SPECIAL ARTICLE

Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS

Report of the Guideline Development Subcommittee of the American Academy of Neurology

Sarah L. Minden, MD
Anthony Feinstein, PhD, MD
Rosalind C. Kalb, PhD
Deborah Miller, PhD
David C. Mohr, PhD
Scott B. Patten, MD, PhD
Christopher Bever, Jr., MD, MBA, FAAN
Randolph B. Schiffer, MD
Gary S. Gronseth, MD, FAAN
Pushpa Narayanaswami, MBBS, DM, FAAN

Correspondence to American Academy of Neurology: guidelines@aan.com

ABSTRACT

Objective: To make evidence-based recommendations for screening, diagnosing, and treating psychiatric disorders in individuals with multiple sclerosis (MS).

Methods: We reviewed the literature (1950 to August 2011) and evaluated the available evidence.

Results and recommendations: Clinicians may consider using the Center for Neurologic Study Emotional Lability Scale to screen for pseudobulbar affect (Level C). Clinicians may consider the Beck Depression Inventory and a 2-question tool to screen for depressive disorders and the General Health Questionnaire to screen for broadly defined emotional disturbances (Level C). Evidence is insufficient to support/refute the use of other screening tools, the possibility that somatic/neurovegetative symptoms affect these tools' accuracy, or the use of diagnostic instruments or clinical evaluation procedures for identifying psychiatric disorders in MS (Level U). Clinicians may consider a telephone-administered cognitive behavioral therapy program for treating depressive symptoms (Level C). Although pharmacologic and nonpharmacologic therapies are widely used to treat depressive and anxiety disorders in individuals with MS, evidence is insufficient to support/refute the use of the antidepressants and individual and group therapies reviewed herein (Level U). For pseudobulbar affect, a combination of dextromethorphan and quinidine may be considered (Level C). Evidence is insufficient to determine the psychiatric effects in individuals with MS of disease-modifying and symptomatic therapies and corticosteroids; risk factors for suicide; and treatment of psychotic disorders (Level U). Research is needed on the effectiveness in individuals with MS of pharmacologic and nonpharmacologic treatments frequently used in the non-MS population. ***Neurology*® 2014;82:174–181**

GLOSSARY

BDI = Beck Depression Inventory; **CBT** = cognitive behavioral therapy; **CES-D** = Center for Epidemiologic Studies Depression Rating Scale; **CNS-LS** = Center for Neurologic Study Emotional Lability Scale; **DM/Q** = dextromethorphan and quinidine; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **GHQ** = General Health Questionnaire; **HDRS** = Hamilton Depression Rating Scale; **MDD** = major depressive disorder; **MS** = multiple sclerosis; **NPV** = negative predictive value; **PBA** = pseudobulbar affect; **POMS** = Profile of Mood States; **PPV** = positive predictive value; **SCID-IV** = Structured Clinical Interview for *DSM-IV*; **SEGT** = supportive emotion-focused group therapy; **STAI** = State-Trait Anxiety Inventory; **T-CBT** = telephone-administered cognitive behavioral therapy program; **T-SEFT** = telephone-administered supportive emotion-focused therapy.

Individuals with multiple sclerosis (MS) are at increased risk of emotional disorders. With effective treatments widely available for several emotional disorders, this component of the burden of MS can be reduced.[1,2] Undetected and untreated mental illness may worsen functioning[3] and quality of life,[4–8] decrease treatment adherence,[9] and increase risk of suicide.[10–16] Improved detection, diagnosis, and treatment practices in medical settings where individuals with emotional disorders are often first seen would help ameliorate these negative outcomes. This guideline reviews the evidence and makes recommendations for identifying, diagnosing, and treating psychiatric disorders in individuals with MS.

Supplemental data at www.neurology.org

From the Department of Psychiatry, Brigham and Women's Hospital (S.L.M.), and Department of Neurology, Beth Israel Deaconess Medical Center (P.N.), Harvard Medical School, Boston, MA; Department of Psychiatry (A.F.), University of Toronto, Canada; National Multiple Sclerosis Society (R.C.K.), New York; Mellen Center (D.M.), Cleveland Clinic, OH; Department of Preventive Medicine (D.C.M.), Northwestern University, Evanston, IL; Department of Community Health Sciences & Hotchkiss Brain Institute (S.B.P.), University of Calgary, Canada; VA Maryland Health Care System (C.B.), Baltimore, MD; Santa Fe, NM (R.B.S.); and Department of Neurology (G.S.G.), University of Kansas Medical Center, Kansas City.

Approved by the Guideline Development Subcommittee on January 12, 2013; by the Practice Committee on February 17, 2013; and by the AAN Board of Directors on October 2, 2013.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Among individuals with MS, relative to the general population, lifetime prevalence rates are elevated for major depressive disorder (MDD) (36%–54% vs 16.2%),[17–23] bipolar disorder (13% vs 1%–4.5%),[20,24,25] anxiety disorders (35.7% vs 28.8%),[26,27] adjustment disorders (22% vs 0.2%–2.3%),[28–30]and psychotic disorders (2%–3% vs 1.8%).[31] Suicide may be at least twice as common.[10–16] Prevalence estimates for pseudobulbar affect (PBA) range from 6.5% to 46.2%[32–34]; the prevalence of euphoria is unknown.[35] Depressive and manic/hypomanic symptoms may occur with high-dose corticosteroids,[36] but the association between depressed mood and disease-modifying therapies is unclear.[37]

We use the accepted term *emotional disorders* to signify both disturbances of mood (persistent inner emotional states) and disturbances of affect (changing external expression of emotions).[38] In MS, affect disturbances (e.g., PBA, euphoria, apathy) may result from the pathologic process, whereas mood disturbances (e.g., depressed mood, anxiety) have a multifactorial etiology: MS-related processes, genetic and environment-related predispositions, normal grieving, and adjustment to loss. Disorders of mood and affect may coexist.

We also distinguish symptoms from diagnosable disorders and screening from diagnostic instruments. Symptoms (e.g., depressed mood, anxiety) are reported spontaneously by individuals or elicited through interviews, questionnaires, checklists, and severity rating scales.[39,40,e1–e11] Emotional disorders (e.g., major depressive, dysthymic, bipolar, anxiety, adjustment) are diagnosed according to criteria[38,e12] that stipulate the number and types of symptoms and their duration, intensity, and impact on functioning. Clinicians collect diagnostic information with unstructured, open-ended interviews; researchers use structured[e13–e16] and semistructured[39,e17] interviews. Table 1 lists instruments mentioned in the Class I–III studies cited below; we accepted at face value the instruments used as reference standards.

The project development plan had 9 clinical questions. We found evidence to support recommendations for the 3 below; the remaining 6 are listed later in this article.

1. What clinical evaluation procedures and screening and diagnostic tools can be used to accurately identify symptoms and make diagnoses of emotional disorders in individuals with MS?
2. What are the effective treatments for disorders of mood in individuals with MS?
3. What are the effective treatments for disorders of affect in individuals with MS?

DESCRIPTION OF THE ANALYTIC PROCESS In November 2006, the American Academy of Neurology Guideline Development Subcommittee (appendices e-1 and e-2 on the *Neurology*® Web site at www.neurology.org) convened a panel from North America representing a broad range of relevant expertise, including specialists in psychiatry, psychology, neurology, MS, and guideline development methodology. We searched MEDLINE, EMBASE, CINAHL, Web of Science, and Cochrane for relevant articles (1950 to August 2011). Of 5,145 abstracts obtained, 953 were identified for full article review. Of those 953 articles, 115 were systematically reviewed and rated. See e-Methods for complete methods description and appendices e-3 through e-6 for search strategy, schemes for classification of evidence and recommendations, and a prevalence article listing.

ANALYSIS OF EVIDENCE **Screening and diagnosis.**

Question. What clinical evaluation procedures and screening and diagnostic tools can be used to accurately identify symptoms and make diagnoses of emotional disorders in individuals with MS?

Analysis. We found 4 Class II,[28,e18–e20] 4 Class III,[e21–e24] and 5 Class IV[e25–e29] studies that evaluated screening tools and none that evaluated clinical procedures or diagnostic instruments (tables 1 and e-1).

One Class II study[e18] evaluated the Center for Neurologic Study Emotional Lability Scale (CNS-LS) as a screening tool for PBA. The CNS-LS is a 7-item self-report questionnaire that rates the frequency of episodes of pathologic laughing (4 items) and crying (3 items) on a 5-point scale; higher scores indicate greater frequency. Investigators recruited from 7 community-based general neurology referral centers 90 individuals with MS with or without PBA diagnosed by physicians who conducted clinical interviews. They administered the CNS-LS, used receiver operating characteristic analysis to identify a cut-point of 17 or greater, and found 94% sensitivity, 83% specificity, 87% positive predictive value (PPV), and 92% negative predictive value (NPV). Physician diagnoses were not systematically linked to detailed clinical assessments, however, and the recruitment strategy may have oversampled individuals with more severe PBA.

Another Class II study[e20] examined the ability of the General Health Questionnaire (GHQ)[e4] to detect broadly defined "emotional disturbances" classified using the Present State Examination[e16] as the reference standard. Investigators used a convenience sample of primarily newly diagnosed individuals. Emotional disturbance was common (13/25 subjects), and the GHQ had high sensitivity and specificity (92% each).

A third Class II study[28] investigated performance of the original Beck Depression Inventory (BDI)[40,e1] relative to diagnostic assignment of MDD by the Diagnostic Interview Schedule.[e14] Investigators used a consecutive series of 46 newly diagnosed individuals

Table 1 Instruments cited in the guideline

Name	Type of measure	Mode of administration	Time to complete/no. of items	Applicable guideline recommendations
Beck Depression Inventory (BDI)[40]	Screening	Self-report	21 items	Useful to screen for depressive symptoms (Level C)
Beck Depression Inventory–II (BDI-II)[e1]	Screening	Self-report	21 items	NA
Center for Epidemiologic Studies Depression Rating Scale (CES-D)[e2]	Screening	Self-report	20 items	NA
Chicago Multiscale Depression Inventory (CMDI)[e6]	Diagnostic	Clinician-administered	50 items	NA
Center for Neurologic Study Emotional Lability Scale (CNS-LS)[e18]	Screening	Self-report	7 items	Useful to screen for PBA (Level C)
Composite International Diagnostic Interview (CIDI)[e15]	Diagnostic	Lay-administered	2 h	NA
General Health Questionnaire (GHQ)[e4]	Screening	Self-report	28 items	Useful to screen for depressive symptoms (Level C)
Hamilton Depression Rating Scale (HDRS)[e11]	Screening	Clinician-administered	17–21 items	NA
Hamilton Rating Scale for Anxiety (HAM-A)[e59]	Screening	Clinician-administered	14 items	NA
Hopkins Symptom Checklist (HCL-20)[e56]	Screening	Self-report	20 items	NA
Hospital Anxiety and Depression Scale (HADS)[e51]	Screening	Self-report	14 items	NA
Multiple Sclerosis Impact Scale (MSIS-29)[e29]	Screening	Self-report	29 items	NA
Multiple Sclerosis Quality of Life Inventory (MSQLI)[e57]	Screening	Self-report	10 scales	NA
National Institute of Mental Health (NIMH) Diagnostic Interview Schedule (DIS)[e14]	Diagnostic	Lay-administered	1–3 h	NA
Patient Health Questionnaire (PHQ-9)[e3]	Screening	Self-report	9 items	NA
Positive and Negative Affect Scale (PANAS)[e7,e8]	Screening	Self-report	20 items	NA
Present State Examination (PSE)[e16]	Diagnostic	Clinician-administered	1–2 h	NA
Profile of Mood States (POMS)[e9]	Screening	Self-report	65 items	NA
Satisfaction with Life Scale (SWLS)[e58]	Screening	Self-report	5 items	NA
Schedule for Affective Disorders and Schizophrenia (SADS)[e17]	Diagnostic	Clinician-administered	1–2 h	NA
State-Trait Anxiety Inventory (STAI)[e10]	Screening	Self-report	40 items	NA
Structured Clinical Interview for *DSM-IV* (SCID-IV)[39]	Diagnostic	Clinician-administered	1–2 h	NA
1-Question screen[e24]	Screening	Self-report	1 item	NA
2-Question screen[e31]	Screening	Self-report	2 items	Useful to screen for depressive symptoms (Level C)

Abbreviations: NA = not applicable; PBA = pseudobulbar affect.
Several instruments are copyrighted. Users should check copyright status and consult manuals for proper use.

at an MS clinic and calculated sensitivity, specificity, PPV, and NPV for BDI scores from 9 to 21. Scores from 0 to 9 are usually considered normal, scores over 17 are strongly associated with depressive disorders, and scores from 10 to 17 generally indicate dysphoria but may include other diagnosable depressive disorders.[e30] A cut-point of 13 produced 71% sensitivity, 79% specificity, 70% PPV, and 79% NPV. Although this study showed that the original BDI can detect MDD in individuals with MS, a cut-point of 13 leaves nearly 30% of cases undetected. Cut-points low enough to preserve sensitivity produced a substantial number of false-positive ratings. As specificity was calculated with reference to MDD, some individuals with false-positive ratings may have had adjustment disorders. Because the cut-point was identified in the same test sample, these estimates require replication in an independent sample.

A fourth Class II study[e19] examined performance of a 2-question screening tool developed for use in primary care settings[e31] relative to diagnoses assigned by the Structured Clinical Interview for the *DSM-IV* (SCID-IV).[38] One question asked about depressed mood, the other about diminished interest or pleasure; an affirmative response to either question produced a positive screen. Investigators recruited 260 volunteers from among 502 individuals with MS in a Northern California Kaiser Permanente Medical Care

Group database. As expected, because a *DSM-IV* diagnosis requires either depressed mood or diminished interest or pleasure, the screen identified 66 of the 67 individuals (98.5%) with MDD. Specificity was lower (87%). Investigators observed that among the 13% with false-positive scores, more than half actually had subthreshold depressive disorders; detecting these disorders may have clinical utility. With a 26% observed point prevalence, sensitivity and specificity translated into 72% PPV and 99% NPV, respectively. Self-selection bias and a low response rate may have affected study results.

One Class III study[e24] examined the ability of a 1-question screen ("Are you depressed?") to detect MDD. This method produced a high false-negative rate: 30% of subjects who responded "no" were found to have a depressed mood. The study lacked an acceptable validation standard.

A second Class III study[e21] investigated potential confounding effects of somatic symptom items on BDI ratings. The investigators compared the proportional contribution of each of the 21 items in the original BDI[40] with total scores across 3 groups: individuals with MS, individuals with Diagnostic Interview Schedule–diagnosed MDD, and college students. The proportional contributions of work problems, fatigue, and health concerns were greater in individuals with MS than in the other groups.

A third Class III study[e23] used correlation analysis and structural equation modeling to examine relationships between neurovegetative symptoms assessed by the original BDI[40] (sleep disturbance, fatigue, appetite change, decision-making difficulty, loss of libido) and measures of depressed mood (Chicago Multiscale Depression Inventory),[e6] fatigue, and disability in 76 individuals with MS. Four of the 5 neurovegetative symptoms correlated with depressed mood and fatigue ($p < 0.01$); none correlated with disability.

The last Class III study[e22] determined PPV in a series of MS clinic patients screened for Center for Epidemiologic Studies Depression Rating Scale (CES-D) scores $\geq$16.[e2] Because all subjects scored $\geq$16, NPV could not be calculated. PPV was calculated as the proportion of subjects with a CES-D score $>$16 and diagnosed with a mood disorder in a subsequent clinical interview. The estimates were consistent with those reported elsewhere: 60% PPV for subjects with MDD and 75% for those with major depressive or dysthymic disorder. Diagnoses were not based on a validated diagnostic interview.

Conclusions and recommendations. In individuals with MS, the CNS-LS is possibly effective and may be considered for screening for PBA (Level C, 1 Class II study[e18]). The GHQ[e4] is possibly effective and may be considered for identifying individuals with broadly defined emotional disturbances (Level C, 1 Class II study[e20]). The BDI[40] and a 2-question screen[e31] are possibly effective and may be considered for identifying individuals with MDD (Level C, 1 Class II study each[28,e19]). There is insufficient evidence to support/refute using the CES-D[e2] to screen for depressive symptoms[e22] or a single question to screen for MDD[e24] (Level U, 1 Class III study each); the possibility that somatic or neurovegetative symptoms negatively affect the accuracy of BDI results (Level U, 2 conflicting Class III studies)[e21,e23]; and the use of specific instruments or clinical evaluation procedures to diagnose emotional disorders in individuals with MS (Level U).

Clinical context. Because emotional disorders may be unrecognized in medical settings, validated screening tools might improve identification of individuals who could benefit from further evaluation and treatment. The true positive rate of a screening tool depends not only on its sensitivity but also on the point prevalence of the disorder in the population under study. Clinically, false-positive results are not a major concern because individuals with the conditions typically identified (e.g., adjustment and subthreshold depressive disorders) can benefit from further assessment. Administratively, however, screening tools with high false-positive rates unnecessarily increase resource use.[e32]

Treatments. ***Question.*** What are the effective treatments for disorders of mood in individuals with MS?

Analysis. We found 14 studies that evaluated behavioral, psychological, and pharmacologic interventions: 1 Class II,[e33] 7 Class III,[e34–e40] and 5 Class IV[e41–e45] (table e-2). As is common in the psychological literature, these studies provided test statistics but not effect size measures. Where feasible, we calculated Cohen *d*, a measure of effect size where, generally, $d = 0.20$ is considered a small effect size; $d = 0.50$, medium; and $d = 0.80$, large.[e46]

The Class II study,[e33] a randomized controlled trial, compared a systematic 16-week telephone-administered cognitive behavioral therapy (CBT) program (T-CBT) for treating individuals with MS who had clinically significant depressive symptoms[e47,e48] with a validated telephone-administered supportive emotion-focused therapy (T-SEFT)[e49] to control for nonspecific effects of T-CBT. Enrolled subjects had scores $\geq$14 on the Hamilton Depression Rating Scale (HDRS)[e11] and scores $\geq$16 on the BDI-II.[e1] During treatment, subjects in both arms showed significant improvement. After treatment, the T-CBT group showed significantly greater reductions in diagnoses of MDD (SCID-IV) and depressive symptoms (HDRS) relative to the T-SEFT group (13.3% vs 29.0%, $d = 0.42$, $p = 0.02$). In contrast to the clinician-administered measures (HDRS, SCID-IV), however, self-

report tools produced inconsistent results: significant improvement in positive affect (Positive and Negative Affect Scale)[e7,e8] ($d = 0.48$, $p = 0.008$) for T-CBT relative to T-SEFT, but no significant differences between T-CBT and T-SEFT in depressive symptoms (BDI-II). After 1 year, treatment gains were sustained for both T-CBT and T-SEFT—there was no significant worsening on any measure—but differences between treatments were no longer significant.

An earlier randomized controlled evaluation (Class III)[e37] examined the effects of T-CBT[e47,e48] among individuals with MS with at least moderate baseline levels of depressive symptoms on the Profile of Mood States (POMS) depression scale.[e9] Subjects who received T-CBT had significantly greater improvement in POMS scores than usual care controls ($d = 0.97$, $p = 0.01$).

Another randomized, controlled, nonpharmacologic study (Class III)[e34] compared 6-session, CBT-based "stress inoculation training" (CBT plus relaxation training) with 2 hours of supportive psychotherapy. CBT plus relaxation training produced significantly greater reductions in baseline depressive symptoms on the BDI ($d = 1.43$, $p < 0.05$) and in anxiety on the State-Trait Anxiety Inventory (STAI)[e10] ($d = 0.85$, $p < 0.05$).

A comparative treatment effectiveness study (Class III)[e36] compared 16 weeks of in-person individual CBT,[e47,e48] supportive emotion-focused group therapy (SEGT),[e50] and sertraline for treating individuals diagnosed at baseline with MDD (SCID-IV).[39] Significant improvements in depressive symptoms on the BDI and HDRS were obtained for CBT and sertraline (mean doses, 88.75 mg/d for all participants, 139 mg/d for completers) but not for SEGT. Relative to SEGT, both CBT ($d = 0.58$, $p = 0.003$) and sertraline ($d = 0.46$, $p = 0.047$) produced significantly greater improvements; there were no statistical differences between CBT and sertraline. Treatment gains were maintained at 6-month follow-up for CBT and sertraline. SEGT was significantly less effective than either CBT or sertraline posttreatment. There was no difference in efficacy between CBT and sertraline.

A randomized controlled study (Class III)[e38] compared a 6-session group treatment involving relaxation and imagery (of positive immune function and myelin repair) with a no-treatment control. Enrolled subjects showed significantly elevated baseline anxiety levels on one outcome measure, the STAI,[e10] but not on another, the POMS.[e9] Subjects in the relaxation and imagery group showed significant posttreatment reductions in anxiety on the STAI relative to controls ($d = 0.82$, $p < 0.05$). Given the lack of elevated baseline anxiety levels on the POMS, it is unclear whether these results can be generalized.

A controlled but nonrandomized Class III study[e35] comparing 5 weeks of desipramine (mean dose, 136 mg/d) plus psychotherapy with placebo plus psychotherapy produced inconsistent findings: significant change on the HDRS but not on the BDI. Several issues limit interpretation of the findings, including nonrandomization of subjects and small sample size (n = 28).

A randomized, double-blind, placebo-controlled trial[e39] comparing paroxetine 20 mg/d with placebo for 12 weeks found no differences between them on the primary outcome measures of ≥50% decrease in depressive symptoms and number of subjects scoring ≤7 on the HDRS.[e11] Because the study was underpowered, its results are difficult to interpret. We rated the study Class III because the treatment groups' baseline characteristics were not described, the samples were small, and 23% of subjects withdrew.

A single-blind, randomized, Class III study[e40] looked at the effects of CBT-based group therapy (6 sessions over 12 weeks) in 20 individuals with MS with a score on the Hospital Anxiety and Depression Scale[e51] >7 or >2 on the GHQ[e4] at treatment onset. Treated subjects had fewer depressive symptoms ($p < 0.05$) than a matched control group (n = 20) assigned to a waiting list. Results were nonsignificant when corrected for multiple outcomes, and there were no significant differences in anxiety.

Conclusion and recommendations. For individuals with MS, a 16-week program of individual T-CBT is possibly effective and may be considered in treating depressive symptoms (Level C, 1 Class II study,[e33] 1 Class III study[e37]). There is insufficient evidence to support/refute the efficacy and use of 1) sertraline,[e36] desipramine,[e35] paroxetine,[e39] individual in-person CBT,[e36] individual in-person CBT plus relaxation training,[e34] or CBT-based group therapy[e40] for depressive symptoms; or 2) individual in-person CBT plus relaxation training,[e34] group relaxation and imagery,[e38] or CBT-based group therapy[e40] for anxiety (Level U, 1 Class III study each).

Clinical context. There is evidence supporting the efficacy of pharmacologic and nonpharmacologic therapies for depressed mood and anxiety in individuals without MS. Despite the lack of evidence in individuals with MS, these therapies are frequently used to treat emotional disorders in this population.

Question. What are the effective treatments for disorders of affect in individuals with MS?

Analysis. One Class II study[e52] addressed this question for PBA in a randomized controlled trial comparing dextromethorphan and quinidine (DM/Q) with placebo. Investigators measured presence and severity of PBA with the CNS-LS[e18] and determined the adjusted mean change in CNS-LS score at 4 assessments over 12 weeks. Secondary outcomes

included the number of episodes of laughing or crying, or both, between visits and the proportions of subjects with complete symptom remission and at least a 3-point decrease in mean CNS-LS score. Investigators also used a pain rating scale and measured quality of life and relationships with visual analog scales. Treated subjects had significantly greater reductions in mean CNS-LS scores at all 4 assessments, and significantly more treated subjects showed a 3-point or greater mean score decrease (83.6% treated vs 49.3% untreated; $p < 0.0001$, risk difference 34%, 95% confidence interval 21%–48%). Treated subjects also improved significantly on all secondary outcome measures. Dizziness was the only adverse event that occurred more frequently in the treated (26.3%) vs placebo (9.5%) group, and only one treated subject rated it as severe. This study is Class II because of dropout rates (27.6% treated, 28.4% placebo).

Conclusion and recommendations. DM/Q is possibly effective and safe and may be considered for treating individuals with MS with PBA (Level C, 1 Class II study).[e52]

Clinical context. DM/Q is the only drug approved by the US Food and Drug Administration for PBA treatment, although other drugs are used in clinical practice (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants). There are no randomized placebo-controlled trials of these other agents.

RECOMMENDATIONS FOR FUTURE RESEARCH

Despite advances in clinicians' recognition that emotional disorders are common among individuals with MS, these disorders are often undetected and inadequately treated.[e53–e55] Research is limited, and there are few Class I studies to guide recommendations. Below are examples of studies that could provide evidence to improve detection, diagnosis, and treatment practices.

Screening and diagnosis.

- Head-to-head comparisons of screening tools and diagnostic instruments to determine which best identify particular emotional symptoms (e.g., depressed mood, anxiety) and emotional disorders (e.g., MDD, adjustment disorder)
- Evaluations of methods to train MS clinicians to identify emotional disorders, educate individuals with MS and family members to recognize emotional symptoms, and encourage open discussion of these problems
- Comprehensive evaluations of screening initiatives including feasibility, cost, use of results, and outcomes
- Comparisons of methods to distinguish, in an individual, sources of somatic and neurovegetative symptoms that could be attributed to both an emotional disorder and MS
- Assessments of instruments to screen for and diagnose euphoria, apathy, and emotional dysregulation
- Appraisals of standard screening and diagnostic instruments to identify and determine the prevalence of other psychiatric disorders among individuals with MS

Treatment.

- Large, methodologically rigorous, randomized, placebo-controlled studies to evaluate nonpharmacologic and pharmacologic therapies with strong evidence of efficacy and widespread use for treating emotional disorders in individuals without MS. Examples include the following:
  - Double-blind comparative-effectiveness trials of frequently used antidepressants with attention to their impact on outcomes of different types of emotional symptoms and disorders, MS impairments (e.g., physical, cognitive), and concurrent MS treatments
  - Targeted comparative-effectiveness trials for frequently used types of nonpharmacologic interventions (e.g., CBT, psychotherapy) and different approaches (e.g., individual vs group, telephone vs in-person)
  - Systematic examinations of combinations of pharmacologic and nonpharmacologic therapies (and combinations within modalities[e34])
- Replication of findings of safety and efficacy of DM/Q for PBA in individuals with MS and head-to-head comparisons with other currently used therapies
- Assessments of treatment options for euphoria, apathy, and emotional dysregulation
- Evaluations of health care services for individuals with MS designed to optimize identification and treatment of mental disorders
- Appraisals of telemedicine technologies among individuals with MS who are housebound, have difficulty traveling, or live in remote communities

Additional comments.

- The 6 clinical questions for which recommendations were not made deserve further study:
  - What are the effective treatments for psychotic disorders in individuals with MS?
  - What clinical evaluation procedures and screening and diagnostic instruments can be used to accurately distinguish between MS fatigue and depression in individuals with MS?
  - What are the effects of disease-modifying agents on mood and affect in individuals with MS?
  - What are the effects of corticosteroids on mood and affect in individuals with MS?

- What are the effects of symptomatic treatments on mood and affect in individuals with MS?
- What are the risk factors for suicidal thinking and behavior among individuals with MS?

We included these questions at the outset because they are clinically relevant: individuals with MS may have psychotic disorders and require treatment. Clinicians may have difficulty determining whether fatigue, for example, is due to MS or depressed mood and therefore selecting appropriate treatment. Individuals with MS may experience emotional symptoms while taking disease-modifying therapies, corticosteroids, and symptomatic agents, and may become suicidal. We reviewed studies on these issues, but none met criteria to support recommendations. Neurologists, individuals with MS, and families would welcome well-designed investigations of the effects of interferons on mood. They would also benefit from knowing whether particular characteristics of individuals with MS might predict suicide.

- Cognitive and emotional disorders co-occur, and it can be difficult to determine the source of inattention, distractibility, slowed thought processing, and difficulty concentrating. Further research is needed on screening, diagnosing, and distinguishing these disorders and on effective treatments when they co-occur.
- We reviewed only studies of adults with MS. Future research should address emotional disorders in children and adolescents with MS, including comparisons with adults with MS and children and adolescents without MS.

AUTHOR CONTRIBUTIONS

Sarah L. Minden: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Anthony Feinstein, Rosalind C. Kalb, Deborah Miller, David C. Mohr, and Scott B. Patten: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Christopher Bever, Jr.: study concept and design, acquisition of data, analysis or interpretation of data, study supervision. Randolph B. Schiffer: analysis or interpretation of data. Gary S. Gronseth: study concept and design, analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Pushpa Narayanaswami: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

ACKNOWLEDGMENT

The authors are most grateful to Ralph Benedict, PhD; Dawn Langon, PhD; Nicholas LaRocca, PhD; Peter Arnet, PhD; and John DeLuca, PhD, who contributed significantly to the design and development of this project. The authors also thank Thomas Getchius and Erin Hagen for coordinating the development of the manuscript and Julie Cox for editing the manuscript.

STUDY FUNDING

This evidence-based guideline was funded by the American Academy of Neurology. No author received honoraria or financial support to develop this document.

DISCLOSURE

S. Minden has received honoraria and travel reimbursement for meetings on mood and cognition in MS from Pfizer, Merck-Serono, and Genentech; on fingolimod from Novartis; and on dextromethorphan and quinidine from Avanir; has received research support from the National Multiple Sclerosis Society (NMSS), the Center for Mental Health Services, and the Substance Abuse and Mental Health Services Administration; and has stock in Merck, Schering-Plough, and SmithKline. A. Feinstein has received travel funding from Merck-Serono, Teva, and Bayer; is serving as a member of an editorial advisory board for MS; has received publishing royalties from the *Clinical Neuropsychiatry of Multiple Sclerosis* (Cambridge University Press), *Journalists Under Fire* (John Hopkins University Press), and *Michael Rabin: America's Virtuoso Violinist* (Amadeus Press); and has received honoraria from Merck-Serono, Bayer, Teva, and Biogen. R. Kalb has received publishing royalties from Demos Medical Publishing and Wiley Publishing, and has received honoraria for Can Do Multiple Sclerosis. D. Miller is serving as a journal editor, associate editor, or member of an editorial advisory board for *Journal of Rehabilitation Research & Development*; and has received financial or material research support or compensation from Novartis and the NMSS. D. Mohr has received research support from the NIH. S. Patten is a member of the editorial board of the *Canadian Journal of Psychiatry*, and has received research support from the Government of Alberta's Collaborative Research Grant Initiative, the Canadian Institutes for Health Research, and the Institute of Health Economics. C. Bever received travel funding from the American Academy of Neurology (AAN), the University of Maryland School of Medicine, and the Department of Veterans Affairs; has a patent held or pending for use of hematogenous stem cells in neuronal replacement therapy and gene delivery; has received funding for merit grants from the Department of Veterans Affairs and a pilot grant from the NMSS; and has received license fee payments and royalty payments (or has contractual rights for receipt of future royalty payments) related to the patent disclosed above. Dr. Bever's spouse has received publishing royalties from *Ambulatory Medicine*, Barker et al. R. Schiffer, G. Gronseth, and P. Narayanaswami have no relevant disclosures to report. Go to Neurology.org for full disclosures.

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. Formal practice recommendations are not intended to replace clinical judgment.

CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology*® peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

Received March 18, 2013. Accepted in final form September 17, 2013.

REFERENCES

1. World Health Organization. The Global Burden of Disease: 2004 Update. Geneva, 2008. Available at: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. Accessed February 4, 2011.
2. Goldman Consensus Group. The Goldman Consensus statement on depression in multiple sclerosis. Mult Scler 2005;11:328–337.
3. Arnett PA, Higginson CI, Voss WD, et al. Depressed mood in multiple sclerosis: relationship to capacity-demanding memory and attentional functioning. Neuropsychology 1999;13:434–446.
4. Wang JL, Reimer MA, Metz LM, Patten SB. Major depression and quality of life in individuals with multiple sclerosis. Int J Psychiatry Med 2000;30:309–317.
5. Gulick EE. Correlates of quality of life among persons with multiple sclerosis. Nurs Res 1997;46:305–311.
6. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. Qual Life Res 1995;4:187–206.
7. McIvor GP, Riklan M, Reznikoff M. Depression in multiple sclerosis as a function of length and severity of illness, age, remissions, and perceived social support. J Clin Psychol 1984;40:1028–1033.
8. O'Brien MT. Multiple sclerosis: the relationship among self-esteem, social support, and coping behavior. Appl Nurs Res 1993;6:54–63.
9. Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA. Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. Arch Neurol 1997;54:531–533.
10. Stenager EN, Stenager E, Koch-Henriksen N, et al. Suicide and multiple sclerosis: an epidemiological investigation. J Neurol Neurosurg Psychiatry 1992;55:542–545.
11. Stenager EN, Stenager E. Suicide and patients with neurologic diseases: methodologic problems. Arch Neurol 1992;49:1296–1303.
12. Stenager EN, Koch-Henriksen N, Stenager E. Risk factors for suicide in multiple sclerosis. Psychother Psychosom 1996;65:86–90.
13. Brønnum-Hansen H, Stenager E, Nylev Stenager E, Koch-Henriksen N. Suicide among Danes with multiple sclerosis. J Neurol Neurosurg Psychiatry 2005;76:1457–1459.
14. Sadovnick AD, Eisen K, Ebers GC, Paty DW. Cause of death in patients attending multiple sclerosis clinics. Neurology 1991;41:1193–1196.
15. Feinstein A. Multiple sclerosis, depression, and suicide. BMJ 1997;315:691–692.
16. Feinstein A. An examination of suicidal intent in patients with multiple sclerosis. Neurology 2002;59:674–678.
17. Minden SL, Schiffer RB. Affective disorders in multiple sclerosis: review and recommendations for clinical research. Arch Neurol 1990;47:98–104.
18. Sadovnick AD, Remick RA, Allen J, et al. Depression and multiple sclerosis. Neurology 1996;46:628–632.
19. Minden SL, Orav J, Reich P. Depression in multiple sclerosis. Gen Hosp Psychiatry 1987;9:426–434.
20. Joffe RT, Lippert GP, Gray TA, Sawa G, Horvath Z. Mood disorder and multiple sclerosis. Arch Neurol 1987;44:376–378.
21. Schiffer RB, Caine ED, Bamford KA, Levy S. Depressive episodes in patients with multiple sclerosis. Am J Psychiatry 1983;140:1498–1500.
22. Patten SB, Beck CA, Williams JV, Barbui C, Metz LM. Major depression in multiple sclerosis: a population-based perspective. Neurology 2003;61:1524–1527.
23. Kessler RC, Berglund P, Demler O, et al; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095–3105.
24. Schiffer RB, Wineman NM, Weitkamp LR. Association between bipolar affective disorder and multiple sclerosis. Am J Psychiatry 1986;143:94–95.
25. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2007;64:543–552.
26. Korostil M, Feinstein A. Anxiety disorders and their clinical correlates in multiple sclerosis patients. Mult Scler 2007;13:67–72.
27. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593–602.
28. Sullivan MJ, Weinshenker B, Mikail S, Bishop SR. Screening for major depression in the early stages of multiple sclerosis. Can J Neurol Sci 1995;22:228–231.
29. Casey P, Maracy M, Kelly BD, et al. Can adjustment disorder and depressive episode be distinguished? Results from ODIN. J Affect Disord 2006;92:291–297.
30. Maercker A, Forstmeier S, Enzler-Donatsch A. Adjustment disorders as stress-related disorders: prevalences from a representative community survey. Eur Psychiatry 2007;22(suppl):S321. Abstract P333.
31. Patten SB, Svenson LW, Metz LM. Psychotic disorders in MS: population-based evidence of an association. Neurology 2005;65:1123–1125.
32. Feinstein A, Feinstein K. Depression associated with multiple sclerosis: looking beyond diagnosis to symptom expression. J Affect Disord 2001;66:193–198.
33. Feinstein A, Feinstein K, Gray T, O'Connor P. Prevalence and neurobehavioral correlates of pathological laughing and crying in multiple sclerosis. Arch Neurol 1997;54:1116–1121.
34. Work SS, Colamonico JA, Bradley WG, Kaye RE. Pseudobulbar affect: an under-recognized and under-treated neurological disorder. Adv Ther 2011;28:586–601.
35. Finger S. A happy state of mind: a history of mild elation, denial of disability, optimism, and laughing in multiple sclerosis. Arch Neurol 1998;55:241–250.
36. Minden SL, Orav J, Schildkraut JJ. Hypomanic reactions to ACTH and prednisone treatment for multiple sclerosis. Neurology 1988;38:1631–1634.
37. Feinstein A. Multiple sclerosis, disease modifying treatments, and depression: a critical methodological review. Mult Scler 2000;6:343–348.
38. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. Washington, DC: American Psychiatric Association; 1994.
39. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute; 2002.
40. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571.