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Mood disorders in multiple sclerosis: diagnosis and treatment

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Emotional disturbances are common in MS and consist of disturbances of mood and disturbances of affect. The important mood disorders are major depressive disorder, dysthymic disorder, bipolar disorder, panic disorder, and generalized anxiety disorder. Their relationship to MS is multi-factorial and complex, and the extent to which they are direct consequences of the disease process or psychological reactions to it remains unclear. Whatever their cause, however, the symptoms of mood disorders in people with MS are no different from the symptoms of mood disorders in people without MS, and respond just as well to standard treatments. The disorders of affect are euphoria, pathological laughing and weeping, and other frontal lobe syndromes. These disorders result from demyelination, are some of the most characteristic symptoms of MS, and have the same implications for treatment as do other aspects of the disease. Mood and affective disturbances can cause enormous pain and suffering and lead to significant disruption of family, work, and social life. Physicians who can identify, diagnose, treat, and manage mood and affective disturbances effectively and who can help their patients and family members acknowledge these difficulties, talk about them, and accept psychiatric consultation and treatment can have a dramatic impact on the quality of their lives. This paper outlines the symptoms and diagnostic criteria for mood disorders and affective disturbances, reviews current treatment options, summarizes data from epidemiologic and pathophysiological studies, and suggests areas for future research. *Journal of NeuroVirology* (2000) **6,** S160–S167.

Keywords: multiple sclerosis; mood disorders; affective disorders; depression; euphoria; pathological laughing and weeping

Introduction

Emotional disturbances are common in MS and consist of disturbances of mood and disturbances of affect (Minden and Schiffer, 1990; Minden, 1996). *Mood* refers to a sustained and pervasive emotion that influences perception of self, others, and the world such as depression, elation mania, and anxiety. *Affect* refers to the outward expression of inner feeling states which may be blunted, flat, inappropriate or labile (American Psychiatric Association, 1994).

The relationship of mood disorders to MS is multi-factorial and complex, and the extent to which they are direct consequences of the disease process or psychological reactions to it remains unclear. Symptoms of mood disorders in people with MS are no different from the symptoms of mood disorders in people without MS, and respond just as well to standard treatments.

The disorders of affect–euphoria, pathological laughing and weeping, and other frontal lobe syndromes–result from demyelination, are some of the most characteristic symptoms of MS, and have the same implications for treatment as do other aspects of the disease.

Mood and affective disturbances cause enormous pain and suffering and lead to significant disruption of family, work, and social life. Physicians who can identify, diagnose, treat, and manage these disorders effectively and who can help their patients and family members acknowledge these problems, talk about them, and accept psychiatric consultation and treatment can have a dramatic impact on the quality of their lives (Gerber *et al*, 1989; Perez-Stable *et al*, 1990; Schulberg *et al*, 1985).

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This paper summarizes our current understanding of the prevalence and aetiology of mood and affective disorders, outlines symptoms and diagnostic criteria, reviews current treatment options, and suggests directions for future research. The focus is on diagnostic decision-making since treatments for mood disorders are virtually the same for people with and without MS, except for a few *caveats* in regard to minimizing potential adverse effects.

Mood disorders

The mood disorders most common in MS are the depressive disorders (major depressive disorder, dysthymic disorder, bipolar disorder) and generalized anxiety disorder.

There are no population-based estimates of the prevalence of depressive disorders among people with MS. Estimates in clinical samples vary enormously because of differences in the definitions, instruments, and samples used (Minden and Schiffer, 1990). Studies using semi-structured interviews and formal diagnostic criteria estimated current prevalence rates of major depressive disorder from 14% to 37% (Joffe *et al*, 1987; Areas Bal *et al*, 1991; Moller *et al*, 1994; Minden *et al*, 1987; Sullivan *et al*, 1995; Schiffer *et al*, 1983) and lifetime prevalence rates from 42% to 54% (Joffe *et al*, 1987; Sadovnick *et al*, 1996; Minden *et al*, 1987). These rates of depression are higher in MS patients than in the general population and among patients with general medical conditions (Minden *et al*, 1987), other chronic neurologic conditions (Whitlock and Siskind, 1980; Schiffer and Babigian, 1984), and in some groups of patients with chronic fatigue syndrome (Krupp *et al*, 1994; Pepper *et al*, 1993). The frequency of attempted and completed suicide rates appears to be substantially higher for the MS population than for the general population (Kahana *et al*, 1971; Fisk *et al*, 1998).

Scores on depression severity rating scales are in the mild to moderate range (Joffe *et al*, 1987; Minden *et al*, 1987; McIvor *et al*, 1984) and are significantly higher among people with MS than normal controls (Mohr *et al*, 1997b; DeLuca *et al*, 1993) and samples of people with general medical conditions (Minden *et al*, 1987; Schubert and Foliart, 1993) or cancer (Minden *et al*, 1987). Scores were not higher, however, when compared to those of patients with chronic fatigue syndrome (DeLuca *et al*, 1993; Natelson *et al*, 1995; Johnson *et al*, 1996), spinal cord injury (Rabins *et al*, 1986) or motor neuron disease (Tedman *et al*, 1997).

Studies of the relationship between depression and various disease parameters are inconsistent and confusing. Some studies show no relationship between depression and duration of illness, severity and type of disability (Moller *et al*, 1994; Minden *et al*, 1987; Noy *et al*, 1995; Gilchrist and Creed, 1994), cognitive impairment (Moller *et al*, 1994; Clark *et al*, 1992b; Schiffer and Caine, 1991; Sabatini *et al*, 1996), various magnetic resonance imaging (MRI) measures (Moller *et al*, 1994; Clark *et al*, 1992b; Schiffer and Caine, 1991; Sabatini *et al*, 1996; Barak *et al*, 1996; Tsolaki *et al*, 1994), fatigue (Moller *et al*, 1994), disease activity (Scott *et al*, 1996) or course of illness (Moller *et al*, 1994; Minden *et al*, 1987). Others show a significant relationship with duration (McIvor *et al*, 1984), degree of neurological impairment (Whitlock & Siskind, 1980; McIvor *et al*, 1994; Rabins *et al*, 1986; Tedman *et al*, 1997; Mohr *et al*, 1997a), progressive MS (Rabins *et al*, 1986; Filippi *et al*, 1994), cognitive impairment (Rabins *et al*, 1986; Gilchrist and Creed, 1994; Filippi *et al*, 1994), enlarged ventricles (Rabins *et al*, 1986), lesions in the frontal and temporal lobes and paraventricular areas (Honer *et al*, 1987), left hemisphere (George *et al*, 1994), and left arcuate fasciculus region (Pujol *et al*, 1997), and regional cerebral blood flow asymmetries in the limbic cortex (Sabatini *et al*, 1996). Associations have been reported between depression and sleep disturbance (Clark *et al*, 1992a; Devins *et al*, 1993), fatigue (Schwartz *et al*, 1996), exacerbations (Dalos *et al*, 1983; Noy *et al*, 1995; Cleeland *et al*, 1970), sexual dysfunction (Barak *et al*, 1996), low melatonin secretion and circadian phase lability (Sandyk and Awerbuch, 1993), higher CD4/CD8 ratio (Foley *et al*, 1992), high plasma cortisol levels but normal responses to provocative tests of hypothalamic-pituitary-adrenal axis function (Sternberg and Gold, 1994), and failure to suppress cortisol release after dexamethasone challenge (Fassbender *et al*, 1998). Since there is no higher risk of depression among first-degree relatives of depressed MS patients, a genetic susceptibility to depression is unlikely (Joffe *et al*, 1987; Minden *et al*, 1987; Sadovnick *et al*, 1996). Suicide has been associated with a severe course, age (40–49 years), previous suicidal behaviour, prior mental illness, recent worsening of MS, and moderate disability (Stenager *et al*, 1996).

There are case reports of mania in patients with MS (Kellner *et al*, 1982; Matthews, 1979; Peselow *et al*, 1981; Garfield, 1985; Mapelli and Ramelli, 1981; Solomon, 1978; Kemp *et al*, 1977) and the rate of bipolar disorder appears to be significantly higher in people with MS than in the general population (Joffe *et al*, 1987; Fisk *et al*, 1998; Schiffer *et al*, 1986). Given findings of familial clustering of MS and bipolar disorder and certain major histocompatibility class II markers, there may be a genetic relationship between these disorders (Schiffer *et al*, 1988; Cazzullo *et al*, 1983). ACTH and prednisone may precipitate hypomania and mania, particularly in patients with a history of depression and a family history of depression or alcoholism, and primarily with higher doses (Minden *et al*, 1988; Cass *et al*, 1966).

Anxiety is less well studied, but in one sample of MS patients the rate of anxiety was higher than the rate of depression (90% *versus* 50%) (Noy *et al*,

1995). One study found anxiety to be associated with disease activity but not with duration or severity (Noy *et al*, 1995), whereas another found significant correlations with neurologic disability but not with disease course or cognitive impairment (Stenager *et al*, 1994). Moderately disabled patients appear to be most anxious, most depressed, at highest risk of suicide, and most likely to have difficulty carrying out usual social roles (Rao *et al*, 1991) and maintaining leisure activities (Stenager *et al*, 1989,1991,1994; Rao *et al*, 1991). Panic attacks also occur in people with MS (Andreatini *et al*, 1994; Ontiveros and Fontaine, 1990).

Affective disorders

Estimates of the prevalence of pathological laughing and weeping in MS range from 7% to 95% because of different definitions of the term, incommensurate samples, and variable evaluation methods (Langworthy *et al*, 1941; Surridge, 1969; Pratt, 1951; Sugar and Nadell, 1943; Cotrell and Wilson, 1926). The most recent study used explicit criteria – sudden loss of emotional control (crying or laughing or both) on multiple occasions over 1 month that occurs in response to nonspecific stimuli and lacks an associative, matching mood state (Feinstein *et al*, 1997; Poeck, 1969) – and a validated rating scale (Robinson *et al*, 1993) to estimate a prevalence rate of 10%. The disorder is presumed to result from interruption of corticobulbar tracts involved in control of emotional expression (Robinson *et al*, 1993), and has been shown to be related to chronic progressive MS, intellectual impairment, physical disability, long duration, diffuse, bilateral cerebral disease (Feinstein *et al*, 1997; Black, 1982; Ironside, 1956; Langworthy and Hesser, 1940), right hemisphere damage (Sackheim *et al*, 1982), and lesions in the pons or in areas connecting the right hemisphere with the pons (Tatemichi *et al*, 1987; Yarnell, 1987). It is not related to exacerbations, depression, anxiety, or premorbid or family history of mental illness (Feinstein *et al*, 1997).

Euphoria is a sustained 'mental state of cheerfulness, happiness, [and] ease' in which patients appear 'serene and cheerful', report feeling physically fit and healthy, and display 'an optimism as to the future and the prospects of ultimate recovery which is out of place and incongruous' (Cottrell and Wilson, 1926). It is not an episodic expression of joyous emotion like pathological laughing nor a reversible elated mood like mania which is associated with hyperactivity, pressured speech, and racing thoughts. Rather, euphoria is a persistent frame of mind or outlook, in which there is a disconnection between the intellectual appreciation of one's condition and the emotional response that ought to accompany it. Euphoric patients, however, may also experience significant unhappiness and depression (Surridge, 1969; Sugar and Nadell, 1943).

As with the other affective disorders, euphoria results from demyelination. Estimated prevalence rates are highly variable, ranging from 0% to 63%, because of differences in assessment methods and in severity and duration of illness across samples (Baldwin, 1952; Kahana *et al*, 1971; Pratt, 1951; Braceland and Griffin, 1950; Langworthy *et al*, 1941; Surridge, 1969; Rabins *et al*, 1986; Cotrell and Wilson, 1926). Euphoria is associated with progressive MS, enlarged ventricles, and cognitive impairment (Rabins *et al*, 1986; Gonzalez *et al*, 1994).

Diagnosis and treatment

The question that has preoccupied MS researchers – whether mood disorders are disease-based or reactive – is less important in the clinical setting. In the mental health field, it is generally accepted that mood disorders are heterogeneous in regard to symptoms, course, outcomes, and aetiologies (Keller, 1996; and Hornig-Rohan and Amsterdam, 1996). With efficacious treatments now available, the important issue is to focus on identifying symptoms and making the correct diagnosis; treatment then follows logically (Schulberg and Rush, 1994). Symptoms can be elicited by a symptom rating scale as well as through a clinical interview or a semi-structured research interview which may also be used to asses the symptoms' duration, intensity, and impact on functioning. Following the interview, it is necessary to determine whether the symptoms meet criteria for a mental disorder (American Psychiatric Association, 1994). A mental disorder should not be diagnosed if the symptoms are due to a recent life event such as bereavement or to a physiologic cause such as a medication, a substance of abuse, or a medical condition, or if the symptoms are too brief, too few, too mild, and have too little impact on functioning. For people with MS, it is also necessary to distinguish between symptoms due to a mental disorder and symptoms due to MS, for example, fatigue and diminished ability to think or concentrate (Nyenhuis *et al*, 1995; Mohr *et al*, 1997b; Minden *et al*, 1987).

The literature suggests that people with MS are not adequately treated for their mood disorders (Minden *et al*, 1987). Effective treatment of mental disorders can improve functional status, self-esteem, quality of life, and compliance with medical treatment (Spitzer *et al*, 1995; Mohr *et al*, 1997c). Many decision-making aids are now available to non-psychiatric physicians: clinical practice guidelines for primary care physicians (Depression Guideline Panel, 1993a,b); screening instruments for detecting mental disorders in primary care settings and psychiatric and psychopharmacologic specialists for consultation (Cohen-Cole and Friedman, 1982)

In addition to under-diagnosis and inadequate treatment of mood disorders in MS, the opposite problem also occurs: MS may go unrecognized and

untreated in patients thought to have only psychiatric problems (Salloway *et al*, 1988; Skegg *et al*, 1988; Tomsyck and Jenkins, 1987; Mendez, 1995; Hotoff *et al*, 1994).

In general, a combination of pharmacotherapy and psychotherapy is more effective than either modality alone for treatment of any mental disorder (Weissman, 1979). Individual and group psychotherapy are particularly helpful in the adjustment to MS and can minimize the sequelae of mood disorders; they are also effective treatments for problems in living and personality issues unrelated to MS (Minden, 1992; Crawford and McIvor, 1985; Harting *et al*, 1976; Pavlou *et al*, 1978; Bates *et al*, 1989; Laracombe and Wilson, 1984). Whether the MS patient's primary physician provides the psychotherapy (Schiffer, 1987) or refers the patient to a psychiatrist depends on the primary physician's interest and skill, the severity and complexity of the patient's problems, and the patient's preference. Psychiatric consultation should be sought when the diagnosis is unclear, symptoms are severe, disruptive or life-threatening, and do not respond to standard treatments. Primary physicians should to be sensitive to patients' concerns about referrals, carefully explain the reasons for the consultation, and tell patients what to expect. Patients and family members should be advised of the results of the psychiatric evaluation and actively participate in decision-making about specific treatments and providers. Good communication among the referring physician, the psychiatrist, other mental health caregivers, and the patient and family lead to better outcomes as does a strong and consistent relationship between the patient and family and the MS physician.

There are few systematic studies of pharmacologic treatment of mood disorders in MS, but they and clinical experience indicate that currently available treatments are as effective for people with MS as they are for people without MS (Silver *et al*, 1990). The selective serotonin re-uptake inhibitors (SSRIs) are the treatments of choice for depressive disorders (Gelenberg and Bassuk, 1997). Side-effects are generally mild with SSRIs (Flax, 1991; Browning, 1990), whereas the anticholinergic effects of the older tricyclic antidepressants (TCAs) tend to occur at lower doses in people with MS and patients should be warned about urinary retention, blurred vision, and dry mouth (Schiffer and Wineman, 1990; Scott *et al*, 1995). MonOamine oxidase inhibitors (MAOIs) are not advisable for people with MS because of the potential drug interactions and the wide range of serious and discomforting adverse effects. Clinicians should consult standard texts and the literature for recommended dosages of medications and descriptions of adverse effects.

Lithium carbonate is effective for treating mania (Falk *et al*, 1979) and for preventing manic and depressive reactions to steroids and ACTH (Falk *et al*, 1979). Other treatments such as carbamezapine (Tegretol), valproic acid (Depakote), and lamotragine (Lamictal) are probably also effective. Treatment and management of bipolar disorder should involve consultation with a psychiatrist.

MS patients with generalized anxiety disorder or panic disorder are treated effectively with a combination of psychotherapy and medication including the many available benzodiazepines, buspirone (BuSpar), and the SSRIs and TCAs (Reiman, 1997). Barbiturates (e.g., phenobarbital) and propanediols (e.g., meprobamate) are no longer indicated for the treatment of anxiety. When used for a few weeks at a time to help people cope with a life-crisis such as the diagnosis of MS, the benzodiazepines relieve painful symptoms and do not cause dependence. Treatment for more than a few months, however, produces tolerance and leads to symptoms of withdrawal when the drug is discontinued, particularly with the short-acting agents. Buspirone does not cause sedation, reduce arousal, attention or reaction time, or lead to tolerance or withdrawal although it may take up to 4 weeks to have an effect. The major advantage of the SSRIs in treating anxiety disorders is that they also treat co-existing depression, are taken once per day, have no addictive or abuse potential, and do not produce withdrawal symptoms: unfortunately, some cause a paradoxical increase in anxiety.

Patients with affective disorders and their families may also be helped by psychotherapeutic and psychopharmacologic treatments. Pathological laughing and weeping has been shown to respond to amitriptyline up to 75 mg per day (Schiffer *et al*, 1985), levodopa (Wolf *et al*, 1979; Udaka *et al*, 1984), desipramine (Ironside, 1956), fluoxetine (Seliger *et al*, 1992), and fluvoxamine (Iannaccone and Ferini-Strambi, 1996). There are no known treatments for euphoria; however, explaining the nature of any of the affective disorders to patients and family members can improve their capacity to cope.

Future research

Further research is necessary in several areas. Reliable and valid instruments for diagnosis of euphoria and pathological laughing and weeping are prerequisites for prevalence studies and clinical trials. Large, population-based samples such as that being developed by the National Multiple Sclerosis Society are needed to determine the true prevalence of both mood and affective disorders among people with MS.

Although standard pharmacologic treatments appear to be efficacious for mood disorders in people with MS as they are for others, ongoing development of pharmacologic agents and increasing understanding of neurotransmitters may make more specific and targeted treatments possible.

Given the prevalence of mood and other mental disorders in MS, health services researchers should

study their economic and social consequences, particularly their impact on employment, income, and quality of life (Minden and Marder, 1993).

Policy analyses are needed to examine obstacles to treatment such as lack of health insurance and limited access to specialists, and to identify solutions. Advocacy is essential to enhance access to high quality health and mental health care for all people with MS.

References

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*. 4th edn. American Psychiatric Association, Washington, DC.

Andreatini R, Sartori VA, Leslie JR, Oliveira ASB (1994). Panic attacks in a multiple sclerosis patient. *Biol Psychiatry* **35:** 133–134.

Areas Bal MA, Vazquez-Barquero JL, Pena C, Berciano JA (1991). Psychiatric aspects of multiple sclerosis. *Act Psychiatr Scand* **83:** 292–296.

Baldwin MV (1952). A clinico-experimental investigation into the psychologic aspects of multiple sclerosis. *J Nerv Ment Dis* **115:** 299–342.

Barak Y, Achiron A, Elizur A, Gabbay U, Noy S, Sarova-Pinhas I (1996). Sexual dysfunction in relapsing-remitting multiple sclerosis: magnetic resonance imaging, clinical, and psychological correlates. *J Psychiatry Neurosci* **21:** 255–258.

Bates A, Burns DD, Moorey S (1989). Medical illness and the acceptance of suffering. *Int J Psychiatry Med* **19:** 269–280.

Black DW (1982). Pathologic laughter: a review of the literature. *J Nerv Ment Dis* **170:** 67–71.

Braceland FJ, Giffin ME (1950). The mental changes associated with multiple sclerosis (an interim report). *Res Publ Assoc Nerv Ment Dis* **28:** 450–455.

Browning WN (1990). Exacerbation of symptoms of multiple sclerosis in a patient taking fluoxetine [letter]. *Am J Psychiatry* **147:** 1089.

Cass LJ, Alexander L, Enders M (1966). Complications of corticotropin therapy in multiple sclerosis. *JAMA* **197:** 105–111.

Cazzullo CL, Smeraldi E, Gasperini M, Caputo D (1983). Preliminary correlation between primary affective disorders and multiple sclerosis. In: *New Trends in Multiple Sclerosis Research*. Cazzullo CL, Caputo D, Ghezzi A (eds). Masson Publishing USA Inc: New York, pp. 57–62.

Clark CM, Fleming JA, Li D, Oger J, Klonoff H, Paty D (1992a). Sleep disturbance, depression, and lesion site in patients with multiple sclerosis. *Arch Neurol* **49:** 641–643.

Clark CM, James G, Li D, Oger J, Paty D, Klonoff H (1992b). Ventricular size, cognitive function and depression in patients with multiple sclerosis. *Can J Neurol Sci* **19:** 352–356.

Cleeland CS, Matthews CG, Hopper CL (1970). MMPI profiles in exacerbation and remission of multiple sclerosis. *Psychol Rep* **41:** 373–374.

Cohen-Cole S, Friedman C (1982). Attitudes of non-psychiatric physicians toward psychiatric consultation. *Hospital Community Psychiatry* **33:** 1002–1006.

Cottrell SS, Wilson SAK (1926). The affective symptomatology of disseminated sclerosis. *J Neurol Psychopathol* **7:** 1–30.

Crawford JD, McIvor GP (1985). Group psychotherapy: benefits in multiple sclerosis. *Arch Phys Med Rehabil* **66:** 810–813.

Dalos NP, Rabins PV, Brooks BR, O'Donnell P (1983). Disease activity and emotional state in multiple sclerosis. *Ann Neurol* **13:** 573–583.

DeLuca J, Johnson SK, Natelson BH (1993). Information processing efficiency in chronic fatigue syndrome and multiple sclerosis. *Arch Neurol* **50:** 301–304.

Depression Guideline Panel (1993a). *Depression in primary care: Vol 2. Detection and diagnosis*. Clinical Practice Guideline. No. 5, AHCPR Pub. No. 93-0550. U.S. Department of Health and Human Services, Public Health Service. Agency for Health Care Policy and Research: Rockville, MD.

Depression Guideline Panel (1993b). *Depression in primary care: Vol 2. Treatment of major depression*. Clinical Practice Guideline, No. 5, AHCPR Pub. No. 93-0551. (U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research: Rockville, MD.

Devins GM, Edworthy SM, Paul LC, Manin H, Seland TP, Klein G, Costello CG, Shapiro CM (1993). Restless sleep, illness intrusiveness, and depressive symptoms in three chronic illness conditions: rheumatoid arthritis, end-stage renal disease, and multiple sclerosis. *J Psychosom Res* **37:** 163–170.

Falk WE, Mahnke MW, Poskanzer DC (1979). Lithium prophylaxis of corticotropin-induced psychosis. *JAWA* **241:** 1011–1012.

Fassbender K, Schmidt R, Mossner R, Kischka U, Kuhnen J, Schwartz A, Hennerici M (1998). Mood disorders and dysfunction of the hypothalamic-pituitary-adrenal axis in multiple sclerosis: association with cerebral inflammation. *Arch Neurol* **55:** 66–72.

Feinstein A, Feinstein K, Gray T, O'Connor P (1997). Prevalence and neurobehavioral correlates of pathological laughing and crying in multiple sclerosis. *Arch Neurol* **54:** 1116–1121.

Filippi M, Alveroni M, Martinelli V, Sirabian G, Bresi S, Canal N, Comi G (1994). Influence of clinical vvariables on neuropsychological perforamcne in multiple sclerosis. *Eur Neurol* **34:** 324–328.

Fisk JD, Morehouse SA, Brown MG, Skedgel C, Murray TJ (1998). Hospital-based psychiatric service utilization and morbidity in multiple sclerosis. *Can J Neurol Sci* **25:** 230–235.

Flax JW, Gray J, Herbert J (1991). Effect of fluoxetine on patients with multiple sclerosis [letter]. *Am J Psychiatry* **148:** 1603.

Foley FW, Traugott U, LaRocca NG, Smith CR, Perlman KR, Caruso LS, Scheinberg LC (1992). A prospective study of depression and immune dysregulation in multiple sclerosis. *Arch Neurol* **49:** 238–244.

Garfield DAS (1985). Multiple sclerosis and affective disorders: 2 cases of mania with psychosis. *Psychother Psychosom* **44:** 22–33.

Gelenberg AJ, Bassuk EL (1997). *The Practitioner's Guide to Psychoactive Drugs*, 4th edn. Plenum Medical Book Company: New York.

George MS, Kellner CH, Berstein H, Goust JM (1994). A magnetic resonance imagining investigation into mood disorders in multiple sclerosis: a pilot study. *J Nerv Ment Dis* **182:** 410–412.

Gerber P, Barrett J, Barrett J, Manheimer E, Whiting R, Smith R (1989). Recognition of depression by internists in primary care: A comparison of internist and 'gold standard', psychiatric assessments. *J Gen Intern Med* **4:** 7–13.

Gilchrist AC, Creed FH (1994). Depression, cognitive impairment and social stress in multiple sclerosis. *J Pscyhosom Res* **38:** 193–201.

Gonzalez CF, Swirsky-Sacchetti T, Mitchell D, Lublin FD, Knobler RL, Ehrlich SM (1994). Distributional patterns of multiple sclerosis brain lesions. Magnetic resonance imaging–clinical correlation. *J Neuroimag* **4:** 188–195.

Hartings MF, Pavlou MM, Davis FA (1976). Group counseling of MS patients. *J Chron Dis* **29:** 65–73.

Honer WG, Hurwitz Y, Li DKB (1987). Temporal lobe involvement in multiple sclerosis patients with psychiatric disorders. *Arch Neurol* **447:** 187–190.

Hornig-Rohan M, Amsterdam JD (1996). Treatment-resistent Depression. *Psychiat Clin North Am* **19:** 1–412.

Hotoff MH, Pollock S, Lishman WA (1994). An unusual presentation of multiple sclerosis. *Psychol Med* **24:** 525–528.

Iannaccone S, Ferini-Strambi L (1996). Pharmacologic treatment of emotional lability. *Clin Neuropharmacol* **19:** 532–535.

Ironside R (1956). Disorders of laughter due to brain lesions. *Brain* **79:** 589–609.

Joffe RT, Lipppert GP, Gray TA, Sawa G, Horvath Z (1987). Mood disorder and multiple sclerosis. *Arch Neurol* **44:** 376–378.

Johnson SK, DeLuca J, Natelson BH (1996). Depression in fatiguing illness: comparing ptients with chronic fatigue syndrome, multiple sclerosis and depression. *J Affect Disord* **39:** 21–30.

Kahana E, Leibowitz U, Alter M (1971). Cerebral multiple sclerosis. *Neurology* **21:** 1179–1185.

Keller MB (1996). Mood Disorders. *Psychiat Clin North Am* **19:** 1–178.

Kellner CH, Davenport Y, Post RM, Ross RJ (1982). Rapidly cycling bipolar disorder and multiple sclerosis. *Am J Psychiatry* **141:** 112–113.

Kemp K, Lion JR, Magram G (977). Lithium in the treatment of a manic patinet with multiple sclerosis a case report. *Dis Nerv Syst* **38:** 210–211.

Krupp LB, Sliwinski M, Masur DM, Friedberg F, Coyle PK (1994). Cognitive functioning and depression in patients with chronic fatigue syndrome and multiple sclerosis. *Arch Neurol* **51:** 705–710.

Langworthy OR, Hesser FH (1940). Syndrome of pseudobulbar palsy: an anatomic and physiologic analysis. *Arch Intern Med* **65:** 106–121.

Langworthy OR, Kolb LC, Androp S (1941). Disturbances of behavior in patients with disseminated sclerosis. *Am J Psychiatry* **98:** 243–249.

Laracombe NA, Wilson PH (1984). An evaluation of cognitive-behavior therapy for depression in patients with multiple sclerosis. *Br J Psychiatr* **145:** 366–371.

Mapelli G, Ramelli E (1981). Manic syndrome associated with multiple sclerosis: secondary mania? *Acta Pscychiatr Scan* **81:** 337–349.

Matthews B (1979). Multiple sclerosis presenting with acute remitting psychiatric symptoms. *Neurol Neurosurg Psychiatry* **42:** 859–863.

McIvor GP, Riklan M, Reznikoff M (1984). Depression in multiple sclerosis as a function of length and severity of illness, age, remissions, and perceived social support. *J Clin Psychol* **40:** 1028–1033.

Mendez MF (1995). The neuropsychiatry of multiple sclerosis. *Int J Psychiatry Med* **25:** 123–130.

Minden SL, Schiffer RB (1990). Affective disorders in multiple sclerosis. Review and recommendations for clinical research. *Arch Neurol* **47:** 98–104.

Minden SL, Marder W (1993). Multiple Sclerosis: A Statistical Portrait. A compendium of data on demographics, disability, and health services utilization in the United States. Report to the National Multiple Sclerosis Society.

Minden SL (1996). Neuropsychiatric aspects of multiple sclerosis. *Curr Opin Psychiatry* **9:** 93–97.

Minden SL, Orav J, Reich P (1987). Depression in multiple sclerosis. *Gen Hosp Psychiatry* **9:** 426–434.

Minden SL, Orav J, Schildkraut JJ (1988). Hypomanic reastions to ACTH and prednisone treatment for multiple sclerosis. *Neurology* **38:** 1631–1634.

Minden SL (1992). Psychotherapy for people with multiple sclerosis. *Neuropsychiatry Clin Neurosci* **4:** 1–16.

Mohr DC, Goodkin DE, Gatto N, Van der Wende J (1997a). Depression, coping and level of neurological impairment in multiple sclerosis. *Mult Sclerosis* **3:** 254–258.

Mohr DC, Goodkin DE, Likosky W, Beutler L, Gatto N, Langan MK (1997b). Identification of Beck Depression Inventory items related to multiple sclerosis. *J Behav Med* **20:** 407–414.

Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA (1997c). Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Arch Neurol* **54:** 531–533.

Moller A, Wiedman G, Rohde U, Backmund H, Sonntag A (1994). Correlates of cognitive impairment and depressive mood disorder in multiple sclerosis. *Acta Psychiatr Scand* **89:** 117–121.

Natelson BH, Johnson SK, DeLuca J, Sisto S, Ellis SP, Hill N, Bergen MT (1995). Reducing heterogeneity in chronic fatigue syndrome: a comparison with depression and multiple sclerosis. *Clin Infect Dis* **21:** 1204–1210.

Noy S, Achiron A, Gabbay U, Barak Y, Rotstein Z, Laor N, Sarova-Pinhas I (1995). A new approach to affective symptoms in relapsing-remitting multiple sclerosis. *Compr Psychiatry* **36:** 390–395.

Nyenhuis DL, Rao SM, Zajecka JM, Luchetta T, Bernardin L, Garron DC (1995). Mood disturbance versus other symptoms of depression in multiple sclerosis. *J Int Neuropsychol Sco* **1:** 291–296.

Ontiveros A, Fontaine R (1990). Panic attacks and multiple sclerosis. *Biol Psychiatry* **27:** 672–673.

Pavlou M, Hartings M, Davis FA (1978). Discussion groups for medical patients. *Psychother Psychsom* **30:** 105–115.

Pepper CM, Krupp LB, Friedberg F, Doscher C, Coyle PK (1993). A comparison of neuropsychiatric characteristics in chronic fatigue syndrome, multiple sclerosis, and major depression. *J Neuropsychiatry Clin Neurosci* **5:** 200–205.

Perez-Stable E, Miranda J, Munoz R, Ying Y-W (1990). Depression in medical outpatients: Underrecognition and misdiagnosis. *Arch Int Med* **150:** 1083–1088.

Peselow ED, Fieve RR, Deutsch SI, Kaufman M (1981). Coexistent manic symptoms and multiple sclerosis. *Psychosomatics* **22:** 824–825.

Poeck K (1969). Pathophysiology of emotional disorders associated with brain damage. In: *Handbook of Clinical Neurology*. Vinken PJ, Bruyn GW (eds). North Holland Publishing Co: Amsterdam. pp. 227–231.

Pratt RTC (1951). An investigation of the psychiatric aspects of disseminated sclerosis. *J Neurol Neurosurg Psychiatry* **14:** 326–335.

Pujol J, Bello J, Deus J, Marti-Vilalta JL, Capdevila A (1997). Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. *Neurology* **49:** 1105–1110.

Rabins PV, Brooks BR, O'Donnell P, Pearlson GD, Moberg P, Jubelt B, Coyle P, Dalos N, Folstein MF (1986). Structural brain correlates of emotional disorder in multiple sclerosis. *Brain* **109:** 585–597.

Rao SM, Leo GJ, Ellington I, Naurtz T, Bernardin I, Unverzagt F (1991). Cognitive dysfunction in multiple sclerosis. *Neurology* **41:** 692–696.

Reiman EM (1997). Anxiety. In *The Practitioner's Guide to Psychoactive Drugs*. 4th edn. Gelenberg AJ and Bassuk EL (eds). Plenum Medical Book Company: New York, pp. 213–264.

Robinson RG, Parikh RM, Lipsey JR, Starkstein SE, Price TR (1993). Pathological laughing and crying following stroke: validation of a measurement scale and double-blind treatment study. *Am J Psychiatry* **150:** 286–293.

Sabatini U, Pozzilli C, Pantano P, Koudriavtseva T, Padovani A, Millefiorini E, Di Biasi C, Gualdi GF, Salvetti M, Lenzi GL (1996). Involvement of the limbic system in multiple sclerosis patients.

Sackheim HA, Greenberg MS, Weinman AL, Gur RC, Hungerbuhler JP, Geschwind N (1982). Hemisphere asymmetry in the expression of positive and negative emotions. Neurological evidence. *Arch Neurol* **39:** 210–218.

Sadovnick AD, Remick RA, Allen J, Swartz E, Yee IM, Eisen K, Farquhar R, Hashimoto SA, Hooge J, Kastrukoff LF, Morrison W, Nelson J, Oger J, Paty DW (1996). Depression and multiple sclerosis. *Neurology* **46:** 628–632.

Salloway S, Price LH, Charney DS, Shapiro M (1988). Multiple sclerosis presenting as major depression, a diagnosis suggested by MRI scan but not by CT scan. *J Clin Psychiatry* **49:** 364–366.

Sandyk R, Awerbuch GI (1993). Nocturnal melatonin secretion in multiple sclerosis patients with affective disorders. *Int J Neurosci* **68:** 227–240.

Schiffer RB, Wineman NM (1990). Antidepressant pharmacotherapy of depression associated with multiple sclerosis. *Am J Psychiatry* **147:** 1493–1497.

Schiffer RB, Babigian HM (1984). Behavioral disorders in multiple sclerosis, temporal lobe epilepsy, and amyotrophic lateral sclerosis, an epidemiologic study. *Arch Neurol* **41:** 1067–1069.

Schiffer RB, Caine ED, Bamford KA, Levy S (1983). Depressive episodes in patients with multiple sclerosis. *Am J Psychiatry* **140:** 1498–1500.

Schiffer RB, Caine ED (1991). The interaction between depressive affective disorder and neuropsychological test performance in multiple sclerosis patients. *J Neuropsychiatry Clin Neurosci* **3:** 28–32.

Schiffer RB, Herndon RM, Rudick RA (1985). Treatment of pathologic laughing and weeping with amitriptyline. *N Engl J Med* **312:** 1480–1482.

Schiffer RB (1987). The spectrum of depression in multiple sclerosis. An approach for clinical management. *Arch Neurol* **44:** 596–599.

Schiffer RB, Weitkamp LR, Wineman NM, Guttormsen S (1988). Multiple sclerosis and aaffective disorder, family history, sex, and HLA-DR antigens. *Arch Neurol* **45:** 1345–1348.

Schiffer RB, Wineman NM, Weirkamp LR (1986). Association between bipolar affective disorder and multiple sclerosis. *Am J Psychiatry* **143:** 94–95.

Schubert DS, Foliart RH (1993). Increased depression in multiple sclerosis. A meta-analysis. *Psychosomatics* **34:** 124–130.

Schulberg H, Saul M, McClelland M, Ganguli M, Christy W, Frank R (1985). Assessing depression in primary medical and psychiatric practice. *Arch Gen Psychiatry* **42:** 1164–1170.

Schulberg HC, Rush JA (1994). Clinical practice guidelines in managing major depression in primary care practice. *Am Psychologist* **49:** 34–41.

Schwartz CE, Coulthard-Morris L, Zeng Q (1996). Psychosocial correlates of fatigue in multiple sclerosis. *Arch Phys Med Rehabil* **77:** 165–170.

Scott TF, Allen D, Price TR, McConnell H, Lang D (1996). Characterization of major depression symptoms in multiple sclerosis patients. *J Neuropsychiatry Clin Neurosci* **8:** 318–323.

Scott TF, Nussbaum P, McConnell H, Brill P (1995). Measurement of treatment response to sertraline in depressed multiple sclerosis using the Carroll scale. *Neurol Res* **17:** 421–422.

Seliger GM, Hornstein A, Flax J, Herbert J, Schroeder K (1992). Fluoxetine improves emotional incontinence. *Brain Injury* **6:** 267–270.

Silver JM, Hales RE, Yudofsky SC (1990). Psychopharmacology of depression in neurologic disorders. *J Clin Psychiatry* **51** (Suppl): 31–39.

Skegg K, Corwin PA, Skegg DCG (1988). How often is multiple sclerosis mistaken for a psychiatric disorder? *Psychol Med* **18:** 733–736.

Solomon J (1978). Multiple sclerosis masquerading as lithium toxicity. *J Nerv Ment Dis* **166:** 663–665.

Spitzer RL, Kroenke K, Linzer M, Hahn SR, Williams JBW, Verloin deGruy III F, Brody D, Davies M (1995). Health-related quality of life in primary care patients with mental disorders. Results from the PRIME-MD 1000 study. *JAMA* **274:** 1511–1517.

Stenager E, Knudsen L, Jensen K (1989). Correlation of Beck depression Inventory score, Kurtzke disability status scale and cognitive functioning in multiple sclerosis. In *Mental disorders and cognitive deficits in multiple sclerosis*. Jensen K, Knudsen I, Stenager E, Grant I (eds). John Libbey & Co: London, pp. 147–151.

Stenager E, Knudsen L, Jensen K (1994). Multiple sclerosis: correlation of anxiaety, physicial impairment and cognitive dysfunction. *Ital J Neurol Sci* **15:** 97–101.

Stenager E, Knudsen L, Jensen K (1991). Multiple sclerosis: the impact of physical impairment and cognitive dysfunction on social and sparetime activities. *Psychother Psychosom* **56:** 123–138.

Stenager EN, Koch-Henriksen N, Stenager E (1996). Risk factors for suicide in multiple sclerosis. *Psychother Psychosom* **65:** 86–90.

Sternberg EM, Gold PW (1994). Multiple sclerosis is associated with alterations in hypothalamic-pituitary-adrenal axis function. *J Clin Endocrinol Metab* **79:** 848–853.

Sugar C, Nadell R (1943). Mental symptoms in multiple sclerosis. *J Nerv Ment Dis* **98:** 267–280.

Sullivan MJ, Weinshenker B, Mikail S, Bishop SR (1995). Screening for major depression in the early stages of multiple sclerosis. *Can J Neurol Sci* **22:** 228–231.

Surridge D (1969). An investigation into some psychiatric aspects of multiple sclerosis. *Br J Psychiatry* **115:** 749–764.

Tatemichi TK, Nichols FT, Mohr JP (1987). Pathological crying: a pontine pseudobulbar syndrome [abstract]. *Ann Neurol* **22:** 133.

Tedman BM, Young CA, Williams IR (1997). Assessment of depression in patients with motor neuron disease and other neurologically disabling illness. *J Neurol Sci* **152** (Suppl 1): S75–S79.

Tomsyck RR, Jenkins PL (1987). Psychiatric aspects of multiple sclerosis [clinical conference]. *Gen Hosp Psychiatry* **9:** 294–301.

Tsolaki M, Drevelegas A, Karachristianous, Kapinas K, Divanoglou D, Routsonis K (1994). Correlation of dementia, neuropsychological and MRI findings in multiple sclerosis. *Dementia* **5:** 48–52.

Udaka F, Yamao S, Nagata H, Nakamura A, Kameyama M (1984). Pathologic laughing and crying treated with levodopa. *Arch Neurol* **41:** 1095–1096.

Weissman MM (1979). The psychological treatment of depression. Evidence for the efficacy of psychotherapy alone, in comparison with, and in combination with pharmacotherapy. *Arch Gen Psychiatry* **36:** 1261–1269.

Whitlock FA, Siskind MM (1980). Depression as a major symptom of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **43:** 861–865.

Wolf JK, Santana HB, Thorpy M (1979). Treatment of 'emotional incontinence' with levodopa. *Neurology* **29:** 1435–1436.

Yarnell PR (1987). Pathological crying localization [abstract]. *Ann Neurol* **22:** 133.

Axis I diagnoses including mood and anxiety disorders and personality disorders were ascertained by means of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition / Clinical Version and the Structured Clinical Interview for DSM, Revised Third Edition Personality Disorders, respectively. The Expanded Disability Status Scale (EDSS) was used to determine degree of disability due to MS. Results: The prevalence of any mood, any anxiety and any personality disorders in patients with MS were 40.0%, 38.2% and 45.5%, respectively, which are sign...Â Comorbid anxiety disorders and treatment of depression in people with multiple sclerosis. Rehabil Psychol 2010; 55:255-62. Multiple sclerosis (MS), also known as encephalomyelitis disseminata, is a demyelinating disease in which the insulating covers of nerve cells in the brain and spinal cord are damaged. This damage disrupts the ability of parts of the nervous system to transmit signals, resulting in a range of signs and symptoms, including physical, mental, and sometimes psychiatric problems. Specific symptoms can include double vision, blindness in one eye, muscle weakness, and trouble with sensation or coordination... Disease-modifying therapies in multiple sclerosis. LYMPH NODE.Â Clinical Review & Education Review. Diagnosis and Treatment of Multiple Sclerosis. d Trial had an active comparator. e All patients must have an FDO that includes observation after taking the first dose for at least 6 hours, with pulse. and blood pressure assessment hourly and ECG prior to dosing and at end of observational period. f Increased risk of basal cell carcinoma and melanoma. g Target dose and titration depends on CYP2C9 genotype. h FDO only required in patients with a cardiac history. i Fundus examination only required for patients with a history of diabetes mellitus and uveitis tha... Many people with multiple sclerosis (MS) are diagnosed with a rare form of the disease. Discover early signs, pathophysiology, prognoses, and more.Â We've got the doctor-approved scoop on causes, symptoms, treatments, and a jillion other facts and tips that can make life with MS easier. by Patrick Sullivan Health Writer. March 5, 2020. Medical Reviewer. Shaheen Lakhan, M.D. On this page. Basics. Multiple sclerosis is a chronic disease that affects the central nervous system. In multiple sclerosis, the immune system attacks and damages the protective coating that surrounds the nerves. The damaged coating disrupts the communication between the central nervous system (CNS), which consists of the brain, spinal cord, and optic nerves, and the rest of the body. This results in a wide variety of symptoms.Â The neurologist makes the MS diagnosis and suggests treatment options for the patient. The course and symptoms of MS vary from person to person, and therefore the treatment will be unique for each patient. Other members of an MS treatment team may include: nurses.