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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.

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