Evaluation and treatment of Mood Disorders in Multiple Sclerosis

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Charcot’s behavioral observations (1877)

- “marked enfeeblement of memory”
- “slowness of response”
Freud and Charcot
Major Depression
Diagnostic criteria

• Five or more of the following during the same two week period:

• Depressed mood most of the day
• Markedly diminished interest or pleasure in all activities
• Appetite change with significant weight loss, or weight gain
• Insomnia or hypersomnia nearly every day
• Psychomotor agitation or retardation (observable by others)
• Fatigue or loss of energy nearly every day
• Feelings of worthlessness, excessive, inappropriate guilt
• Diminished ability to think or concentrate
• Recurrent thoughts of death
Rating scales
Rating scales

Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients

Kimia Honarmand\textsuperscript{1,2} and Anthony Feinstein\textsuperscript{1,2}

Abstract
Detecting clinically significant symptoms of depression and anxiety in medically ill patients using self-report rating scales presents a challenge because of somatic confounders. The Hospital Anxiety and Depression Scale (HADS) was developed with this in mind, but has never been validated for a multiple sclerosis population. Our objective was to validate the HADS for multiple sclerosis patients. Multiple sclerosis patients were interviewed for the presence of major depression ($n = 180$) and anxiety disorders ($n = 140$) with the Structured Clinical Interview for DSM-IV disorders. A receiver operating characteristic (ROC) analysis was undertaken to assess which HADS cut-off scores give the best yield with respect to diagnoses of major depression and all anxiety disorders defined by the Structured Clinical Interview for DSM-IV. A threshold score of 8 or greater on the HADS depression subscale provides a sensitivity of 90\% and specificity of 87.3\% (ROC area under the curve 0.938). The same cut-off score gives a sensitivity of 88.5\% and a specificity of 80.7\% on the anxiety subscale (ROC area under the curve 0.913), but for generalized anxiety disorder only. The study confirms the usefulness of the HADS as a marker of major depression and generalized anxiety disorder, but not other anxiety disorders, in multiple sclerosis patients.

Keywords
multiple sclerosis, major depressive disorder, anxiety disorders, Hospital Anxiety and Depression Scale (HADS)

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Major Depression
Prevalence

- lifetime prevalence in patients attending MS clinics approaches 50%
- However, prevalence is also raised in a community based sample.
  - In a study of 115,071 Canadians, the 12 month prevalence of depression in MS patients exceeded that in healthy subjects (odds ratio: 3.4)
  - In subjects ages 18-45 years, the 12 month prevalence was 25.7%.
- Rates increased in relation to other neurological disorders.
MS related depression: community data

- Administrative health data which show elevated age standardized prevalence rates of all mental comorbidities apart from schizophrenia in MS patients compared to the general population, most notably with respect to depression (31.7% vs. 20.5%) (Marrie et al., 2013).

- Even higher rates of depression, i.e. approaching 50%, were reported in a large UK MS registry (N>4000).

- Individuals with lower socioeconomic status bear a disproportionate burden in terms of higher prevalence, missed diagnosis, and inadequate treatment of depression.
The clinical importance of depression

- Effects on cognition
- Suicidal intent and completion
- Quality of Life
- Depression is treatable
Suicidal intent and MS

- Lifetime suicidal intent: 29%
- Lifetime suicide attempt: 6.4%
- Lifetime diagnosis of major depression
- Severity of major depression ($\uparrow$ HAD scores)
- Living alone
- Alcohol abuse

70% sensitivity, 95% specificity, overall 87% predictive ability

- 35% of suicidal patients had received no Rx
- 66% of patients with current major depression not received Rx
- Of the 9 patients who had attempted suicide, 4 had never been given antidepressant Rx
- These data fit with those from Mohr et al (Multiple Sclerosis. 2006:12:204-208) who showed that over half the depressed MS patients in a neurological clinic were not receiving antidepressant medication and of those depressed patients on treatment, a quarter were receiving sub-therapeutic doses.
Suicide

• 7.5x the general population rate
• 2x the general population rate and increased relative to other neurological disorders (Stenager and Stenager, 1992)
• At risk: males, < 30 yrs, first 5 years of illness
Lifetime prevalence:

- General Anxiety Disorder: 18.6% versus 5.1% in the general population
- Panic Disorder: 10.0% versus 3.5% in the general population
- Obsessive Compulsive Disorder: 8.6% versus 2.5% in the general population
Anxiety and somatic confounders in MS

- As with depression, beware of symptom overlap (somatic confounders) between MS and anxiety.
- The Hospital Anxiety and Depression Scale controls for this.
Anxiety with Depression in MS

- 7786 adults with MS
- 54.1% had excessive symptoms of anxiety
- 46.9% had excessive symptoms of depression
- SPMS associated with more depression than other disease types.
- Women with RRMS more anxious than men with RRMS
Anxiety and alcohol

Anxiety rather than depression predicted excessive alcohol consumption

Finding not replicated by Beier et al (J. Neurol Sci., 2014: 15: 122-7) who found excessive alcohol consumption in 40% of 157 subjects and found no link with anxiety or depression.
Treating anxiety in MS

- Little strong data
- What data there are suggest CBT is effective
- No pharmacologic trials
Stress inoculation training is a form of CBT with muscle relaxation and it effectively treated anxiety.

Multiple sclerosis (MS) is a common demyelinating disease that affects the central nervous system. Clinical symptoms vary widely and affect sensory-tactile, motor, visual, bladder, and bowel functioning. Multiple sclerosis has profound social and psychological consequences. Disruptions in schooling, employment, sexual and family functioning, friendships, and activities of daily living occur. Psychological distress includes anxiety, depression, poor body image, and low self-esteem (VanderPlate, 1984). Because of these challenges to the MS patient's ability to cope, the need to develop efficacious psychological interventions is paramount.

The literature on psychological interventions in MS primarily comprises case reports and uncontrolled group studies of hypnotherapy (Brown, 1986) biofeedback (B. Pinto-Kaufman, B. Pinto-Kaufman) in MS. The current study also measures disease variables that could easily confound outcome findings (disease duration, severity, and current exacerbation status). In addition, coping measures were assessed that tap both coping outcome (e.g., depression, state anxiety, psychological distress) and coping mediators (e.g., locus of control, trait anxiety, problem-focused coping).

The current study utilized a stress inoculation training (SIT) program that was specially adapted to augment coping in MS by increasing psychological symptom control and by modifying potential coping mediators. The SIT is a short-term, cognitive-behavioral psychotherapeutic intervention that seeks to enhance coping by ameliorating affective distress and by providing a behavioral rehearsal of coping strategies.
CBT effective for treating anxiety in MS

Anxiety and MS (not a RCT)

Cognitive behaviour therapy for common mental disorders in people with Multiple Sclerosis: A bench marking study

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b Department of Psychology, Queen's University Belfast, Belfast, UK
c Department of Psychology, University of Ulster, Londonderry, UK
d University of Ulster, Magee Campus, Londonderry, UK
e Institute of Community Health Nursing, Queen's University Belfast, Belfast, UK

Objective: The aims were (a) to test the effectiveness of a nurse-led cognitive behavioural therapy (CBT) program to assist adjustment in the early stages of multiple sclerosis (MS) and (b) to determine moderating factors of treatment including baseline distress, social support (SS), and treatment preference.

Method: Ninety-four ambulatory people with MS within 10 years of diagnosis were randomized to receive 8 individual sessions of CBT (n = 48) or supportive listening (n = 46), most delivered on the telephone, in a multicenter randomized controlled trial. The primary outcomes were distress and functional impairment. Secondary outcomes included global improvement, acceptance of illness, and dysfunctional cognitions. Assessments were completed at home and were coordinated by a blind assessor. Data were analyzed by intention-to-treat using multilevel models. Results: The CBT group was significantly less distressed at the end of treatment (estimated General Health Questionnaire group difference = 3.2 points, 95% CI 1.1 to 5.4 points) and at the 12-month follow-up (estimated group difference = 3.2 points, 95% CI 0.01 to 6.4 points). There were no differences between the groups on functional impairment. The CBT group also demonstrated significantly greater improvements on secondary outcomes at the end of treatment but not at the 12-month follow-up. CBT participants with poor SS and/or clinically defined levels of distress at baseline showed significantly greater gains on both primary outcomes. Treatment preference did not moderate treatment effects. Conclusion: CBT is more effective than supportive listening in reducing distress in people with MS. CBT appears most effective for patients with poor SS and high levels of distress. The loss of gains in the secondary outcomes by 12 months suggests further follow-up sessions may be warranted.

Keywords: adjustment, distress, cognitive behavioral therapy (CBT), multiple sclerosis (MS), randomized controlled trial (RCT)
Etiology of depression
Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis

J. Pujol, MD; J. Bello, MD; J. Deus, PhD; J.L. Martí-Vilalta, MD; and A. Capdevila, MD

Article abstract—Depression is a common mood disturbance in multiple sclerosis (MS) patients. Epidemiologic data suggest a causative relationship between depressive symptoms and cerebral demyelination, although a specific lesion site responsible for depressed mood has not been identified. Given that depression in neurologic disease is closely related to frontal and temporal lobe damage, we focused our study on investigating the extent to which lesions in the white matter connecting both cerebral lobes may account for depressive symptoms in MS. Forty-five patients were assessed using the Beck Depression Inventory and an MRI protocol conceived to quantify lesions separately in the basal, medial, and lateral frontotemporal white matter. The presence of lesions in the left suprainsular white matter, the region that mainly includes the arcuate fasciculus, was specifically associated with depressive symptoms, accounting for a significant 17% of the depression score variance. Although a multifactorial origin is suspected for depression in MS, this finding gives support to the existence of a direct negative effect of demyelination on mood.

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


Figure 1. Sagittal reformatted images (left in A, B, and C) showing the level and extent of the three different white matter regions considered in the axial analysis (basal [A], periventricular [B], and lateral [C]), and representative proton density axial images (right in A, B, and C) on which lesion measurements were performed.
Figure 3. Plot of Beck scores with coronal lesion areas of the left arcuate fasciculus region. Although the relationship was significant ($r = 0.43, p = 0.001$), high depression scores were registered in patients with no lesions in this region.

Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis.
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Figure 4. (A-F) Representative coronal inversion-recovery images of the six patients with the highest lesion scores of the left arcuate fasciculus region. Note that the bulk of the left arcuate fasciculus was substantially damaged in each case (arrow). L = left; R = right; IP = inferoposterior; IA = inf eroanterior.
MS, Depression and MRI changes

- Increased hyper and hypo-intense lesion volume in the left medial inferior frontal cortex
- Reduced gray matter volume in the anterior temporal region
Diffusion tensor imaging abnormalities in depressed multiple sclerosis patients

A Feinstein¹,², P O’Connor¹,³, N Akbar¹,², L Moradzadeh², CJM Scott² and NJ Lobaugh¹,²
MS, Depression, lesion segmentation

Figure 2. Stepwise process to obtain parcellated normal-appearing brain tissue (NABT) segmented according to tissue type. (a) $T_1$-weighted image with traced hypointense lesions, (b) $T_2$-weighted image with traced hyperintense lesions, (c) NABT and white matter hyperintensity (WMH) segmentations parcellated according to Semi-Automated Brain Region Extraction-defined regions (blue = cerebrospinal fluid (CSF); light gray = white matter; dark gray = grey matter; black = lesions; red = hypointense lesions).
MS, Depression, brain parcellation

Figure 1. Magnetic resonance imaging sagittal view demarcating medial brain regions using Semi-Automated Brain Region Extraction. ABG/T, anterior basal ganglia/thalamus; AT, anterior temporal; IP, inferior parietal; MIF, medial inferior frontal; MOF, medial orbitofrontal; MSF, medial superior frontal; O, occipital; PBG/T, posterior basal ganglia/thalamus; PT, posterior temporal; SP, superior parietal.
Fig. 3. Stepwise process to derive fractional anisotropy (FA) and mean diffusivity (MD) from normal-appearing brain tissue parcellated according to Semi-Automated Brain Region Extraction (SABRE)-defined regions. (a) FA image in diffusion tensor imaging (DTI) space; (b) FA normal-appearing white matter (NAWM) image; (c) NAWM mask, parcellated according to SABRE; (d) MD image in DTI space; (e) MD normal-appearing grey matter (NAGM) image; (f) NAGM mask, parcellated according to SABRE.
Table 2. Mean regional fractional anisotropy and mean diffusivity differences between depressed \( (n = 30) \) and non-depressed \( (n = 32) \) patients with multiple sclerosis

<table>
<thead>
<tr>
<th>Region</th>
<th>FA ( \text{BDI} \leq 19 )</th>
<th>FA ( \text{BDI} &gt; 19 )</th>
<th>MD ( \text{BDI} \leq 19 )</th>
<th>MD ( \text{BDI} &gt; 19 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior temporal normal appearing white matter ( (n = 62) )</td>
<td>0.209 (±0.020)</td>
<td>0.197 (±0.016)*</td>
<td>2.99 (±0.25)</td>
<td>3.14 (±0.20)*</td>
</tr>
<tr>
<td>Left anterior temporal normal appearing gray matter ( (n = 62) )</td>
<td>2.94 (±0.51)</td>
<td></td>
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<td></td>
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<tr>
<td>Right inferior frontal lesion ( (n = 56) )</td>
<td></td>
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</table>

*Significant difference between groups at \( p = 0.01 \).

BDI, Beck Depression Inventory; FA, fractional anisotropy; MD, mean diffusivity.
## MS, Depression and Diffusion Tensor Imaging

**Imaging predictors of depression**

<table>
<thead>
<tr>
<th>MRI variables</th>
<th>Percentage variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions + atrophy</td>
<td>23.7%</td>
</tr>
<tr>
<td>Lesions + atrophy + regional DTI indices (MD of NAGM and FA of NAWM)</td>
<td>35.1%</td>
</tr>
<tr>
<td>Lesions + atrophy + regional DTI indices (MD of NAGM and FA of NAWM + MD of right inferior frontal lesions)</td>
<td>43.6%</td>
</tr>
</tbody>
</table>
Smaller Cornu Ammonis 2–3/Dentate Gyrus Volumes and Elevated Cortisol in Multiple Sclerosis Patients with Depressive Symptoms
Gold et al, Biological Psychiatry 2010, 68, 553-9
Hypothalamic–pituitary–adrenal axis dysregulation in patients with comorbid relapsing–remitting multiple sclerosis (RRMS) and major depressive disorder (MDD).

Gold S M et al. J Neurol Neurosurg Psychiatry 2011;82:814-818
From: Mood Disorders and Dysfunction of the Hypothalamic-Pituitary-Adrenal Axis in Multiple Sclerosis: Association With Cerebral Inflammation

Figure Legend:
Mean±SEM scores on depression and anxiety scales for patients with multiple sclerosis (MS) with and without gadolinium-enhancing MS plaques. HRSD indicates Hamilton Rating Scale for Depression; SDS, Zung Self-Reporting Depression Scale; HRSA, Hamilton Rating Scale for Anxiety; and SAS, Zung Self-Reporting Anxiety Scale. Asterisk indicates P<.05; dagger, P<.01.
From: Mood Disorders and Dysfunction of the Hypothalamic-Pituitary-Adrenal Axis in Multiple Sclerosis: Association With Cerebral Inflammation


Figure Legend:
Mean±SEM serum levels of cortisol in patients with multiple sclerosis (MS) with and without gadolinium enhancement of MS plaques.
Processing emotions in MS
(patients without Major Depression and PBA excluded)

# MS, Depression and brain imaging: summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Imaging modality</th>
<th>Number of subjects</th>
<th>Rating Scale</th>
<th>Clinical diagnosis</th>
<th>Imaging findings</th>
<th>Laterality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabatini, U. et al.</td>
<td>1996</td>
<td>SPECT</td>
<td>N=20 (n=10 depressed &amp; n=10 non-depressed)</td>
<td>DSM-III</td>
<td>Major depression</td>
<td>Increased perfusion in limbic areas.</td>
<td>Left</td>
</tr>
<tr>
<td>Pujol, J. et al.</td>
<td>1997-2000</td>
<td>MRI</td>
<td>N=45</td>
<td>BDI-II</td>
<td>None</td>
<td>Increased T2 lesions in the arcuate fasciculus associated with somatic and affective symptoms</td>
<td>Left</td>
</tr>
<tr>
<td>Fassbender, K. et al.</td>
<td>1998</td>
<td>MRI + Gd</td>
<td>N=73 (n=23 RRMS, n=17 healthy control group A, n=33 healthy control group B)</td>
<td>DSM-III-R, HRSD, ZSRDS</td>
<td>Major depression</td>
<td>Increased Gd+ lesions linked to increased cortisol and a positive dexamethasone suppression test</td>
<td>None reported</td>
</tr>
<tr>
<td>Bakshi, R. et al.</td>
<td>2000</td>
<td>MRI</td>
<td>N=48 (n=19 depressed &amp; n=29 non-depressed)</td>
<td>DSM-IV criteria for unipolar depression, HRSD, BDI</td>
<td>Major depression</td>
<td>Superior frontal, superior parietal and temporal T1 lesions, lateral and third ventricular enlargement, frontal atrophy.</td>
<td>Left</td>
</tr>
<tr>
<td>Berg, D. et al.</td>
<td>2000</td>
<td>MRI</td>
<td>N=78</td>
<td>DSM-IV</td>
<td>Major depression</td>
<td>Increased T2 lesion load in whole brain, parietal and frontal lobes and the cerebellum.</td>
<td>Right</td>
</tr>
<tr>
<td>Feinstein, A. et al.</td>
<td>2004</td>
<td>MRI</td>
<td>N=40 (n=21 depressed, n=19 non-depressed)</td>
<td>DSM-IV</td>
<td>Major depression</td>
<td>T2 and T1 lesion volume in medial inferior prefrontal cortex, anterior temporal atrophy.</td>
<td>Left</td>
</tr>
<tr>
<td>Passamonti, L. et al.</td>
<td>2009</td>
<td>fMRI</td>
<td>N=24 (n=12 MS subjects, n=12 healthy control subjects)</td>
<td>None</td>
<td>Reduced functional connectivity between ventrolateral PFC and amygdala.</td>
<td>Bilateral</td>
<td></td>
</tr>
<tr>
<td>Gold, S.M. et al.</td>
<td>2010</td>
<td>MRI</td>
<td>N=49 (n=20 RRMS &amp; n=29 healthy control subjects)</td>
<td>BDI-II</td>
<td>None</td>
<td>Hippocampal atrophy particularly in CA2-3 and dentate gyrus linked to increased cortisol.</td>
<td>Left</td>
</tr>
<tr>
<td>Feinstein, A. et al.</td>
<td>2010</td>
<td>MRI plus DTI</td>
<td>N=62 (n=30 depressed, n=32 non-depressed)</td>
<td>BDI-II</td>
<td>None</td>
<td>Increased T1 lesion volume in right medial inferior frontal region, atrophy of left superior frontal region, lower FA, higher MD in left anterior temporal normal-appearing white and grey matter, higher MD in right inferior frontal hyperintense lesions.</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Gold, S.M. et al.</td>
<td>2014</td>
<td>MRI</td>
<td>N=109 (females only)</td>
<td>CES-D</td>
<td>None</td>
<td>Reduced hippocampus thickness.</td>
<td>Right</td>
</tr>
</tbody>
</table>
Psychosocial causes of depression

- From the journal: June 15, 1917.
  - I sit all day in my chair, moving 8 feet to my bed at night, and 8 feet from it to my chair in the morning—and wait. The assignment is certain.

- From the journal: October 3, 1918.
  - I am grateful to-day for some happy hours plucked triumphantly from under the very nose of Fate, and spent in the warm sun in the garden...A Lark sang...I sat by some Michaelmas Daisies and watched the Bees, Flies and Butterflies
Deprivation
Psychosocial etiology

- Uncertainty (Lynch et al, 2001)
- Inadequate coping strategies (Mohr et al, 1997; Pakenham et al, 1997; Aikens et al, 1997; Jean et al, 1997; Pakenham 1999)
- Helplessness (Shnek et al, 1997; Patten et al, 2002; van der Werf, 2003)
- Poor social relationships (Maybury and Brewin, 1984)
- Loss of recreational activities (Voss et al 2002)
- High levels of stress (Patten et al, 2000)
- Fatigue (Lobentanz et al, 2004)
Treating Major Depression:
Medication

- Only Two RCTs
- Desipramine (tricyclic antidepressant)
- Paroxetine (SSRI)
- Medication effective
- Side effects troubling: anticholinergic problems
  - Dry mouth
  - Constipation
  - Sedation
  - Blurred vision
  - Sexual difficulties
### Effects of Antidepressants

<table>
<thead>
<tr>
<th>Neurotransmitter System Receptor</th>
<th>Noradrenaline</th>
<th>Serotonin 5-HT₁</th>
<th>Serotonin 5-HT₂</th>
<th>Serotonin 5-HT₃</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SINGLE ACTION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>nefazodone</td>
<td>o</td>
<td>+</td>
<td>-</td>
<td>o</td>
</tr>
<tr>
<td><strong>DUAL ACTION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>MAOI</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>venlafaxine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>mirtazapine</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
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</table>

- **Stimulation**
- **o No effect**
- **- Blockade or decrease**

Mirtazapine: Mechanism of Action

- Antidepressant Effect
- Anxiolytic Effect

Noradrenergic neurotransmission

- Prevents:
  - Nausea
  - Vomiting
  - Headache

Serotonergic neurotransmission

- Prevents:
  - Agitation
  - Sexual dysfunction
  - Sleep Improvement

Prevents:
- Nausea
- Vomiting
- Headache
- Sedation
- Increased appetite
- Weight gain
Major Depression: Psychotherapy

- Cognitive-behavior Rx vs. Supportive-expressive Rx vs. sertraline Rx over 16 weeks. (Mohr et al, 2005).
- Can be given effectively over the telephone.
- Mindfulness Based Therapy (Grossman et al, 2010)
Management of psychiatric disorders in MS
Recommendations from the American Academy of Neurology @014)

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

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

Correspondence to
American Academy of Neurology
guidelines@aan.com
Management of psychiatric disorders in MS
Recommendations from the American Academy of Neurology for depression

- **Recommended for assessment:**
  - General Health Questionnaire
  - Beck Depression Inventory Revised
  - Two Question Approach (Are you depressed? Have you lost interest or pleasure in activities you formerly enjoyed?)

- **Treatment:**
  - Cognitive behavior therapy (telephone administered)
  - Not enough evidence for antidepressant medication
CBT in MS: Review and meta-analysis
Hind et al BMC Psychiatry 2014; 14

- 3 studies of CBT delivered individually
- 3 studies of CBT delivered in a group
- 1 study of CBT delivered by computer

Conclusion: CBT effective for treating depression in MS, but optimum duration of treatment and most effective modality of delivery still needed to be determined according to patient characteristics.
Stress management

- 24 weeks of treatment
- Less Gd+ lesions
- Less cumulative lesion load
- Effects not sustained beyond 24 weeks
- No clinical benefits, including mood
Exercise

- There is, as yet, no exercise study in MS with depression as the primary endpoint
- No study has used a structured interview to define depression
- Data from other studies (n=7) are equivocal
- Hard to draw conclusions from inadequate methodologies, but there is untapped potential that needs to be studied further
ECT

- Potentially very useful
- Very severe depression
- Failed other treatments
- If you are concerned about high suicide risk
- Risk of MS relapse? Gd enhanced MRI can be predictive here
Pathological laughing and crying
Pathological laughing and crying (Pseudobulbar affect)

- Crying without sadness
- Laughter without happiness (mirth)
- Up to 10% of MS patients affected to various degrees

Prevalence and Neurobehavioral Correlates of Pathological Laughing and Crying in Multiple Sclerosis

Anthony Feinstein, PhD, MD; Karen Feinstein, MA; Trevor Gray, MD; Paul O’Connor, MD

Objectives: To establish the point prevalence of pathological laughing and crying (PLC) in multiple sclerosis (MS). To define associated neurological, emotional, and cognitive correlates of PLC.

Design: A consecutive sample of 152 patients with clinically or laboratory definite MS were screened for PLC, defined as sudden, involuntary displays of laughing or crying or both, without associated subjective feelings of depression or euphoria. Thereafter, a case-control design was followed with patients with PLC matched to patients with MS without PLC on age, gender, physical disability (Expanded Disability Status Scale), duration of MS, and premorbid IQ.

Settings: An MS outpatient clinic, the population representative of a large urban catchment area.

Patients: Fifteen of 152 patients had PLC, 11 of whom (mean [SD] age, 43.7 [8.3] years, 7 women) agreed to further testing. Thirteen patients with MS without PLC acted as controls.

Main Outcome Measures: Neurological examination, Pathological Laughter and Crying Scale, Hospital Anxiety and Depression Scale, 28-item General Health Questionnaire, and the Wechsler Adult Intelligence Scale-Revised.

Results: The point prevalence of PLC in MS was 10%. Patients had a mean Expanded Disability Status Scale score of 6.5, had had MS for a mean (SD) of 10 (5.8) years, and had entered a chronic-progressive phase of their illness. Pathological laughing and crying was not associated with disease exacerbations. Compared with controls, patients were not more depressed or anxious, but had a greater decline in IQ.

Conclusions: Pathological laughing and crying as distinct from emotional lability affects 1 in 10 patients with MS. It occurs in severely physically disabled patients, generally with long-standing disease. The presence of cognitive deficits relative to controls implies more extensive brain involvement.

Arch Neurol. 1997;54:1116-1121
Pseudobulbar affect in MS: an MRI study

- Two groups of MS subjects
- PBA versus normal mood/affect change (n=14 for each group).
- All underwent neurological examination, cognitive testing (BRNB) and detailed MRI scanning
PBA associated with more lesions in the following areas:

<table>
<thead>
<tr>
<th>Region</th>
<th>Sig.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global lesion volume</td>
<td>T2</td>
<td>.001</td>
</tr>
<tr>
<td>Brain stem</td>
<td>T1</td>
<td>.003</td>
</tr>
<tr>
<td>Medial inferior frontal L</td>
<td>T2</td>
<td>.004</td>
</tr>
<tr>
<td>Medial inferior frontal R</td>
<td>T2</td>
<td>.002</td>
</tr>
<tr>
<td>Medial superior frontal R</td>
<td>T2</td>
<td>.008</td>
</tr>
<tr>
<td>Inferior parietal L</td>
<td>T2</td>
<td>.000</td>
</tr>
<tr>
<td>Inferior parietal R</td>
<td>T2</td>
<td>.001</td>
</tr>
</tbody>
</table>
MRI regions
Pseudobulbar Affect: Associated With Lesions at Various Locations

- Facial muscles
- Anterior association cortex
- Motor cortex
- Posterior association cortex
- Orbitofrontal cortex
- Pons
- Medulla
- To respiratory muscles
Major Depression and Pathological Laughing and Crying: Comparison of MRI variance

<table>
<thead>
<tr>
<th>Major Depression</th>
<th>40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological laughing and crying</td>
<td>~ 75%</td>
</tr>
</tbody>
</table>
Pseudobulbar affect

Rx:
- low dose amitriptyline
- SSRI
- levodopa and amantadine
- Neudexta (dextromethorphan/quinidine)

Response to treatment in PBA = 48-72 hours
Response to treatment in major depression = 10-14 days
Bipolar Affective Disorder

- Twice the rate of the general population
- Grandiosity or persecutory beliefs
- Elevated or irritable mood
- Increased motor activity
  - Rapid speech, flight of ideas
  - Reckless behavior (financial, sexual)
- Treatment: mood stabilising medications (lithium, valproic acid) and, if necessary, antipsychotic medication (olanzapine, risperidone, quetiapine)
Euphoria vs. bipolar affective disorder

- **Euphoria**
  - A fixed state of mental wellbeing
  - Point prevalence: 9-13%
  - Severely disabled
  - Atrophy, heavy lesion load
  - Cottrell and Wilson defined 4 states:
    - Euphoria sclerotica (cheerful)
    - Eutonia sclerotica (feels well)
    - Pes sclerotica (optimism)
    - Emotional lability
  - **Treatment:** None
Psychosis
(Patten et al, 2005)

- Of 2.45 million residents of Alberta over 15 years of age, 10,367 had MS (prevalence of 330/100,000)
- Rates of psychosis increased relative to the general population:
  - 15-24 years: OR=11.1
  - 25-44 years: OR = 7.4
  - 45-64 years: OR = 5.6
  - 65+ years : OR = 1.9
Treatment: newer antipsychotic medication such as olanzapine, risperidone, ziprasidone, quetiapine
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- Paul O'Connor
- Liesly Lee
References