 17263010]

Rickards 2005

Rickards H. Depression in neurological disorders: Parkinson's disease, multiple sclerosis, and stroke. *Journal of neurology, neurosurgery, and psychiatry* 2005;76 Suppl 1:i48-52. [PubMed: 15718222]

Rickards 2006

Rickards H. Depression in neurological disorders: an update. *Current opinion in psychiatry* 2006;19(3):294-8. [PubMed: 16612216]

Rodgers 1996

Rodgers J, Bland R. Psychiatric manifestations of multiple sclerosis: a review. *Canadian journal of psychiatry. Revue canadienne de psychiatrie* 1996;41(7):441-5. [PubMed: 8884033]

Russo 2003

Russo S, Boon JC, Korf J, Haagsma EB. Mirtazapine for the treatment of interferon-induced psychopathology. General hospital psychiatry 2003;25(6):497. [PubMed: 14706418]

Sandyk 1993

Sandyk R, Awerbuch GI. Nocturnal melatonin secretion in multiple sclerosis patients with affective disorders. The International journal of neuroscience 1993;68(3-4):227-40. [PubMed: 8063528]

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Scott TF, Nussbaum P, McConnell H, Brill P. Measurement of treatment response to sertraline in depressed multiple sclerosis patients using the Carroll scale. Neurological research 1995;17(6):421-2. [PubMed: 8622794]

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Scott TF, Allen D, Price TR, McConnell H, Lang D. Characterization of major depression symptoms in multiple sclerosis patients. The Journal of neuropsychiatry and clinical neurosciences 1996;8(3):318-23. [PubMed: 8854304]

Shafey 1992

Shafey H. The effect of fluoxetine in depression associated with multiple sclerosis. Canadian journal of psychiatry. Revue canadienne de psychiatrie 1992;37(2):147-8. [PubMed: 1562960]

Silver 1990

Silver JM, Hales RE, Yudofsky SC. Psychopharmacology of depression in neurologic disorders.  
The Journal of clinical psychiatry 1990;51 Suppl:33-9. [PubMed: 2404002]

Solomon 1978

Solomon JG. Multiple sclerosis masquerading as lithium toxicity. The Journal of nervous and mental disease 1978;166(9):663-5. [PubMed: 690625]

Tsai 2007

Tsai SJ. Glatiramer acetate could be a potential antidepressant through its neuroprotective and anti-inflammatory effects. Medical hypotheses 2007;69(1):145-8. [PubMed: 17196755]

Tsivgoulis 2007

Tsivgoulis G, Triantafyllou N, Papageorgiou C, Evangelopoulos ME, Kararizou E, Sfagos C, et al. Associations of the Expanded Disability Status Scale with anxiety and depression in multiple sclerosis outpatients. Acta neurologica Scandinavica 2007;115(1):67-72. [PubMed: 17156268]

Wallin 2006

Wallin MT, Wilken JA, Turner AP, Williams RM, Kane R. Depression and multiple sclerosis: Review of a lethal combination. Journal of rehabilitation research and development 2006;43(1):45-62. [PubMed: 16847771]

Wilken 2007

Wilken JA, Sullivan C. Recognizing and treating common psychiatric disorders in multiple sclerosis. *The neurologist* 2007;13(6):343-54. [PubMed: 18090712]

