
CRITICAL REVIEW

Depression in multiple sclerosis: Review and theoretical proposal

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Abstract

Because of its high prevalence and implications for quality of life and possibly even disease progression, depression has been intensively studied in multiple sclerosis (MS) over the past 25 years. Despite the publication of numerous excellent empirical research papers on this topic during that time, the publication of theoretical work that attempts to explain depression in a comprehensive way is scarce. In this study, we present a theoretical model that attempts to integrate existing work on depression in MS and provide testable hypotheses for future work. The model suggests that risk for depression begins with the onset of MS. MS results in disease-related changes such as increased lesion burden/brain atrophy and immunological anomalies that are associated with depression in MS, but explain only a relatively limited proportion of the variance. Common sequelae of MS including fatigue, physical disability, cognitive dysfunction, and pain, have all been shown to have an inconsistent or relatively weak relationship to depression in the literature. In the model, we propose that four variables—social support, coping, conceptions of the self and illness, and stress—may moderate the relationship between the above common MS sequelae with depression and help to explain inconsistencies in the literature. (*JINS*, 2008, 14, 691–724.)

Keywords: MS, Brain atrophy and lesion damage, Depression and cognitive functioning, Stress and coping, Fatigue, Pain, Social support

INTRODUCTION

The prevalence of depression is high in multiple sclerosis (MS), a chronic and common autoimmune disease that results in the destruction of myelin and gray matter atrophy in the central nervous system. The lifetime risk for depression has been estimated at around 50% (Patten & Metz, 1997; Sadovnick et al., 1996), compared with a lifetime risk in the general population of around 10–15% (American Psychiatric Association, 1994). Because of its high prevalence, importance to quality of life and patients' well-being (Kenealy et al., 2000), association with suicidality (Feinstein et al., 2002), and possible influence on the disease course itself (Ackerman et al., 2000; Dalos et al., 1983; Franklin et al., 1988; Mohr et al., 2000), depression has been intensively studied in MS. Nonetheless, although sev-

eral brief, focused reviews of the literature have been conducted (Dalton & Heinrichs, 2005; Siegert & Abernethy, 2006), and a practical consensus statement on depression published (Goldman Consensus Group, 2005) in recent years, no comprehensive theoretical model of depression in MS has been articulated. The goal of this article is to present an integrated theoretical model of depression in MS that links key findings in the literature, identifies gaps based on existing work, and makes suggestions for future research. We will begin with the articulation of a theoretical model that integrates a variety of factors that have been found to be associated with depression in MS. Following this, we will devote much of the rest of the review to providing some empirical support for the theoretical model.

A MODEL OF DEPRESSION IN MS

A model of depression in MS, incorporating several variables that have been shown to be associated with depression in MS samples, is shown in Figure 1. The onset of MS,

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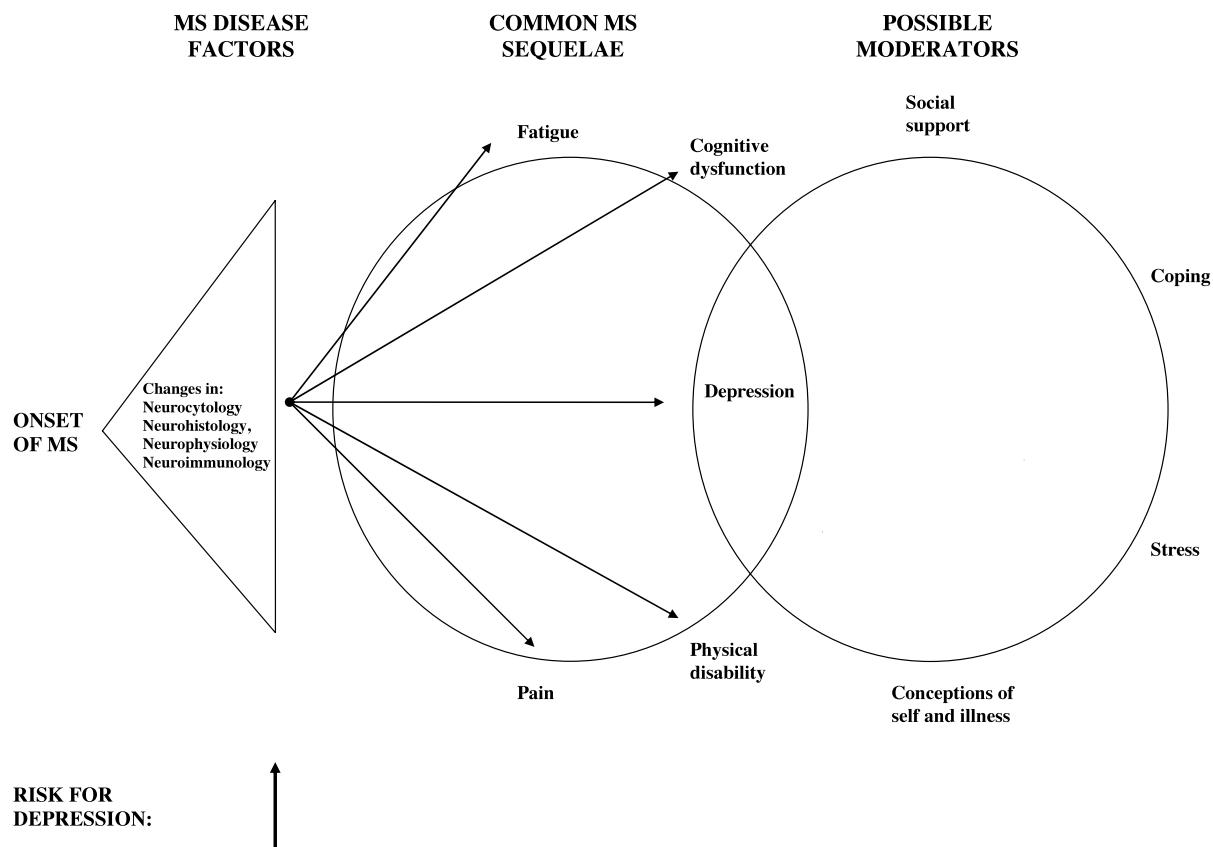


Fig. 1. Model of depression in multiple sclerosis (MS): Disease factors predict common MS sequelae.

depicted at the far left side of the figure, denotes the beginning of risk for depression in MS. As detailed later, all of the factors included in the model have some evidence supporting their association with depression. The "MS Disease Factors" have been directly associated with depression as well as with physical disability, cognitive dysfunction, pain, and fatigue. The "Common MS Sequelae" variables, including depression, are arranged in a circle, as evidence shows that they may be associated with one another as well as being related to disease factors and moderating variables. The "Possible Moderator" variables, which represent factors related to the external circumstances of individuals with MS or to their internal representations of those circumstances, are theorized to impact the relationship between the common MS sequelae and depression, but they have also been shown to be directly associated with depression in MS. They, too, are arranged in a circle, as they are theorized to interact with one another in addition to the common MS sequelae. Although depression is at the intersection of the two circles because it is the focus of the current review, any one of the common MS sequelae could be moved into the intersection from whence associations with disease factors and possible moderators could be systematically investigated. Thus, there is no implicit statement on the direction of influence in the model; rather, dynamic and complex relationships among the variables are likely, as described throughout.

We now turn to a review of the evidence supporting the association of the variables depicted in the model with depression in MS. Although most of the research on these variables has been correlational, thus making causal inferences problematic, the literature that has developed over the past 20 years provides impressive insight into the range of factors that *may* causally contribute to depression in MS. The review will start with disease factors associated with depression in MS. It will then examine some common MS sequelae that are sometimes associated with depression, followed by an examination of possible moderators in the relationship between these common MS sequelae and depression.

In the tables accompanying this article, where possible, we provide effect sizes for the different associations reported. Using the Cohen's (Cohen & Cohen, 1983) framework, effect sizes (Cohen's d) between .20 and .49 were considered small, .50 to .79 moderate, and .80 and above large. Correlations from .20 to .29 were considered small, those from .30 to .49 moderate, and those .50 and above large.

FACTORS ASSOCIATED WITH DEPRESSION IN MS

MS Disease-Related Factors

A detailed review of the MS disease factors associated with depression in MS is beyond the scope of the present article.

However, it is assumed that disease factors are distal causes of depression in MS either directly or *via* their influence on other variables in the model (see Figure 1). Of relevance to the current review is the finding that most studies have shown that risk for depression follows the onset of MS (Joffe et al., 1987; Minden et al., 1987; Sadovnick et al., 1996) (but cf. Sullivan et al., 1995).

The weight of most recent work favors an association between depression and demyelination, suggesting some disease-related contribution to depression in MS (Bakshi et al., 2000a; Berg et al., 2000; Fassbender et al., 1998; Feinstein, 2004; Pujol et al., 1997, 2000; Reischies et al., 1988; Zorzon et al., 2001). Certain brain regions may contribute disproportionately, as at least five published studies have reported greater temporal region involvement in depressed compared with nondepressed MS patients (Berg et al., 2000; Feinstein et al., 2004; Honer et al., 1987; Pujol et al., 1997; Zorzon et al., 2001).

Depression in MS also appears to be related to changes in important immunological parameters caused by the disease process. Several studies show that higher levels of T4+ (helper/inducer) cell counts (Foley et al., 1988) and higher levels of central nervous system (CNS) inflammation, as measured by cerebrospinal fluid white blood cell counts (Fassbender et al., 1998), are associated with greater depression. Decreased depression has also been associated with reduced interferon-gamma production over time (Mohr et al., 2001). Longitudinally, MS patients' period of greatest depression during a 2-year interval coincided with lower CD8+ (suppressor/cytotoxic) cell counts and higher CD4/CD8 ratio (Foley et al., 1992). Taken together, the existing data suggest that depression in MS is associated with neuroimmunological and neurophysiological abnormalities.

Some associations have been established among disease-related factors and the common MS sequelae outlined in the model. Fatigue has been shown to be significantly associated with hyperintense MRI lesions in the brainstem and midbrain in at least one study (Moller et al., 1994), and with measures of axonal integrity (Tartaglia et al., 2004). Cognitive problems in MS are associated with the extent of lesion damage in the brain (Arnett, 2003; Rao et al., 1989a), gray matter hypointensities (Brass et al., 2006), and especially atrophy (Benedict et al., 2006). Gray matter atrophy has also been shown to be associated with physical disability in MS (Pirko et al., 2007), and primary dysfunction or lesion of the CNS is associated with pain in MS (Mersky & Bogduk, 1994).

Common MS Sequelae Associated With Depression That May Be Moderated by Other Variables

For the common MS sequelae shown in Figure 2, findings regarding their association with depression in the literature have been mixed. Inconsistent or weak associations between a predictor and criterion variable often indicate the existence of moderators (Baron & Kenny, 1986). Consideration

of moderator variables may help to clarify the mixed relationships reported in the literature. Details on the studies summarized in this section can be found in Table 1. Note that the acronyms in this table and in Table 2 are defined in the Appendix.

Fatigue

Up to 88% of MS patients complain of significant fatigue (Krupp et al., 1988), and 28% report fatigue as one of their most troubling symptoms. Additionally, fatigue has been identified by MS patients as the one symptom most responsible for them having to cut back on their work hours (Smith & Arnett, 2005), and patients identify fatigue as a central factor in their subsequently becoming unemployed (Edgley et al., 1991; Jackson et al., 1991). Thus, fatigue has significant real world consequences for patients.

The existing data examining the relationship between fatigue and depression in MS are more consistent than with the other sequelae. Eight studies have reported significant associations, whereas four have reported null results. Notably, all four studies reporting null results had much smaller sample sizes than the eight studies reporting significant associations, so low statistical power is likely to be an important contributor to the null findings. Two studies reported large effect sizes (Bakshi et al., 2000b; Fisk et al., 1994; Kroencke, 2000), one medium (Flachenecker et al., 2002), and four small (Krupp et al., 1988, 1989; Schwartz et al., 1996; Vercoulen et al., 1998). Three reported both medium and small effect sizes (Mohr et al., 2003; Schreurs et al., 2002; Voss et al., 2002), and one reported both medium and large effects (Kroencke, 2000). Although results did not reach traditional levels of statistical significance due to low statistical power, Krupp and colleagues' as well as the study by Vercoulen et al. had effect sizes in the small range. Thus, the bulk of the evidence suggests a relationship between depression and fatigue in MS that is in the small to moderate range of effect size.

Physical disability

The relationship between physical/neurological disability and depression in MS is more mixed in the literature than that between depression and fatigue. When operationalized using Kurtzke's (Kurtzke, 1983) Expanded Disability Status Scale (EDSS), some studies (11) have found no relationship between physical disability and depression. However, a comparable number of studies (11) have reported positive findings. The null findings in at least five studies (Fassbender et al., 1998; Minden et al., 1987; Moller et al., 1994; Pujol et al., 1997; Sabatini et al., 1996) can be attributed, in part, to small sample size. Another study (Ron & Logsdail, 1989) appeared to use a nonstandardized measure of disability. However, the remaining studies reporting null findings (Beatty et al., 1990; Huber et al., 1993; Provinciali et al., 1999; Rabins et al., 1986; Schreurs et al., 2002) had reasonably large sample sizes and used standard measures of depression and dis-

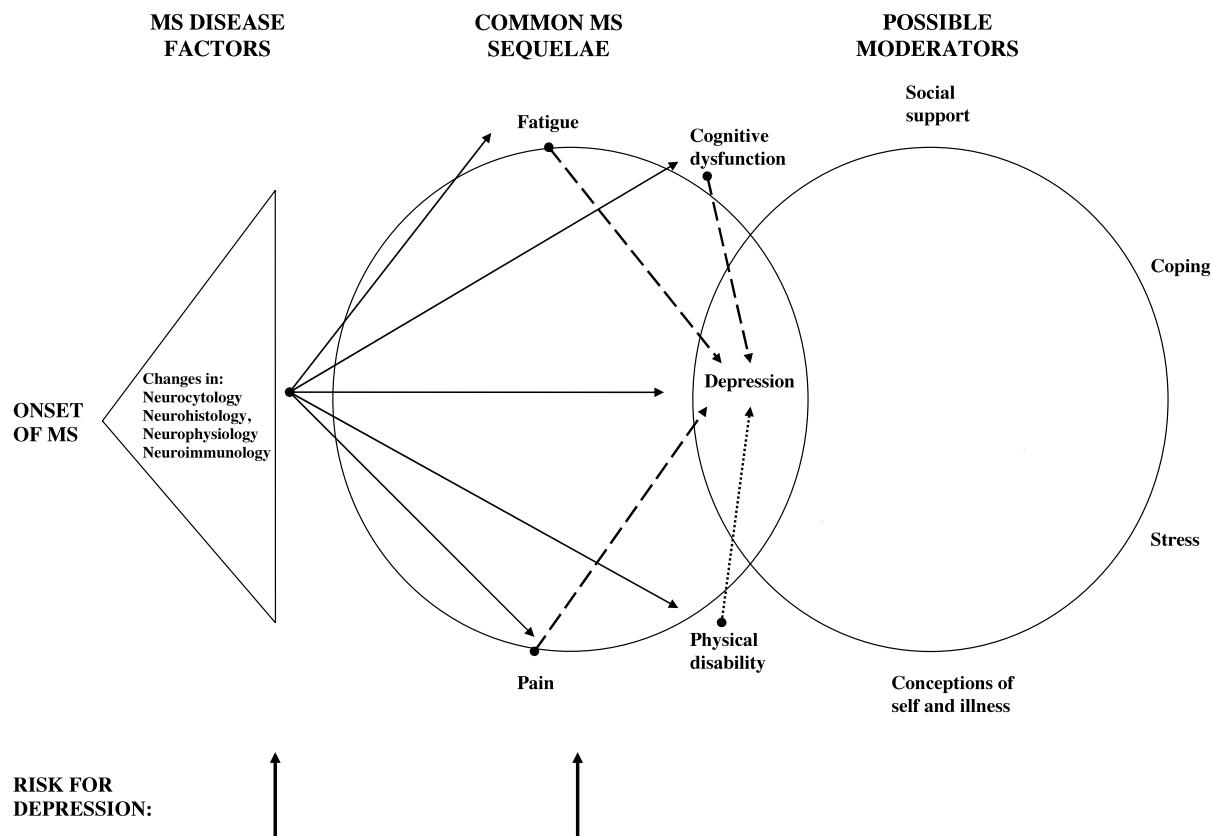


Fig. 2. Model of depression in multiple sclerosis (MS): Common MS sequelae predict depression. *Note.* The different types of lines in this and subsequent figures indicate the strength or weakness of the evidence supporting the influence of a particular factor on MS-related depression: An unbroken line indicates that evidence consistently supports the influence of that factor, a dashed line indicates that evidence for the influence of a particular factor appears to be less consistent on the surface but is more consistent when subject to careful analysis, and a dotted line indicates that the evidence supporting the influence of the particular factor is decidedly mixed. The thickness of the lines reflects the number of studies that have examined the influence of a particular variable on MS-related depression: Thicker lines indicate a greater number of studies, whereas thinner lines indicate fewer studies.

ability. Mixed findings such as these suggest the presence of moderators.

Regarding effect sizes, four studies reported moderate effect sizes (McIvor et al., 1984; Mohr et al., 1997; Pujol et al., 2000; Zorzon et al., 2001), one large (Kneebone & Dunmore, 2004) and another small (Voss et al., 2002), with two studies reporting both small and moderate effect sizes (Devins et al., 1993; Lynch et al., 2001). Due to the way the data were presented, it was not possible to estimate effect sizes for three studies but the findings they reported were statistically significant (Chwastiak et al., 2002; Goodin & the Northern California MS Study Group, 1999; Janssens et al., 2003). Taken together, these positive findings suggest that the effect size for the relationship between depression and physical disability in MS is in the moderate range.

Cognitive dysfunction

Approximately 50% of MS patients display significant cognitive impairments (Brassington & Marsh, 1998; Rao et al.,

1991), and cognitive impairments occur both with and without depression. As Table 1 illustrates, existing studies are evenly divided between studies that reported null effects (12) and those reporting significant associations (10). Regarding the studies reporting null findings, the majority (10 of 12) were characterized by small sample sizes, suggesting that low statistical power could account for the absence of significant effects (DeLuca et al., 1994; Fischer, 1988; Grafman et al., 1991; Krupp et al., 1994; Millefiorini et al., 1992; Minden & Schiffer, 1990; Moller et al., 1994; Rao et al., 1984, 1989b; Schiffer & Caine, 1991). The other study reporting null findings (Good et al., 1992) excluded significantly depressed MS patients from their sample.

Studies reporting significant associations between depression and cognitive performance in MS patients have involved correlating standard measures of depression with measures of cognitive functioning within a heterogeneous MS sample (Aikens et al., 1997; Arnett, 2005; Arnett et al., 2002; Denney et al., 2004; Landro et al., 2004) or comparing depressed and nondepressed MS groups (Arnett

et al., 2001, 1999a,b; Beatty et al., 1988; Gilchrist & Creed, 1994).

Studies reporting positive associations did so using a variety of depression measures [e.g., BDI, CES-D, and Chicago Multiscale Depression Inventory (CMDI)] that were either examined continuously or used to create extreme depressed/nondepressed groups. It was not possible to calculate effect size in five of the studies. In the other five, three effect sizes were large (Aikens et al., 1997; Arnett et al., 2001, 2002), and two moderate (Arnett, 2005; Landro et al., 2004).

Taken together, a critical examination suggests that studies with adequate sample sizes generally have reported a positive association between depression and cognitive dysfunction in MS of moderate to large effect size.

Pain

Over 50% of MS patients (Kassirer & Osterberg, 1987; Moulin et al., 1988; Stenager et al., 1991, 1995), and as many as 86% (Indaco et al., 1994), report pain at some time during the course of their MS. As many as 32% of MS patients rate pain as one of their worst symptoms, and a 5-year longitudinal study on pain in MS showed that pain problems increased substantially over time (Stenager et al., 1991, 1995). Findings from studies that have examined the relationship between pain and depression have been mixed, with roughly equal numbers of studies showing a positive *versus* a null relationship. Despite this inconsistent relationship, it is important to note that not only have few studies been published in this area but, of the three studies with null findings, two (Indaco et al., 1994; Newland et al., 2005) had significant methodological flaws that may have accounted for their results. All of the studies reporting positive findings used adequate sample sizes, and three of the four (Archibald et al., 1994; Kalia & O'Connor, 2005; Tedman et al., 1997) used rigorous measures of pain and standard and well-validated measures of depression or distress. The remaining study (Ehde et al., 2003) used a well-validated measure of depression, but the measure of pain was simply four items on a mail-in survey questionnaire and MS diagnosis was based upon self-report. In terms of effect size, two revealed small and two a moderate effect size. Taken together, if the quality of the study is factored into the analysis, the weight of the evidence supports a relationship between depression and pain in MS, with effect size in the small-moderate range (see Table 1).

As the previous section shows, the research literature on these four common MS sequelae—fatigue, physical disability, cognitive dysfunction, and pain—shows that on the surface their association with depression is mixed. If the literature is critically evaluated, however, the association between depression and three of these sequelae—fatigue, cognitive dysfunction, and pain—shows consistently positive associations with studies that use adequate sample sizes and good methodology. The studies on physical disability and depression are evenly divided between those with null

findings *versus* those with positive associations. A more critical analysis continues to show a mixed literature overall, which suggests the presence of moderator variables that may help to explain these inconsistencies. For fatigue, cognitive dysfunction, and pain, though a critical analysis suggests a more consistent relationship for these variables with depression, the fact that such relationships are less robust suggests that they may be moderated by other variables.

Factors That May Moderate the Relationship Between Common MS Sequelae and Depression

Before turning to our discussion of possible factors that may moderate the relationship between common MS sequelae and depression, it is important to clarify our intent regarding moderator variables. According to Baron and Kenny (1986) moderation involves the interaction between two variables, one of which is an independent variable and the other the moderator, which significantly predict some outcome variable after the independent effects of the two predictors have been controlled. In the case of our proposed model, each of the common MS sequelae in our model would be considered independent variables, whereas the proposed moderator variables would be the moderators. Any interaction between one of the common MS sequelae and a moderator variable could theoretically lead to depression if the interaction between the severity of the MS sequelae and a given moderator variable was great enough. Generally, more interactions between the common MS sequelae and the moderators are theorized to lead to greater risk for depression. Based upon the research literature, the common MS sequelae may or may not significantly predict depression directly. Regardless, their interaction with the moderator variables is predicted to elevate risk for depression.

It could be argued that the variables we identify as potential moderators would be better conceptualized as mediators. The distinction between moderation and mediation is important. According to Baron and Kenny (Baron & Kenny, 1986) moderation occurs when one variable (the moderator) affects the direction or intensity of the relation between a second (independent) variable and a third (dependent) variable. In contrast, mediation occurs when one variable (the mediator) *explains* the relationship between a second (independent) and third (dependent) variable. Although a mediational model may be possible in some instances, we characterize our model as predominantly moderational for two reasons. First, in the case of mediation, both the independent variable and the mediator are expected to significantly and consistently predict the dependent variable. However, at least one of the common MS sequelae that we propose as an independent variable fails to meet this requirement, and the extent to which the other three sequelae meet it is debatable. Critical evaluation of the literature on the relationship between physical disability and depression shows that physical disability (the independent variable)

Table 1. Studies examining the relationship between common disease sequelae and depression in MS

Studies examining fatigue and depression in MS—Null (negative) findings (4)							
Study	Depression measure(s)	Fatigue measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations/Comments
Krupp et al. (1988)	CES-D	Structured interview, VAS	N = 32 (course type not reported)	N = 33 NHC (matched on age and sex)	Correlations	No significant correlation between VAS-rated fatigue and CES-D scores in MS group ($r^2 = .08$)	Small sample size
Krupp et al. (1989)	CES-D	FSS VAS	N = 25 CP = 100%	N = 29 Systemic lupus erythematosus patients N = 20 NHC	Correlations	No significant correlation between FSS-rated fatigue and CES-D scores in MS group ($r^2 = .07$) but significant correlation in SLE group ($r^2 = .21$)	Small sample size
Moller et al. (1994)	SCID-I IMPS HRSD MADRS	FSS	N = 25 RR = 72% CP = 28% in 2 groups: depressed (6) nondepressed (19)	No control group	Correlations & group comparisons	No significant FSS differences between depressed and nondepressed MS groups and no significant correlations	Small sample size
Vercoulen et al. (1998)	BDI-excluded fatigue item	CHIS-fatigue subscale	N = 50 RR = 62% CP = 38%	N = 51 Chronic fatigue syndrome (matched on age, sex, education)	Used SEM to test model of fatigue in MS and CFS groups	Including depression as causal factor in fatigue led to weaker model of fatigue, while excluding depression led to stronger model of fatigue in MS group; $d = .41$ for BDI-CHIS correlation	Possible selection bias in MS group, which had only mild neurological dysfunction
Studies examining fatigue and depression in MS—Significant (positive) findings (8)							
Study	Depression measure(s)	Fatigue measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Fisk et al. (1994)	MHI	FIS	N = 85 RR = 42% CP = 31% RP = 20% Benign = 7%	N = 20 patients with hypertension	Used multiple regression correlations	FIS significantly predicted MHI, accounting for 38% of the variance in mental health outcome when entered into the regression model first	Mood measure did not assess depression directly but rather overall well-being and distress
Schwartz et al. (1996)	AIMS-Depression subscale	MAF	N = 139 RR = 42% CP = 58%	No control group	Hierarchical multiple regression	Depression significantly correlated with ($r = .17$) and significant predictor of MAF-rated fatigue severity ($\beta = .28$)	No NHC group
Kroencke et al. (2000)	ZSDS	FSS	N = 207 RR = 66% PP = 22% SP = 12%	No control group	Correlations and multiple regression	Fatigue and depression scores were highly correlated ($r = .58$) even when corrected for overlapping symptoms ($r = .44$) and depressed mood was significant predictor of fatigue	
Bakshi et al. (2000b)	BDI HDI	FSS	N = 71 RR = 70% SP = 30% Divided into groups by fatigue and depression: Fatigue = 46% Depressed = 15%	N = 71 Divided into groups by fatigue and depression: non-fatigue = 20% nondepressed = 26%	Group comparisons	After controlling for physical disability:-BDI & HDI scores significantly correlated with FSS scores ($r = .56$ for both);-HDI & BDI scores significantly higher in fatigued than non-fatigued MS group ($d' = 8.89$ and 7.69, respectively);-FSS scores significantly higher in depressed than nondepressed MS group ($d' = 4.0$)	Significant relationship between fatigue and depression might have been found by using extreme groups

Table 1. Continued

Studies examining fatigue and depression in MS—Significant (positive) findings (8) (continued)							
Study	Depression measure(s)	Fatigue measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Flachenecker et al. (2002)	BDI	FSS MFSS MFIS VAS	N = 151 RR = 62% SP = 33% PP = 5%	No control group	Correlations and group comparisons	FSS significantly correlated with BDI scores ($r = .41$), even with fatigue item removed, and significantly higher in depressed than nondepressed MS ($R^2 = .16$) BDI significant predictor of fatigue ($r = .41$), after controlling for disease course and physical disability	
Schreurs et al. (2002)	BDI	MFI	N = 98 (course type not reported, but majority presumed to be RR)	No control group	HMRA. SEM to test relationship between fatigue and depression over 1-year period	At same time point, BDI significant predictor of Mental Fatigue ($\beta = .39$) and Reduced Activity ($\beta = .29$) subscales of MFI and Mental Fatigue subscale significant predictor of BDI ($\beta = .35$) Longitudinally, depression predicted Physical (but not Mental) Fatigue and Reduced Activity, but no fatigue dimensions preceded depression. Findings suggest that relationship between depression and physical and mental fatigue can change over time	Study continued over just 1 year and assessed patients at just two time points Possible selection bias due to questionnaire non-response rate (25%)
Voss et al. (2002)	CMDI-Mood subscale	FIS-Physical Fatigue subscale	N = 76 RR = 63% SP = 25% PP = 9% PR = 3%	No control group	Used SEM to assess relationship between fatigue, depression, and other variables	FIS-Physical Fatigue subscale scores directly and significantly predicted depression as measured by CMDI-Mood subscale scores ($r = .42$, path coefficient = .24)	
Mohr et al. (2003)	BDI—fatigue item omitted	FAI	N = 60, RR & SP included, number of each not specified. 3 treatment groups: CBT = 22 SEGP = 22 Sertraline = 16	No control group	Compared pre- and post-treatment scores on fatigue measures after 16-week treatment course for depression HMRA to assess relationship of change in depression to change in fatigue	Total FAI and Global Fatigue Severity subscale significantly reduced over course of treatment ($\eta^2 = .09$ and .12, respectively) across all three groups Reduction in total FAI marginally associated with decline in overall BDI scores ($R^2 = .05$), but reduction in total FAI and in GFS subscale significantly associated with decreases in BDI mood items ($R^2 = .09$ for both)	No placebo control condition
Studies examining physical disability and depression in MS—Null (negative) findings (11)							
Study	Depression measure(s)	Physical disability measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations/Comments
Rabins et al. (1986)	GHQ-depression subscale	KDSS	N = 87 RR = 31% CP = 44% PR = 22%	N = 16 SCI	Correlations	No significant correlation between disability status and depressive symptom scores	Emotional distress might have been underestimated in the sample as participants who failed to complete the study (16%) had higher mean GHQ scores

(continued)

Table 1. Continued

Studies examining physical disability and depression in MS—Null (negative) findings (11) (continued)							
Study	Depression measure(s)	Physical disability measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations/Comments
Minden et al. (1987)	BDI HDRS, derived from SADS	EDSS	N = 50 RR = 36% CP = 50% SP = 14%	N = 35 NHC	Correlations	No significant correlation between disability status and BDI-rated depression ($r = -.05$) or between disability and the occurrence of MDD the previous year	
Ron & Logsdail (1989)	CIS-D BDI	3-point scale: 0 = able to walk unaided; 1 = walking with aid; 2 = wheelchair	N = 116 (course type not reported)	N = 48 physically disabled patients with rheumatic or neurological conditions N = 40 NHC	Correlations	No significant correlation between disability status and CIS-Depression ratings	
Beatty et al. (1990)	BDI	EDSS AI	N = 85 RR = 49% CP = 51%	No control group	Correlations	No significant correlation between disability, as measured by EDSS or AI, and BDI-rated depression; disability not significant predictor of BDI scores	
Huber et al. (1993)	BDI	EDSS	N = 89 (course type unspecified) 2 disability groups: split into mild mild = 27 moderate/severe = 62	N = 47 NHC	Group comparisons	No significant differences between mild and moderate/severe disability groups on BDI depressive symptoms scores	Looked at BDI subscale scores—somatic, vegetative, mood, and self-reproach—as well as total scores
Moller et al. (1994)	SCID-I IMPS HDRS MADRS	EDSS	N = 25 RR = 72% CP = 28% Split in 2 groups: depressed = 6 nondepressed = 19	19 nondepressed MS	Correlations and group comparisons	Physical disability (EDSS), was unrelated to depression No significant differences on EDSS scores between depressed and nondepressed groups	Small sample size
Sabatini et al. (1996)	BDI HDRS	EDSS	N = 10 depressed MS RR = 100%	N = 10 nondepressed MS RR = 100% matched for age, sex, functional disability	Group comparisons	No significant differences on EDSS scores between groups	Small sample size
Pujol et al. (1997)	BDI	EDSS	N = 45 RR = 69% CP = 31%	No control group	Correlations	No significant relationship between EDSS disability status and BDI-rated depression	Small sample size
Fassbender et al. (1998)	HRSD ZSDS	EDSS	N = 23 MS RR = 100%	N = 17 NHC (matched for age and sex)	Correlations	No significant association between scores on HRSD-rated depression and EDSS scores	MS patients were experiencing exacerbations at the time of the study, and only 4 of 23 MS patients were clinically depressed
Provinciali et al. (1999)	BDI	EDSS LHS	N = 83 (course type not reported) divided into 3 groups according to severity of EDSS-rated disability. EDSS <3.0 n = 43, >3.5 <6.0 n = 19, >6.0 n = 21	No control group	Group comparisons	No significant correlation between BDI-rated depression and EDSS scores No significant differences between disability groups on BDI-rated depression	Minimal inclusionary and exclusionary criteria used Disability subgroups too small and unbalanced for adequate analysis of relationship between disability and depression

Table 1. Continued

Studies examining physical disability and depression in MS—Null (negative) findings (11) (continued)							
Study	Depression measure(s)	Physical disability measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations/Comments
Schreurs et al. (2002)	BDI	SIP—Physical Summary Scale	N = 98 (exact numbers by course type not reported; majority presumed to be RR)	No control group	Used SEM to test relationship between physical disability and depression over 1-year period	Longitudinally, no significant association between BDI and SIP—Physical Summary Scale	No zero-order correlations between BDI and SIP reported Study continued over just 1 year and assessed patients at just 2 time points
Studies examining physical disability and depression in MS—Significant (positive) findings (11)							
Study	Depression measure(s)	Physical disability measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
McIvor et al. (1984)	BDI	KDSS	N = 120 RR = 50% Non-specific progressive = 50%	No control group	Correlations, regression	EDSS and BDI scores were significantly correlated ($r = .39$); disability status a significant predictor of severity of depressive symptoms	Only non-cerebellar spinal cord MS patients used in sample
Millefiorini et al. (1992)	SCID for DSM-III-R, MMPI-depression subscale	EDSS	N = 18 RR = 100% divided into 3 groups: major depression = 6 minor depression = 7 no depression = 5	No control group	Group comparisons, correlations	EDSS disability scores significantly higher in MDD patients than in mildly or nondepressed patients ($\eta = .47$) EDSS disability scores significantly correlated with MMPI depression scores for overall MS group	All participants were in the early stages of MS (<5 years) and were only mildly disabled
Devins et al. (1993)	POMS CES-D SCL-90R	EDSS SIP—Physical Summary Scale	N = 94 (RR & CP % not specified)	No control group	Psychosocial well-being factor, produced by principal-components analysis; HMR correlation	Psychosocial well-being factor correlated significantly with SIP scores ($r = -.23$) but not with EDSS scores In HMR correlations, when controlling for recent stressful life events, SIP scores significantly and uniquely related to psychosocial well-being factor (partial $r = -.34$) but EDSS scores not significantly related to psychosocial well-being factor	
Mohr et al. (1997)	BDI	EDSS	N = 91 (course type unspecified) split into disability groups: high = 23 Low = 68	No control group	Group comparisons	Mean BDI depressive symptom score was significantly higher in high than in low impairment group ($\eta = .64$)	Low response rate (46% of patients who were surveyed by mail sent in BDI)
Goodin et al. (1999)	Mailed survey	Mailed survey	N = 493 of which 168 (34%) responded RR = 58% SP = 22% PP = 20%	No control group	Correlations	Depression, as assessed by self-report, significantly associated with EDSS ($p = .006$)	Self-report measure of disability Possible selection bias due to low response rate

(continued)

Table 1. Continued

Studies examining physical disability and depression in MS—Significant (positive) findings (11) (continued)							
Study	Depression measure(s)	Physical disability measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Pujol et al. (2000)	BDI including symptom subscales	EDSS	N = 45 RR = 69% CP = 31%	No control group	Correlations	EDSS significantly correlated with BDI Performance Difficulties scale (work difficulty, fatigability, indecisiveness, loss of libido), $r = .37$	
Lynch et al. (2001)	ZSDS corrected for overlap with MS symptoms	EDSS	N = 188 RR = 67% PP = 20% SP = 13%	No control group	Correlations and multiple regression	EDSS scores significantly correlated with ZSDS-rated depressive symptoms ($r = .33$), even when controlling for education ($r = .28$) EDSS disability scores significantly predicted ZSDS depressive symptom scores ($\beta = .26$)	
Zorzon et al. (2001)	HDRS	EDSS	N = 95 split into subgroups depressed = 18 nondepressed = 77	N = 97 chronic disease patients N = 110 NHC both groups matched for age and sex	Group comparisons	HDRS and EDSS scores significantly related in Spearman rank correlation analysis ($r = .30$)	
Voss et al. (2002)	CMDI-Mood subscale	SIP-Physical Summary Scale	N = 76 RR = 63% SP = 25% PP = 9% PP PR = 3% PR	No control group	SEM	Physical disability (SIP) significantly associated with CMDI depressive symptoms ($r = .23$) Physical disability (EDSS) not significantly associated with CMDI depressive symptoms ($r = .04$)	Self-report measures of disability
Chwastiak et al. (2002)	CES-D from mailed survey	EDSS-self report from mailed survey	N = 1374 MS of which 739 (54%) responded RR = 52% PP = 18% SP = 30% organized into 3 disability groups	No control group	Correlated EDSS and depression scores (CES-D ≥ 16) Compared CES-D scores across three disability groups: minimal, intermediate, and advanced	EDSS significantly associated with clinical depression (CES-D ≥ 16): intermediate disability group 3 times more likely ($\chi^2 = 16.7$, $p < 0.001$, odds ratio = 3.10) and advanced disability group 6 times more likely ($\chi^2 = 33.8$, $p < 0.001$, odds ratio = 6.04) to report depressive symptoms than minimal severity group Significantly higher ($p < 0.0001$) CES-D depression scores in intermediate and advanced disability groups (mean = 17.6 and 18.3, respectively) than in minimal disability group (mean = 11.6)	Self-report measure of disability No data on non-responders to mailed survey
Janssens et al. (2003)	HADS	EDSS	N = 101 (course type unspecified) divided into disability groups: high = 37 low = 63	N = 78 NHC (partners of MS participants)	Compared two MS disability groups on HADS depression scores, with age and sex as covariates	MS patients in moderate to severe disability group reported significantly greater levels of depressive symptoms than those in minimal disability group ($p < 0.001$)	Only recently diagnosed MS patients examined, possibly limiting generalizability

Table 1. Continued

Studies examining cognitive dysfunction and depression in MS—Null (negative) findings (12)							
Study	Depression measure(s)	Cognitive dysfunction measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Rao et al. (1984)	MMPI	WMS subtests, FVRT, MSO, 7/24	N = 44 CP = 100% split into 3 memory groups: severe = 9 mild = 19 normal = 16	N = 44 NHC (matched for age and education)	Group comparisons	Mildly impaired memory group had higher depression scores on MMPI than both normal and severely impaired memory group	Difference between mildly impaired and normal memory groups might reflect fact that greater proportion of mildly impaired memory group taking psychoactive medications compared with normal group
Fischer (1988)	BDI	WMS-R	N = 45 RR = 38% RP = 40% CP = 22% split into 3 memory groups: severe = 9 mild = 25 normal = 11	No control group	Group comparisons	No significant difference in BDI-rated depression scores between groups in overall comparison	Mild memory group had BDI score 5 points higher than severe memory group, but statistical significance of this difference was not tested directly
Rao et al. (1989b)	ZSDS	DS, BPMT, SRT, COWA, verbal recall, story recall	N = 37 (course type not specified)	N = 26 NHC (matched for age, education, sex, and verbal IQ)	Correlations	No significant correlations between ZDSD and any cognitive index in MS group	Small sample size
Minden et al. (1990)	BDI	WMS, AVLT, DS, DSMT, FT, COWAT, BNT, HVOT, WCST, Luria 3-step	N = 50 RR = 36% CP = 50% PR = 14%	N = 35 NHC matched for age, gender, and education	Correlations	No significant correlations between BDI scores and any cognitive index	Small sample size
Rao et al. (1991)	ZSDS	MMS, WAIS-R subtests, BPIT, VSRT, 7/24, COWAT, PT, WCST, BCT, RPM, RT, MS, PASAT, Stroop, BNT, HVOT, JLO, FR, VFD	N = 100 RR = 39% CP = 19% CS = 42%	N = 100 NHC (matched on age, sex, education)	Group comparisons	Depressed MS patients did not fail significantly more tests than nondepressed MS patients, although significance was borderline (.09)	Findings were of borderline significance Used depression measures that included neurovegetative depression symptoms that overlapped with MS symptoms
Schiffer & Caine (1991)	SADS BDI HRSD	BNT, COWAT, TMT, list, story, and figure learning and recall, clock drawing, math test and hand-writing sample, finger-thumb tapping	N = 11 MS with MDD (course type unspecified)	N = 8 MS without MDD, matched for age and disability	Compared cognitive performance for individual patients both before and after a clinically diagnosed depressive episode	No significant differences on neuropsychological performance measures during dysthymic and euthymic episodes (average test-retest interval of 7 months)	Patients showed significant improvement on a verbal memory and a verbal fluency task Small sample size Authors assumed that improving depression would improve all areas of cognitive function
Grafman et al. (1991)	ZSDS	HFMT, PA	N = 41	N = 45 NHC, matched for age, sex, and education	Correlations	No significant correlation between ZSDS and any cognitive indices	Used depression measure that included neurovegetative depression symptoms that overlapped with MS symptoms Small sample size

(continued)

Table 1. Continued

Studies examining cognitive dysfunction and depression in MS—Null (negative) findings (12) (continued)							
Study	Depression measure(s)	Cognitive dysfunction measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Good et al. (1992)	BDI MMPI-Depression subscale	COWAT, WAIS-R VIQ and PIQ	N = 84 RR = 100% divided into 2 cognitive impairment groups: with = 26 without = 58	N = 48 NHC, matched for age, sex, education, and SES	Group comparisons	No significant group differences on either depression index	Excluded significantly depressed MS patients from sample
Millefiorini et al. (1992)	SCID for DSM-III-R, MMPI-depression subscale	AVLT, 7/24, Babcock, CFT, WCST, RPM, TMT, BNT, COWAT, HVOT, Digit Span	N = 18 RR = 100% divided into 3 groups: major depression = 6 minor depression = 7 no depression = 5	No control group	Group comparisons	No significant group differences	All patients were in early stage of MS (<5 years) Small sample size
DeLuca et al. (1994)	BDI	VSRT, PASAT, WAIS-R Voc, DS	N = 23 RR = 35% CP = 44% PR = 17% Stable = 4%	N = 23 NHC	Within group correlations	No significant correlations between BDI scores cognitive indices within MS group	Small sample size
Krupp et al. (1994)	CES-D	WAIS-R, WMS, WRAT, Stroop, TMT, SDMT, BCT, VSRT, BVRT, COWAT, FOT	N = 20 MS N = 20 CFS (matched for age, education, and fatigue severity)	N = 20 NHC (matched for age and education)	Group comparisons	No association between cognitive deficits and depression in MS group (differences between MS and control groups on neuropsychological tests did not change with CES-D rated depression as covariate)	Groups not matched on severity of depression (25% of CFS, compared to .05% of MS group had concurrent MDD or dysthymia) and patients with CES-D > 35 excluded from study
Moller et al. (1994)	SCID-I IMPS HDRS MADRS	SIDAM	N = 25 MS RR = 72% CP = 28% split in 2 groups: depressed = 6 nondepressed = 19	19 nondepressed MS	Correlated scores on cognitive impairment and depression measures Compared SIDAM cognitive impairment scores and depression scores between groups	No significant association between SIDAM-rated cognitive impairment and depression scores No significant differences between depressed and nondepressed groups on SIDAM scores	Small sample size Small sample size
Studies examining cognitive dysfunction and depression in MS—Significant (positive) findings (10)							
Study	Depression measure(s)	Cognitive dysfunction measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Beatty et al. (1988)	BDI	MMSE, BNT, BPMT, list learning, verbal fluency	N = 38 CP = 100% split into depressed and nondepressed groups, but no breakdown provided for n's	N = 26 NHC (matched for age and education)	Group comparisons	Depressed MS patients performed significantly ($p < .05$) worse on MMSE, BPMT, list learning, verbal fluency, and recall/recognition of public events	

Table 1. Continued

Studies examining cognitive dysfunction and depression in MS—Significant (positive) findings (10) (continued)							
Study	Depression measure(s)	Cognitive dysfunction measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Gilchrist & Creed (1994)	CIS-D and ICD-9 criteria	RSPM, AVLT, MHVS, BVRT	N = 24 RR = 96% CP = 4% split into groups: depressed = 8 nondepressed = 15	No control group	Non-parametric comparison of differences on depression scores and neuropsychological tests between groups	Significantly more of depressed than nondepressed group showed cognitive impairment on RSPM and AVLT Significantly more of depressed than nondepressed group showed significant cognitive impairment (abnormal > 2+ tests)	Failed to control statistically for significantly older age in depressed group Experimenter expectancy effects (experimenter not blind to diagnostic status) might have influenced results
Aikens et al. (1997)	BDI	QMSE	N = 27 (disease course not specified)	No control group	Used bivariate and multiple regression correlations	BDI scores significantly correlated with QMSE scores ($r = -.51$)	No breakdown of how subscales of QMSE correlated with BDI scores
Arnett et al. (1999b)	CMDI BDI	SDMT-Oral, PASAT, VE, CVLT, 7/24, RBMT-Faces	N = 61 RR = 57% SP = 30% PP = 10% PR = 3% split into 2 groups: depressed mood = 20 without depressed mood = 41	N = 8 NHC	Group comparisons	Depressed mood MS group performed significantly worse than both nondepressed groups on capacity-demanding speeded attentional tasks (PASAT, SDMT, VE) but not on capacity-nondemanding tasks Significantly more of depressed mood MS group was impaired on capacity-demanding tasks	Most patients not clinically depressed
Arnett et al. (1999a)	CMDI BDI	Reading span and word span tasks	N = 60 RR = 57% SP = 30% PP = 10% PR = 3% split into 2 groups: depressed mood = 19 without depressed mood = 41	N = 8 NHC	Group comparisons	Depressed mood MS group performed significantly worse than nondepressed group on reading span task—a demanding task of working memory—but not on a non-demanding word span task	Most patients not clinically depressed
Arnett et al. (2001)	CMDI BDI	TOL	N = 63 RR = 50% SP = 34% PP = 12% PR = 4% split into 2 groups: depressed mood = 15 without depressed mood = 35	No control group	Group comparisons	Depressed mood MS group required significantly more time and made significantly more moves per trial than nondepressed group on TOL A significant amount of variance in CMDI depression scores was predicted by performance on speeded attentional/working memory tasks (25%) and TOL-moves per trial (8%)	Most patients not clinically depressed
Arnett et al. (2002)	CMDI BDI	SDMT-Oral, PASAT, VE, TOL, Reading Span	N = 55 RR = 55% SP = 29% PP = 13% PR = 4%	No control group	Hierarchical regression analyses	Performance on cognitive tasks significantly predicted CMDI-rated depression scores ($R^2 = .30$)	Most patients not clinically depressed

(continued)

Table 1. Continued

Studies examining cognitive dysfunction and depression in MS—Significant (positive) findings (10) (continued)							
Study	Depression measure(s)	Cognitive dysfunction measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Denney et al. (2004)	CES-D	TOL, WCST	N = 71 RR = 55% PP = 45%	N = 40 NHC	Used depression measure as covariate in analyses	CES-D depression scores were a significant covariate between groups ($p = 0.001$) when looking at the cognitive factor of “planful problem solving”	
Landro et al. (2004)	BDI	SDMT, PASAT, WCST	N = 26 RR = 92% PP = 8%	N = NHC	Used HRM	BDI depression scores were significantly correlated with SDMT ($r = -0.38$, $d = .80$, $p = 0.006$) and PASAT ($r = -0.28$, $d = .60$, $p = 0.049$); BDI depression scores significantly predicted performance on SDMT and PASAT ($p < 0.05$ for both) in multiple regression analyses	
Arnett (2005)	CMDI BDI	SDMT-Oral, PASAT, VE, CVLT, VSRT, 7/24, TOL, TOH, Reading Span	N = 53 RR = 58% SP = 28% PP = 11% PR = 2%	No control group	Used bivariate and multiple regression correlations	Speeded attention, working memory, and planning tasks significantly correlated with mood and negative evaluative CMDI symptoms ($r = -.18$ to $.49$), but only negative evaluative CMDI symptoms remained significantly correlated with these cognitive tasks three years later ($r = -.33$ to $.48$)	Most patients not clinically depressed
Studies examining pain and depression in MS—Null (negative) findings (3)							
Study	Depression measure(s)	Pain measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Stenager et al. (1991)	BDI	Clinical interview	N = 117 (course type unspecified) split into 2 groups: pain = 76 pain-free = 41	N = 41 pain-free MS	Group comparisons	No significant differences between MS pain and MS pain-free groups on BDI-rated depressive symptom scores	Depression scores of MS group currently experiencing pain were 2 points higher than MS pain-free group Small sample size
Indaco et al. (1994)	BDI HRDS	Clinical interview	N = 122 (course type unspecified) split into 2 groups: pain = 70 pain-free = 52	N = 52 pain-free MS	Group comparisons	No significant differences between pain and pain-free MS groups on BDI- or HRDS-rated depressive symptoms	Unclear whether MS patients in pain group were experiencing pain at time of study or had simply experienced it in past
Newland et al. (2005)	MDS-Resident Assessment Version	ADL	N = 139 MS long-term care residents w/ pain (course type not specified)	N = 108 MS long-term care residents w/o pain (course type not specified) N = 40,963 non-MS long-term care residents	Compared MS and non-MS groups	No significant differences in levels of depressive symptoms in MS LTC residents with and without pain MS residents <i>without</i> pain were at greater risk for depressive symptoms 90 days later than MS residents with pain Measures of pain and depression weak (<2 items) Diagnostic criteria for depression not reported	Unclear what criteria used to divide MS patients into those with and without pain MS groups significantly different on education

Table 1. Continued

Studies examining pain and depression in MS—Significant (positive) findings (4)							
Study	Depression measure(s)	Pain measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Archibald et al. (1994)	MHI	Structured interview	N = 85 RR = 40% PR = 26% CP = 29%	No control group	Compared MHI scores for MS patients with and without pain	Mean MHI scores significantly higher for MS group with pain than for group without pain ($\eta^2 = .41$)	Depressive symptoms not assessed directly by MHI
Tedman et al. (1997)	BDI HADS	SF-36 (bodily pain scale)	N = 92 (course type unspecified)	N = 40 MND	Used bivariate correlations to examine relationship between depression and pain within groups	SF-36 pain scores significantly correlated with BDI-rated depressive symptoms in MS group ($r = -.29$)	Diagnosis of clinically definite MS patients not confirmed by independent neurological examination
Ehde et al. (2003)	CES-D	4 items on a mail-in survey questionnaire	N = 442 RR = 52% PP = 19% SP = 29%	No control group	Compared MS patients with and without pain and used ordinal logistic regression to examine relationship between pain and other variables	Significantly more MS patients endorsing pain than those not endorsing pain scored > 16 on CES-D (53% vs. 33%, $p < 0.001$) In MS patients endorsing pain, patients reporting pain-related interference with activity had higher mean CES-D scores (17.1 vs. 22.7, effect size = .50) and were twice as likely to show CES-D score > 16 (OR = 2.03) than patients reporting no pain-related interference with activity	Possible sampling bias from response rate to mail survey questionnaires (54%) All measures self-report and no information on non-responders
Kalia & O'Connor (2005)	HADS	SF-36 (bodily pain subscale) MPQ-SF	N = 99 RR = 52% SP = 25% PP = 23%	Published data on SF-36 rated pain in rheumatoid arthritis and osteoarthritis patients	Compared high- and low-HADS score MS groups on SF-36 bodily pain scores Bivariate correlations also used	Compared with low HADS group, high HADS group reported significantly more severe pain SF-36 bodily pain scale significantly correlated with HADS depressive symptom scores ($r = -.27$) for women ($r = -.44$) but not men ($r = -.06$)	

Note. See Appendix for listing of all acronyms.

inconsistently predicts depression (the dependent variable), a pattern of results that favors a moderational rather than mediational model. Critical analysis of the relationship between the other three MS sequelae and depression shows that some of the relationships may be more consistent than a cursory examination of the literature makes them appear. Although it is possible that the relationship between these three sequelae—fatigue, pain, or cognitive dysfunction—and depression could be mediated by the variables we are proposing as moderators, inconsistencies in the literature appear when sample sizes and methodological parameters are not ideal. These inconsistencies suggest that the relationships are not robust and may best be explained when moderators are considered, making a mediation model less appealing.

A second reason that we mostly focus on moderation in our model is that there are several studies in the MS literature, which we describe below, that show evidence for significant interactions (i.e., moderation) between the common MS sequelae we have identified and the moderators in predicting depression. Although not all of the proposed moderational relationships have been empirically tested or validated in the MS literature, enough have to warrant further theorizing on other possible moderating relationships. We hope that our proposed model will lead to other empirical tests of moderational relationships, with the additional

suggestion that possible mediational relationships could still be explored.

We now review evidence pertaining to proposed moderators in the model. The proposed moderators represent factors related to either the external circumstances of individuals with MS or to their internal representation of those circumstances. These variables have been shown to have a more consistent relationship with depression in MS (see Figure 3). The specific studies summarized by this section are presented in more detail in Table 2.

Stress/negative life events/stress appraisal

Most studies on stress and depression in MS have been examined in the context of coping. Whether studies measure either general stress or MS-specific stress, the association between stressful events and depression is consistent in the literature. As shown in Table 2, all eight studies reported some positive associations between depression and stress in MS. One study reported small effect size (Kneebone & Dunmore, 2004), two reported moderate (Devins *et al.*, 1996; McCabe & de Judicibus, 2005), two large (Aikens *et al.*, 1997; Gilchrist & Creed, 1994), one small and moderate (Pakenham, 1999), and for two (Patten *et al.*, 2000; Ron & Logsdail, 1989) it was not possible to determine effect size. Although the studies in this section were

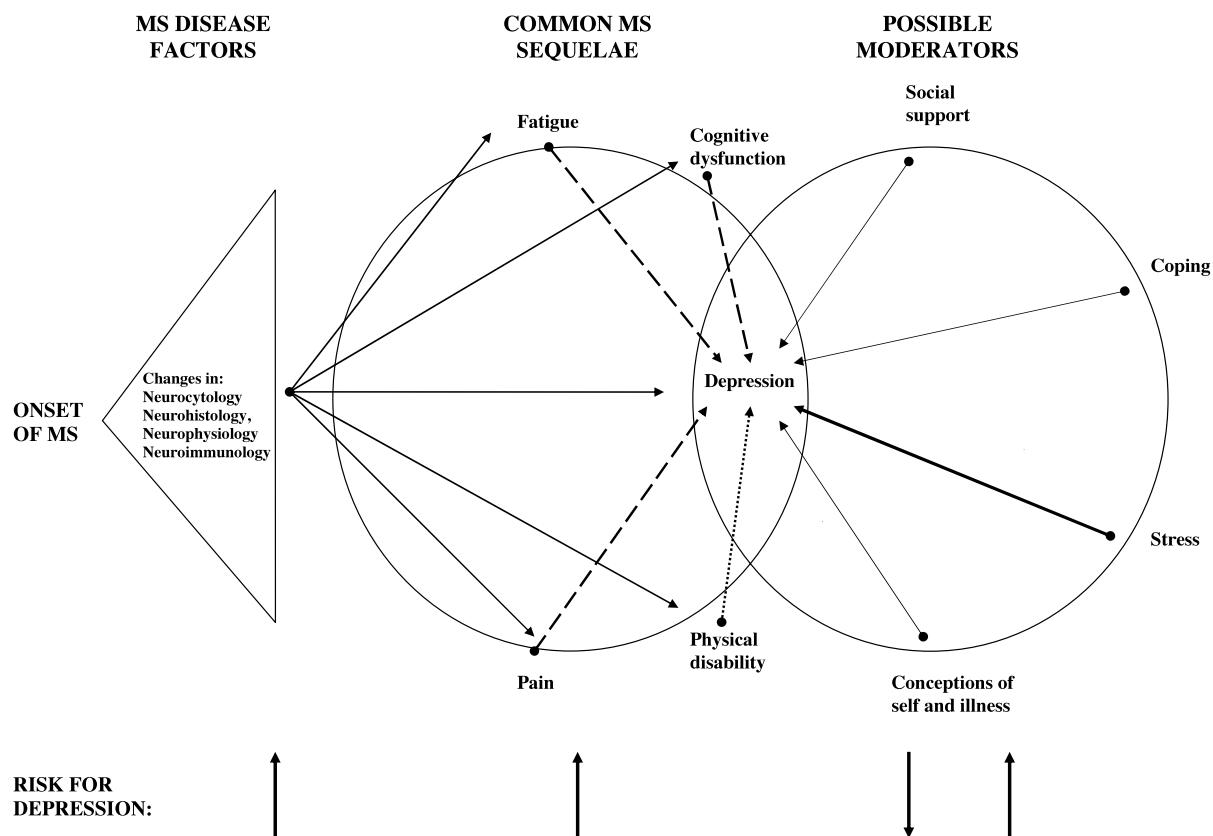


Fig. 3. Model of depression in MS: Possible moderators predict depression.

Table 2. Studies examining relationship between proposed moderators and depression in MS

Studies examining stress and depression in MS—Significant (positive) findings (8)							
Study	Depression measure(s)	Stress measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations/Comments
Ron & Logsdail (1989)	CIS-D BDI	SSSI	N = 116 MS	N = 48 physically disabled patients with rheumatic or neurological conditions; N = 40 NHC	Used MANOVA to examine association between SSSI scores and CIS-D depression scores	CIS-D depression ratings significantly associated with degree of social stress as assessed by SSSI ($p < 0.005$)	Different methods used for determining psychiatric symptoms in patients groups and in NHC group
Gilchrist & Creed (1994)	CIS-D and ICD-9 criteria	SSSI	N = 24 RR = 96% CP = 4% split into 2 groups: depressed = 8 nondepressed = 15	No control group	Non-parametric comparison of differences on depression scores and stress measures between groups Correlation	Significantly more of depressed than nondepressed group reported social stress, especially in areas of family relationships, marriage, and occupation, and depressed group reported significantly higher levels of stress than nondepressed group Significant correlation between CIS and SSSI ($r = -.73$)	Failed to control statistically for significantly older age in depressed group
Devins et al. (1996)	CES-D	Checklist developed for use in chronically ill populations	N = 174 (course type unspecified)	No control group	Used bivariate correlation and HMR	The measure of recent stressful life events significantly correlated with CES-D depressive symptoms ($r = .35$) When used as a covariate in the HMR analyses, stressful life events significantly predicted depressive symptoms ($\beta = .35$)	No reliability or validity data included for measure of recent stressful life events
Aikens et al. (1997)	BDI	LES	N = 27 (disease course not specified)	No control group	Used bivariate and multiple regression correlation	LES stress scores significantly correlated with concurrent BDI scores ($r = .77$), even after accounting for physical disability and cognitive status ($\Delta R^2 = .34$) LES stress scores at time 1 also significantly predicted BDI scores 6 months later ($r = .67$), even after accounting for physical disability and cognitive status ($\Delta R^2 = .20$) LES stress scores at time 2 significantly predicted BDI scores 6 months later ($r = .66$), again after accounting for physical disability and cognitive status ($\Delta R^2 = .19$)	Small sample size and over-representation of higher educational attainment and milder physical disability might limit generalizability of results
Pakenham (1999)	BDI	SRRS	N = 122 RR = 50% CP = 50% 96 participants completed the 12-month study	No control group	Used bivariate and multiple regression correlation	SSRS-rated stressful life events significantly correlated with concurrent BDI scores ($r = .29$) and greater threat appraisals significantly associated with higher levels of BDI symptoms concurrently ($\Delta R^2 = .14$) but not 12 months later	Study examined changes over a 12-month period which might have been too short for more significant associations to emerge
Patten et al. (2000)	CIDI-A	GCSI	N = 136 RR = 43% SP = 31% PP = 22% PR = 4%	No control group	Compared MS patients with and without lifetime prevalence of a major depressive episode	Significantly greater proportion of MS patients with than without lifetime prevalence of a major depressive episode reported 1+ recent and 1+ chronic stressors	

(continued)

Table 2. Continued

Studies examining stress and depression in MS—Significant (positive) findings (8) (continued)							
Study	Depression measure(s)	Stress measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations/Comments
Kneebone & Dunmore (2004)	CES-D	RLCQ	N = 495 RR = 45% CP = 33% Unknown = 18%	No control group	Used bivariate and multiple regression correlation	Measures of life stress on RLCQ significantly associated with CES-D depressive symptoms ($r = .29$) Interaction between RLCQ life stress and negative attributional style significantly predicted CES-D depressive symptoms ($\beta = .13$)	Possible self-selection bias due to voluntary completion of survey questionnaires and possible misleading results due to missing data Diagnoses not confirmed by neurological evaluation
McCabe & de Judicibus (2005)	POMS-SF Depression subscale	EPC	N = 113 (course type not specified)	No control group	Used HMR correlation to examine relationship between economic pressure and emotional well-being	Financial stress as measured on EPC significantly predicted POMS-SF depressive symptoms ($\beta = .27$, $R^2 = .18$)	
Studies examining relationship between coping and depression in MS—Significant (positive) findings (7)							
Study	Depression measure(s)	Coping measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Arnett et al. (2002)	CMDI Mood and Evaluative Subscales	COPE	N = 55 RR = 55% PP = 13% SP = 29% PR = 4%	No control group	Correlations	Avoidance Coping positively correlated with depression index ($r = .62$) and marginally significant negative relationship ($p < .10$) between Active Coping and depression index ($r = -.25$)	Most patients not clinically depressed
Arnett & Randolph (2006)	CMDI Mood and Evaluative Subscales	COPE	N = 53 RR = 58% PP = 11% SP = 28% PR = 2%	No control group	Examined changes in depressed mood and coping at two time points 3 years apart	Patients who demonstrated improved mood, also demonstrated an increase in active coping from time 1 to time 2 Patients whose mood worsened, showed a decrease in active coping strategies	Most patients not clinically depressed
McCabe et al. (2004)	POMS-SF	WOC	N = 381 Course not specified	N = 291 individuals from general population	Compared MS and non-MS groups in terms of coping and association between coping and depression in MS sample	Individuals with MS were more likely than individuals from the general population to adopt a detached style of coping, and less likely to engage in problem-focused coping and seeking social support as a coping strategy. For men, high levels of wishful thinking ($sr^2 = .06$), low levels of problem focused coping ($sr^2 = .02$) and low focus on the positive ($sr^2 = .02$) independently predicted depression. For women, high amounts of wishful thinking ($sr^2 = .10$) independently predicted depression	While many indices of coping were found to be related to depression, this study examined coping factors entered in the regression equation with 11 other variables. A more focused approach may have yielded larger relationships between coping variables and depression

Table 2. Continued

Studies examining relationship between coping and depression in MS—Significant (positive) findings (7) (continued)							
Study	Depression measure(s)	Coping measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Tesar et al. (2003)	BDI	FDCQ	N = 14 Therapy Group recruited from MS outpatient unit. Course not specified	N = 15 No treatment group from MS outpatient unit. Course not specified	Examined pre-post and 2-month follow-up BDI and coping scores within treatment and control groups. Examined differences between groups at three time points	Treatment group showed significant within group improvement in BDI scores. Treatment group demonstrated less depressive coping over treatment, but no change in active or avoidance coping. The treatment group used significantly less depressive coping at treatment end and at 2-month follow-up compared to control group	Small sample. Few participants (38%) met threshold for depression. No random assignment of treatment groups. No effect sizes reported
Pakenham (2001)	BDI	WCC; CMSS	N = 113 Course not specified	No control group	Assessed relationship between new measure of coping in MS (CMSS) and BDI. Compared WCC and CMSS in terms of ability to explain variance in depression in MS sample	Two of seven CMSS factors correlated with BDI: problem-solving ($r = -.23$) and acceptance ($r = -.54$). CMSS explained more variance in BDI than WCC	
Mohr et al. (1999)	POMS	PEMS	N = 94 RR = 100%	No control group	Factor analysis of 63-item questionnaire, derived from interview with 50 MS patients	Found three factors solution: Demoralization, Deterioration in Relationships, and Benefit Finding. Demoralization ($r = .36$) and Deterioration in Relationships ($r = .31$) were associated with depression. Benefit-Finding was mildly associated with anxiety ($r = .21$) and anger ($r = .21$)	
Pakenham (2005)	BABS (Positive and Negative Affect)	19-item BFS (from Mohr et al. [1999])	N = 414 RR = 27% CP = 73%	No control group	Factor analysis of BFS. Assessed relationship between BFS and positive and negative affect scales of BABS	Found two factor solution: Personal Growth and Family Relations Growth. Family Relations related to negative affect ($r = -.13$). Personal Growth ($r = .23$) and Family Relations Growth ($r = .22$) related to positive affect	
Studies examining social support and depression in MS—Significant (positive) findings (5)							
Study	Depression measure(s)	Social support measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
McIvor et al. (1984)	BDI	PSSI	N = 120 non-hospitalized patients with only spinal cord form of MS	No control group	Assessed relationship between depression and length of illness, disability, social support and illness course	Perceived social support from family ($r = -.60$) and friends ($r = -.71$) was best indicator of depression. Age ($r = .22$), disability ($r = .39$) and illness course ($r = .26$) were also related to depression in M	

(continued)

Table 2. Continued

Studies examining social support and depression in MS—Significant (positive) findings (5) (continued)							
Study	Depression measure(s)	Social support measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
McCabe et al. (2004)	POMS-SF	WHOQOL-100 Social Support facet scale	N = 381 Course not specified	N = 291 individuals from general population	Assessed relationship between depression and social support in men and women with MS	Social support and depression were related for women ($r^2 = .02$) but not for men	This study examined social support in a regression equation with 15 other variables. A more focused approach may have yielded larger relationships between social support and depression
Schwartz (1999)	CES-D	FES	N = 44 couples One member of couple with MS Course not specified	No control group	Assessed relationship between depression and family conflict, independence in family, and patient-rating of responses to disability by non-disabled partner	Family conflict ($r = .43$) and greater independence ($r = -.51$) were significantly related to depressive symptoms. Also, patient-rating of more negative responses to patient disability behaviors was positively associated with depression ($r = .64$), while encouraging responses to well behaviors was negatively related ($r = -.33$)	Sample consisted of moderately to severely disabled participants (EDSS $M = 5.6$, $SD = 1.6$)
Feinstein et al. (2002)	HADS	SSSI	N = 40 MS patients with past suicidal intent Overall patient characteristics: N = 140 RR = 56% SP = 32% PP or PR = 6%	N = 100 MS patients without history of suicidal intent	Compared patients with and without suicidal intent on depression, anxiety, alcohol and substance abuse and social support	Suicidal intent was associated with an elevated depression score, lifetime history of alcohol abuse and living alone. Suicidal intent group demonstrated significantly less social support relative to stress compared to never-depressed group	No effect sizes reported
King & Arnett (2005)	HADS	SSSI	N = 64 RR = 64% SP = 25% PP = 9% PR = 2%	No control group	Examined depression, fatigue, cognitive functioning as predictors of dyadic adjustment	Patient-reported dyadic adjustment significantly associated with patient depression ($r = -.48$) and fatigue ($r = -.31$). Significant other dyadic adjustment related to patient depression ($r = -.38$), fatigue ($r = -.30$) and executive functioning impairments ($r = .37$). Stepwise regression revealed depression as only significant of dyadic relationship rated by either member of dyad	

Table 2. Continued

Studies examining conceptions of the self & illness and depression in MS—Significant (positive) findings (8)							
Study	Depression measure(s)	Conceptions of the self and illness measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Shnek et al. (1995)	CES-D	CBQ; MSAI; MSBS	N = 80 Course not specified	No control group	Assessed if depression in MS is predicted by learned-helplessness, self-efficacy or cognitive distortions	Greater learned helplessness ($r = .61$), lower self-efficacy ($r = -.47$) and greater cognitive distortions ($r = .26$) all predicted depression. When entered into a regression together, after controlling for demographic and disease-related variables, only learned helplessness and lower-self-efficacy predicted depression	
Kneebone & Dunmore (2004)	CES-D	ASQ-S	N = 495 RR = 45% CP = 32.5% Unknown = 18% *Note percentages do not add to 100% in paper	No control group	Assessed whether negative attributional style is associated with depression in MS	Greater use of Stable ($r = .37$) and Global ($r = .44$) negative attributional style was associated with higher depression scores	
Smith & Young (2000)	BDI; HADS	RSD/H	N = 88 (course not specified)	Nondepressed control group with MS	Compared depressed and nondepressed individuals with MS on likelihood of rating disability as greater than physician	Individuals meeting threshold for depression by BDI or HADS cutoffs were over 3 times more likely to perceive their own disability as worse than a physician	
Jopson & Moss-Morris (2003)	HADS	IPQ-R	N = 168 RR = 28.8% SP = 10% CP = 42.4% Benign = 14.1%	No control group	Assessed whether illness representations (identification, cause, timeline, consequences and cure/control) were related to depression in MS	After controlling for illness severity, authors found illness representations were related to HADS depression scores ($\Delta R^2 = .26$). Specifically, beliefs that the illness results in serious consequences ($\beta = .23$), poor personal control ($\beta = -.21$) and psychological attributions for the illness ($\beta = .19$) were most strongly related to depression scores	
Evers et al. (2001)	IRGL-ADMS	ICQ	N = 167 RR = 53% SP = 41% RP = 2% PP = 4% Analyses also included 263 individuals with rheumatoid arthritis	No control group	Assessed whether helplessness, acceptance or benefit finding were related to negative and positive mood in MS and RA	Negative mood was associated with helplessness ($r = .62$), acceptance ($r = -.54$) and perceived benefits ($r = -.18$). Positive mood was also associated with helplessness ($r = -.53$), acceptance ($r = .50$) and perceived beliefs ($r = .29$)	
Fournier et al. (1999)	BDI	LOT; GSES; ASQ; OPPQ; O&P	N = 73 Course not specified	No control group	Examined different aspects of optimism and their relation to depression in MS	General optimism ($r = -.53$) and unrealistic optimism for positive ($r = -.47$) and negative ($r = -.40$) events had a negative relationship with depression. Depression was positively associated with generalized pessimism and defensive pessimism	

(continued)

Table 2. Continued

Studies examining conceptions of the self & illness and depression in MS—Significant (positive) findings (8) (continued)							
Study	Depression measure(s)	Conceptions of the self and illness measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
de Ridder et al. (2000)	BDI	LOT	N = 96 Course not specified	No control group	Assessed relationship between optimism and pessimism and depression	Optimism ($r = -.47$) and pessimism ($r = .53$) were related to depression	
Bruce & Arnett (2005)	CMDI Mood and Evaluative subscales	ARST	N = 95 RR = 68% PP = 2% SP = 30%	No control group	Using a performance based measure of affective memory bias, compared nondepressed, mildly depressed and moderately depressed groups on memory bias at 3 time points	Nondepressed participants showed a bias for positive words at the encoding stage, compared to no affective bias by mildly or moderately depressed participants ($\eta^2 = .13$). At delay, nondepressed group again displayed positive bias, but mildly and moderately depressed groups demonstrated negative bias ($\eta^2 = .14$). Assessing additive nature of initial plus delay bias produced a larger between group effect size ($\eta^2 = .23$)	Depression examined continuously rather than categorically
Studies examining the moderating effect of coping on the relationship between physical disability and depression in MS							
Study	Depression measure(s)	Coping measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Lynch et al. (2001)	ZSDS	WOC	N = 188 67% RR; 21% PP; 13% SP	No control group	Examined association between SDS and WOC, HS and UIS, and possible moderating effect of coping on physical disability	Depression was correlated with all emotion-focused coping variables ($r = .24$), but not problem focused coping variables ($r = -.09$), after controlling for education. No interaction was found between escape-avoidance coping and disability	Entered interaction variable after entering four psychological variables accounting for 40% of the variance in depression. Did not examine the possible moderating effect of problem-focused coping
Mohr et al. (1997)	BDI	WOC, including Wineman scales	N = 101 Course not specified	No control group	Compared low disability and high disability groups on BDI, examined WOC as a covariate and assessed moderating effect of physical disability on coping	Found high disability group had higher BDI scores than low disability group. Escape Avoidance (EA; $\eta^2 = 0.53$) and Planful Problem-Solving (PP; $\eta^2 = 0.22$) scales were related to BDI. Relationship between PP and BDI was stronger for high disability group than low disability group ($\eta^2 = 0.21$). Relationship between Cognitive Reframing and BDI greater for high impairment group than low impairment group ($\eta^2 = 0.26$)	Authors suggested importance of coping dependent on degree of physical impairment, but due to cross-sectional design, coping could also be seen as a moderator between EDSS scores and depression

Table 2. Continued

Studies examining the moderating effect of coping on the relationship between cognitive dysfunction and depression in MS							
Study	Depression measure(s)	Coping measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Arnett et al. (2002)	CMDI	COPE	N = 55 RR = 55% SP = 29% PP = 13% PR = 4%	No control group	Assessed moderating effect of coping on relationship between cognitive dysfunction and depression ($\Delta R^2 = .18$ for active coping interaction and $.08$ for avoidance coping interaction). Individuals with high levels of cognitive dysfunction who used either high levels of avoidance coping or low levels of active coping showed more mood and negative evaluative depression symptoms	Active and avoidance coping moderated the relationship between cognitive dysfunction and depression ($\Delta R^2 = .18$ for active coping interaction and $.08$ for avoidance coping interaction). Individuals with high levels of cognitive dysfunction who used either high levels of avoidance coping or low levels of active coping showed more mood and negative evaluative depression symptoms	Only depression symptoms examined, not clinical depression, per se
Studies examining the moderating effect of coping on the relationship between stress and depression in MS							
Study	Depression measure(s)	Coping measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Pakenham (1999)	BDI; BSI	WCC	N = 134 CP = 50% RR = 50%	No control group	Assessed moderating effect of coping on relationship between stress appraisal and global distress	Emotion focused coping moderated the relationship between stress and global distress ($\Delta R^2 = .04$). Individuals with high levels of stress and emotion focused coping showed more distress	Did not report on possible moderating effects of coping on depression. Used broad measure of distress rather than a depression measure
Pakenham (2005)	BSI	BFS	N = 477 CP = 27% RR = 73%	No control group	Assessed moderating effect of benefit finding on relationship between stress appraisal and adjustment	Family Growth Factor of BFS moderated the relationship between stress appraisal and global distress ($\Delta R^2 = .02$). Individuals with high levels of stress and reporting high family relations growth reported less global distress than those with low family relations growth	Used broad measure of distress rather than a depression measure

(continued)

Table 2. Continued

Studies examining the moderating effect of conceptions of the self and illness on the relationship between stress and depression in MS							
Study	Depression measure(s)	Conceptions of the self and illness measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Kneebone & Dunmore (2004)	CES-D	ASQ-S	N = 495 CP = 32.5% RR = 45% Unknown = 18%	No control group	Assessed if ASQ-S global and stable attributions would moderate relationship between Negative Life Events (Time since last exacerbation and RCLQ) and depression	After controlling for disability, the authors found report of global attributions moderated effects of stress, conceptualized both as time since exacerbation ($\beta = -.13$) and according to the RCLQ ($\beta = .13$), on depression. Negative life events predicted depression when global attributions were high, but did not predict depression when global attributions were low	
Study examining the moderating effect of conceptions of the self and illness on the relationship between pain and depression in MS							
Study	Depression measure(s)	Conceptions of the self and illness measure(s)	Patient characteristics	Control group characteristics	Methodology	Key findings	Limitations
Breeney & Arnett (2008)	CMDI Mood & Evaluative subscales combined	Performance based Affective Reading Span Test (ARST)	N = 93 RR = 68% PP = 2% SP = 30%	No control group	Hierarchical regression analyses	After main effects entered, interaction between stress appraisal index (hassles minus uplifts) and negative memory bias index from ARST = $\Delta R^2 = .09$, $p < .01$, $\beta = -.30$	Depression examined continuously rather than categorically
Bruce et al. (2007)	CMDI Mood and Evaluative Subscales	ASRT	N = 93 RR = 69% SP = 29% PP = 2%	No control group	Examined the moderating effect of affective memory bias, on the relationship between pain and depression	Pain did not significantly predict depression. Memory bias at free recall predicted CMDI mood ($\Delta R^2 = .14$), and evaluative ($\Delta R^2 = .10$) subscales. Retention Bias also predicted CMDI mood ($\Delta R^2 = .07$), and evaluative ($\Delta R^2 = .05$) subscales. Patients with high levels of pain and demonstrating a negative affective memory bias (AMB) reported more depressive symptoms relative to patients with pain and positive AMB. The interaction explained as much as 8% of the variance after accounting for variance explained by memory bias and pain	

Note. See Appendix for listing of all acronyms.

of mixed quality, positive findings always emerged, suggesting that the relationship between depression and stress in MS is a robust one and likely of moderate to large effect size.

Coping

Coping and stress/hassles are commonly linked in the coping literature, because coping strategies are typically used in response to stressful events. Lazarus and Folkman's (1984) stress and coping model has been commonly applied to the chronic illness literature in general, as well as to MS. According to this model, a central factor moderating the relationship between stress and adjustment is coping (Pakenham, 1999). More specifically, coping strategies that patients use appear to put them at greater or lesser risk for depression.

Coping has been conceptualized in different ways. Traditionally, theorists have identified two broad ways of coping with stressors: Problem-focused and emotion-focused. Problem-focused strategies aim to alter the source of stress, whereas emotion-focused strategies attempt to reduce the emotional distress elicited by a situation (Lazarus, 1993). As Table 2 illustrates, high levels of depression are typically associated with emotion-focused coping whereas low levels of depression are associated with problem-focused coping in MS.

Some investigators have suggested that these broad categories of coping are not unitary constructs and have developed alternative ways of conceptualizing coping. Carver and colleagues (1989) identified active and avoidance coping scales. Greater use of avoidance coping strategies and less use of active coping strategies have been shown to be associated with higher levels of depression symptoms (Arnett et al., 2002). Longitudinally, greater use of active coping strategies has been associated with improved mood in MS patients over a 3-year period, whereas decreased use of such strategies is associated with worsening mood (Arnett & Randolph, 2006).

Despite the unpredictability of MS, most studies have found that emotion-focused and avoidant coping strategies are consistently positively associated with depression, whereas problem-focused and active coping strategies are inversely related to depression (see Table 2).

Social Support/Psychosocial Factors

Outside the MS literature, Sarason and colleagues (1983) have noted that individuals with fewer social supports and/or greater dissatisfaction with those supports are more likely to experience negative affect. Consistent with this more general observation, the relationship between social support and depression in MS is very consistent. Although only a few studies have examined this relationship, they have shown that patients with better social support are less likely to be depressed than patients with poorer social support (McIvor et al., 1984; Schwartz & Kraft, 1999).

Conceptions of self and illness

Studies examining the association of conceptions of the self and illness with depression in MS are relatively few in number. One way of thinking about conceptions of the self and others is *via* cognitive schemas. Cognitive schemas represent ways in which we organize our understanding of ourselves, our relations with others, and our place in the world. Although most studies assessing cognitive schema in MS have used self-report measures, performance-based measures can also be used. In fact, performance-based measures may avoid the shared method variance that can lead to possible correlations between self-report measures of cognitive schema and self-report measures of depression. A recent study used a performance based measure, the affective reading span task, to quantify negative cognitive schema in a group of MS patients and found that depressed MS patients showed evidence of a negative bias compared with nondepressed MS patients (Bruce & Arnett, 2005).

Using self-report measures, negative cognitive schema have been operationalized in a variety of ways, including lower self-efficacy (Shnek et al., 1995), internal and global attributions of negative life events (Kneebone & Dunmore, 2004), perception of disability and illness variables related to MS (Smith & Young, 2000), and negative outcome expectancies and unrealistic thinking (Fournier et al., 1999). The finding that efficacy expectancies and outcome expectancies predicted depression *via* emotion-oriented coping (Fournier et al., 1999) is one of the few mediational findings reported in this literature. In this model, MS patients with negative expectancies of their ability to cope and expectations of negative outcomes are more likely to use emotion-oriented coping that, in turn, leads to depression.

Negative cognitive schema can also be examined by looking at patients' representations of their illness. Guided by a model of illness representation developed by Leventhal and colleagues (1984), Jopson and Moss-Morris (2003) evaluated the role of illness representations in both general adjustment and depression in MS. Even after controlling for illness severity, beliefs in the serious consequences of the illness, in poor personal control, and in psychological causes of the illness, all significantly predicted depression.

Evers and colleagues (2001) note that, when faced with the long-term stress of a chronic disease like MS, cognitive schema can be re-evaluated in at least three ways: (a) To emphasize the negative meaning of the event (e.g., helplessness, hopelessness); (b) to diminish the aversive meaning of the event (e.g., acceptance); and (c) to add a positive meaning to the event (e.g., benefit finding). In their sample of MS patients, they found that helplessness was directly correlated, and acceptance and perceived benefits inversely correlated, with negative mood. Evers and colleagues' study also underscores the potential importance of positive, as well as negative, cognitions in relation to MS patients' risk for depression.

To summarize, stress and stress appraisal, coping variables, social support, and conceptions of the self and illness

all appear to be consistently associated with depression in MS. But how do these moderating variables impact the relationship between depression and the common MS sequelae? A handful of studies have examined the moderating effect of coping but, to our knowledge, only two studies have examined conceptions of the self and illness (in the form of cognitive schemas) and none have examined social support as possible moderators in the relationship between depression and the sequelae. What follows is a review of the few studies that have examined these proposed moderator variables. More detail on each study can be found in Table 2 and Figure 4. Note in Figure 4 that, in the interest of clarity, most of the interactions represented are those that have empirical support in the literature with at least one study; a few hypothetical interactions are also presented. It is assumed, however, that an interaction between any of the common MS sequelae and any of the moderator variables can lead to depression. Another impor-

tant assumption is that interactions between moderators can also predict depression, and two areas where this has been empirically supported are discussed below and also represented in the model in Figure 4 with intersecting arrows.

Studies Examining Moderating Variables of Common MS Sequelae

Cognitive dysfunction and coping

Using Carver and colleagues' COPE (1989) to measure active and avoidant coping strategies, we found that both coping strategies significantly moderated the relationship between cognitive dysfunction and depression (Arnett et al., 2002). Specifically, MS patients with cognitive difficulties were only at risk for depression if they used high levels of avoidance coping or low levels of active coping.

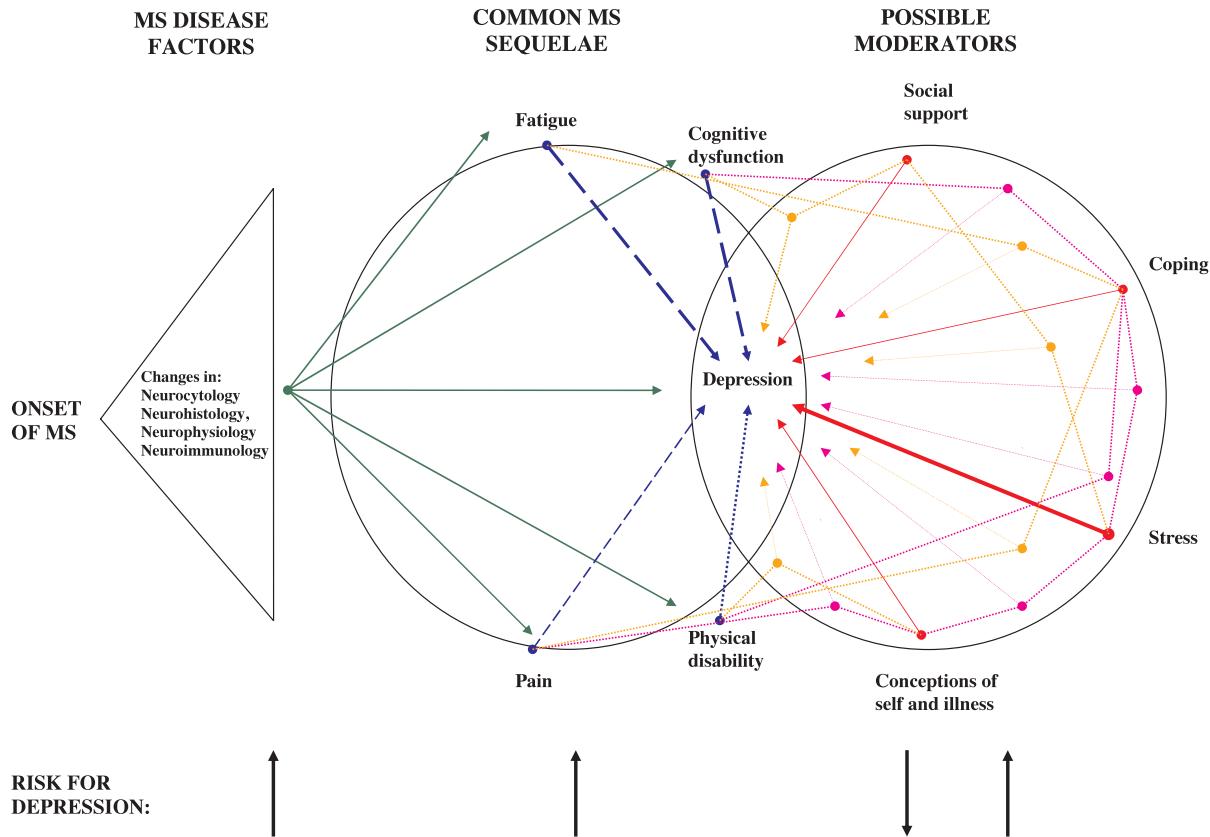


Fig. 4. Model of depression in MS: Possible moderators interact with common MS sequelae to predict depression.
Note. The differently colored arrows convey the category of variable in this figure: Green represents MS disease factors and blue represents common MS sequelae. The red arrows represent possible moderators. Note that the risk for depression either decreases or increases with the occurrence of the moderating variables in the right-hand circle depending upon whether they are in the adaptive or the maladaptive direction, as indicated by the upward and downward arrows underneath the right-hand circle. Empirically supported interactions between moderating variables and common MS sequelae, or between proposed moderators, are represented by pink lines from each variable intersecting at a small pink circle with an arrow leading to depression. A few hypothesized, but as yet untested, interactions between moderating variables and common MS sequelae, or between proposed moderators, are represented by orange lines from each variable intersecting at a small orange circle with an arrow leading to depression. Other possible interactions based upon the model could be derived as well

Pain and conceptions of the self and illness

In a recent study (Bruce et al., 2007), we used the affective reading span task mentioned earlier to examine whether affective memory biases moderated the relationship between pain and depression in MS. The interaction of negative bias and pain significantly predicted variance in depression. Specifically, patients with negative biases experienced more depressive symptoms as pain increased. Additionally, patients with positive biases experienced fewer depressive symptoms as pain increased. Our results highlighted both the potentially adverse effects of negative cognitive bias and the potentially protective effects of a positive cognitive bias.

Physical disability and coping

Lynch and colleagues (2001) reported that coping did not moderate the significant relationship they found between disability and depression. However, they examined the interaction variable of coping and physical disability only after they had first entered individual predictors for coping and physical disability, along with measures of hope and illness uncertainty. All of these variables had significant zero-order correlations with depression scores, enough to account for 40% of the variance when entered into a simultaneous regression analysis, leaving little variance to be accounted for by interaction variables. A more focused approach might have revealed a more significant moderating influence of coping on the relationship between disability and depression in MS.

Taking a different tack, Mohr and colleagues (1997) suggested that level of physical disability moderated the relationship between coping and depression in MS. They found significant interactions between physical disability and two types of active coping in predicting depression. However, given the cross-sectional nature of these data, their findings could just as easily suggest coping as a moderator of physical disability. The findings from this study are at least consistent with the notion that coping moderates the relationship between disability and depression.

To review, a few studies have empirically examined the moderators in the proposed model in relation to the common MS sequelae and depression. Evidence supports some of the proposed relationships—for example, coping as a moderator of physical disability or cognitive dysfunction, and conceptions of the self and illness as a moderator of pain—but the data are admittedly sparse at this point. Although much of this aspect of the model is speculative and remains to be tested, it is designed to provide a theoretical framework for future work.

Studies Examining Interactions Between Moderators

Although most of the model focuses on the moderator variables influencing the outcome of common MS sequelae, moderator variables can also interact with one another to predict depression. There is some empirical evidence in the

literature that this occurs for at least two of the possible interactions.

Stress and coping

Pakenham (1999) examined a model of stress, stress appraisal, and coping in MS. He found that stress appraisal interacted with emotion-focused coping to significantly predict distress. Specifically, patients appraising high levels of stress and using emotion-focused coping showed more distress.

In another study, Pakenham (2005) examined benefit-finding coping as a moderator of stress appraisal and adjustment and reported a significant interaction. Patients reporting high benefit finding in the context of high stress appraisals reported lower distress, whereas those reporting low benefit finding in the context of high stress appraisals reported higher distress.

One caveat to this work is that, Pakenham used a measure which includes a subscale for depression but is not specific to depression. Because he did not analyze the depression subscale specifically, he reported broad-based distress rather than depression. Nonetheless, we included the results of these two studies because they are among the few in the MS literature that examine the interaction of stress and coping in predicting psychological adjustment and distress.

Stress and conceptions of the self and illness

Kneebone and Dunmore (2004) examined the possibility that negative cognitive schema, as reflected in attributional style, moderate the relationship between negative life events (i.e., stress) and depression in MS. Consistent with Abramson and colleagues' view that negative life events represent the beginning of a causal chain that leads to a hopelessness type of depression (Abramson et al., 1989), Kneebone and Dunmore found that negative life events—both general negative events and those specific to MS—interacted significantly with global negative attributions in predicting depression in their MS sample. More specifically, they found that negative life events predicted depression when global attributions for negative events were high but not when global attributions for negative events were low.

Congruent with the above study, we (Beeney & Arnett, 2008) found that cognitive schema, measured using a performance-based measure of memory bias to avoid same method bias, moderated the relationship between stress appraisal and depression in MS. Similarly to Kneebone and Dunmore, we found that MS patients' reports of high amounts of stressful events relative to uplifting events were associated with depression only when patients evidenced a negative memory bias.

How the Model Works

We now present a detailed explanation of how the model might work in light of the empirical evidence described above (see Figure 4). Concomitant and subsequent to the onset of MS, patients experience disease-related changes.

These changes represent a distal level of risk for depression. Although they play a central role in the model, such changes do not explain all of the variance in depression; hence, the need for other explanatory factors.

Arrows lead from disease-related changes to fatigue, pain, cognitive dysfunction, and physical disability, because evidence has shown that these changes are associated with such symptoms. Common MS sequelae can further increase risk for depression in MS. The inconsistency or lack of robustness of the relationship between these common MS sequelae and depression, however, suggests that the extent to which these factors increase the risk for depression is moderated by other variables, such as stress, coping, social support, and conceptions of the self and illness.

When the influence of these moderator variables is in the adaptive direction, then the common MS sequelae are *less* likely to lead to depression. When the influence of these variables is in the maladaptive direction, the common MS sequelae are *more* likely to lead to depression. For example, good social support, positive conceptions of the self and illness, higher levels of problem-focused or active coping, and lower levels of emotion-focused or avoidance coping have been consistently associated with reduced depression in MS. In contrast, poor social support, negative conceptions of the self and illness, lower levels of problem-focused or active coping, and higher levels of emotion-focused or avoidance coping have been associated with increased depression.

Some of the interactions between common MS sequelae and the proposed moderators which can influence depression in MS have been supported by at least one study in the literature. These include physical disability and coping, cognitive dysfunction and coping, and pain and conceptions of the self and illness. At least two studies support the influence of interactions between proposed moderators, including stress and coping as well as stress and conceptions of the self and illness. The majority of the proposed interactions, however, whether between common MS sequelae and proposed moderators or between two moderating variables, have not been empirically tested. We propose them here because, in the case of the four common MS sequelae, inconsistent or lack of robust relationships have been reported in the empirical literature. As noted, such inconsistent or weak relationships between variables in a literature suggest the presence of moderators.

In MS-related depression, common MS sequelae may be influenced by both external circumstances (e.g., stressful events or social support) as well as internal representations of those external circumstances (e.g., coping style, conceptions of self and illness). It further suggests that external circumstances can themselves be affected by internal representations of those circumstances. Coping and conceptions of the self and illness have proved to be moderators for some of the common MS sequelae already (i.e., physical disability, cognitive dysfunction, and pain) in relation to depression, and so we reasoned that they might be likely candidates for moderators of the other variable, namely fatigue. Regarding the other proposed moderators, stress

and social support, there are as yet no empirical studies showing that they moderate any of the common MS sequelae in relation to depression. Nonetheless, we identified both variables as potential moderators based upon their consistent relationship with depression in the MS literature as well as the consideration that high levels of stress or poor social support might magnify the effects of MS symptomatology. Similarly, coping and conceptions of the self and illness have proved to interact with other proposed moderators already (i.e., stress) in MS-related depression, and so we reasoned that other interactions between proposed moderators—such as stress and social support, coping and social support, or coping and conceptions of self and illness—might influence depression in MS as well.

In the model, any of the proposed interactions are theorized to be sufficient to lead to depression. This conclusion is based upon evidence from several individual studies showing that one interaction can be a significant predictor of depression. With that said, it is further proposed that individuals who have more extensive and severe common MS sequelae, along with moderator variables in the maladaptive direction, are going to be at greatest risk for depression. In sum, the interaction of all these variables is not necessary for depression to result, as even one interaction is sufficient. However, the more interactions that are present, the greater the risk for depression.

The model is not intended to be linear and unidirectional. We assume that depression feeds back to the moderator variables and possibly to other variables as well, including fatigue, cognitive dysfunction, and pain. By design, the time course of risk is not specified. Given the variability of symptomatology in most MS patients, common sequelae can appear at any time during the disease course. The model is also neutral with regard to *how* the individual comes to have low levels of social support, negative conceptions of the self and illness, or maladaptive coping. It simply states that if these variables are present within individuals who experience one or more of the common MS sequelae, then these common sequelae will more likely be associated with depression. The degree to which the sequelae are present increases the risk for depression in MS. In turn, the likelihood that these sequelae get manifested in depression is importantly influenced by the presence of the proposed moderators.

Possible testable hypotheses from the model can range from simple two-factor associations to complex, multi-factor interactions. For example, more studies could be conducted to bolster the few to date showing an association between pain and depression, social support and depression, or conceptions of the self and illness with depression. Hypothesized interactions between common MS sequelae and proposed moderators that remain to be demonstrated include those between fatigue and coping or fatigue and conceptions of self and illness in relation to depression. More complex interactions that might significantly predict depression in MS which have yet to be investigated include predictions that physical disability will interact with conceptions of self and illness, cognitive dysfunction will inter-

act with social support, pain will interact with coping, and stress will interact with social support. These proposed hypotheses do not represent an exhaustive list of the possible associations and interactions between common MS sequelae, possible moderators, and depression in MS that could be tested; a more comprehensive list of possible combinations can be derived from Figure 4.

SUMMARY AND CONCLUSIONS

Depression is highly prevalent in MS and is generally stable longitudinally. It is associated with disease-related changes as well as with several common disease sequelae, all of which have significant negative consequences for patients' quality of life. Although depression in MS develops after disease onset, research suggests that it is very treatable. Because of the stability of depression in MS and the fact that it is unlikely to remit without treatment, it can have devastating long-term consequences for patients' day-to-day functioning.

The present review of the research literature was conducted to provide an overview of key factors associated with depression in MS and to present a theoretical model that integrates these key factors. An attempt was also made to identify gaps in the empirical literature. Although some aspects of the model are supported by research, many aspects remain speculative and in need of further testing. This is especially true for the interaction between the common sequelae and the moderator variables in predicting depression in MS. Future research is clearly necessary to evaluate the validity of these relationships.

Another important limitation is that the proposed model is largely based on cross-sectional data. Although causal relationships are proposed in the model, the causal nature of the relationships remains unclear. Additionally, many of the hypothesized relationships may be reciprocal rather than unidirectional. While future cross-sectional research to test these hypothesized relationships is important, longitudinal data would provide a more powerful test of how these relationships in MS evolve over time.

Depression has been intensively studied in MS over the past 20–25 years because of its high prevalence, implications for quality of life, and possibly its influence on disease progression. Despite the publication of numerous excellent empirical papers on this topic, theoretical work that attempts to integrate the range of research findings into a comprehensive explanatory model is scarce. The present study has taken a step toward incorporating existing empirical work into a coherent, testable, theoretical model of depression in MS that we hope will provide a better understanding of past work as well as directions for future research. Ultimately, we hope that this review and theoretical model will help clinicians and researchers to understand the multitude of factors that are associated with depression in MS, leading to better care for patients suffering from this devastating disease.

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APPENDIX A

General Tables Appendix: Acronyms of Measures Defined According to Category

Cognitive Schema

- ARST: Affective Reading Span Task
 ASQ: Attributional Style Questionnaire
 ASQ-S: Attributional Style Questionnaire-Survey
 CBQ: Cognitive Beliefs Questionnaire
 GSES: Generalized Self-Efficacy Scale
 ICQ: Illness Cognitions Questionnaire
 IPQ-R: Illness Perceptions Questionnaire-Revised
 LOT: Life Orientation Test
 MSAI: Multiple Sclerosis Attitudes Index
 MSBS: Multiple Sclerosis Beliefs Scale
 O&P: Optimism and Pessimism Scale
 OPPQ: Optimism-Pessimism Prescreening Questionnaire
 RSD/H: Rankin Scale of Disability/Handicap

Cognition

- AVLT: Auditory Verbal Learning Test
 BCT: Booklet Category Test
 BFRT: Benton Facial Recognition Test
 BNT: Boston Naming Test
 BPIT: Brown Peterson Interference Test
 BPMT: Brown Peterson Memory Test
 BVRT: Benton Visual Retention Test
 CFT: Complex Figure Test
 COWAT: Controlled Oral Word Association Test
 DS: Digit Span
 FR: Facial Recognition
 FT: Finger Tapping
 FVRT: Free Verbal Recall Test
 HFMT: Hasher Frequency Monitoring Task
 HVOT: Hooper Visual Organization test
 JLO: Judgment of Line Orientation
 LTM: Long Term Memory
 MHVS: Mill Hill Vocabulary Scale
 MMSE: Mini Mental Status Exam
 MST: Sternberg's Memory Scanning Task
 MSO: Memory Span for Objects
 PA: Paired Associates Learning Test
 PASAT: Paced Auditory Serial Addition Test
 PT: President's Test

RBMT: Rivermead Behavioral Memory Test

RPM: Raven's Progressive Matrices

SDMT: Symbol Digit Modalities Test

7/24: 7/24 Spatial Recall

SIDAM: Structured Interview for Diagnosis of Alzheimer Dementias

STM: Short Term Memory

Stroop: Stroops' Color-Word Interference Test

TMT: Trail Making Test

TOL: Tower of London

VE: Visual Elevator

VFD: Visual Form Discrimination

VSRT: Verbal Selective Reminding Task

WAIS-R: Wechsler Adult Intelligence Scale, Revised

WCST: Wisconsin Card Sorting test

WMS: Wechsler Memory Scale

Coping

BABS: Bradburn Affect Balance Scale

BFS: Benefit Finding Scale

CMSS: Coping with Multiple Sclerosis Scale

COPE: No acronym

FDCQ: Freiburg Disease Coping Questionnaire

PEMS: Psychosocial Effects of Multiple Sclerosis

WCC: Ways of Coping Checklist—Revised

WOC: Ways of Coping

Depression

AIMS: Arthritis Impact Measurement Scale—depression subscale

BDI: Beck Depression Inventory

BSI: Brief Symptom Inventory

CES-D: Center for Epidemiological Studies Depression Scale

CIDI: Composite International Diagnostic Interview

CIS: Clinical Interview Schedule

CIS-D: Clinical Interview Schedule for Depression

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition

GHQ: General Chronic Health Questionnaire—depression subscale
HADS: Hospital Anxiety and Depression Scale
HAM-D: Hamilton Depression Inventory
HDI: Hamilton Depression Inventory
HRSD: Hamilton Rating Scale for Depression
IMPS: Inpatient Multidimensional Psychiatric Scale
IRGL-ADMS: Impact of Rheumatic Diseases on General Cognitions Questionnaire
MADRS: Montgomery-Asberg Depression Rating Scale
CMDI: Chicago Multiscale Depression Inventory
MHI: Mental Health Inventory
MMPI: Minnesota Multiphasic Personality Inventory
POMS: Profile of Mood States
POMS-SF: Profile of Mood States—Short Form
SADS: Schedule for Affective Disorders and Schizophrenia
SCID I: Structured Clinical Interview for DSM-III-R
SDS: Self-Report Depression Scale
ZSDS: Zung Self-Report Depression Scale

Fatigue

CHIS: Checklist of Individual Strengths—fatigue subscale
FAI: Fatigue Assessment Instrument
FIS: Fatigue Impact Scale
FSS: Fatigue Severity Scale
MAF: Multidimensional Assessment of Fatigue
MFI: Multidimensional Fatigue Inventory
MFIS: Modified Fatigue Impact Scale
MS-FSS: MS-specific Fatigue Severity Scale
VAS: Visual Analogue Scale

Pain

ADL: Activity of Daily Living Scale
MPQ-SF: McGill Pain Questionnaire—Short Form
SF-36: 36-item Short Form Health Survey

Physical Disability Measures

AI: Ambulation Index
EDSS: Expanded Kurtzke Disability Status Scale
KDSS: Kurtzke Disability Status Scale
SIP: Sickness Impact Profile

Social Support

FES: Family Environment Scale
PSSI: Perceived Social Support Inventory
SSSI: Social Stress and Support Interview
WHOQO: World Health Organization Quality of Life-100 Scale

Stress

EPS: Economic Pressure Scale
GCSI: General Chronic Stress Index
LES: Life Experiences Survey
LHS: London Handicap Scale
RLCQ: Recent Life Changes Questionnaire
SRRS: Social Readjustment Rating Scale
SSSI: Social Stress and Support Interview

Other

CP: Chronic Progressive
CS: Chronic Stable
PP: Primary Progressive
PR: Progressive Relapsing
RR: Relapsing Remitting
SP: Secondary Progressive
NHC: Normal Healthy Controls
SCI: Spinal Cord Injury
MDD: Major Depressive Disorder
MND: Motor Neuron Disease
CFS: Chronic Fatigue Syndrome
HT: Hypertensive
RT: Reaction Time
LTC: Long Term Care
CBT: Cognitive Behavioral Therapy
SGP: Supportive Group Psychotherapy
HMR: Hierarchical Multiple Regression
SEM: Structural Equation Modeling
MDS: Minimum Data Set