Pseudobulbar Affect

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Laughter and crying.

Which is not the same as happiness and sadness.
Disclaimers

- Research support from the MS Society of Canada, Canadian Institute of Health Research, Consortium of MS Centres, Bristol Myers Squibb
- Speaker’s honorarium: Novartis.
Aims

• To understand the similarities and differences between mood and affect.
• To appreciate the neural mechanisms of laughter and crying.
• To understand the clinical and real-world consequences of mood uncoupling from affect.
• To learn about the pharmacologic treatment of pathological affect.
The neuropsychiatric history of laughing and crying

- Hippocrates (460-370 BC)
- Laughter, sorrow, joy are all controlled by the brain.
The neuropsychiatric history of laughing and crying

- Charles Darwin (1809-1882)
- Naturalist, biologist, geologist.
- Brain disorders like stroke, senility, hemiplegia associated with weeping.
Darwin’s contributions to the understanding of emotional expression.
According to Paul Ekman.

- *The Expression of the Emotions in Man and Animals* published only one year after the *Descent of Man*. He wrote it in 4 months just before he compiled the 6th and last edition of *On the Origin of Species*.
- Ekman highlights what he sees as Darwin’s five major contributions to the field.
  - Darwin viewed emotions, like anger, fear disgust, as separate entities.
  - Facial expression as a rich source of information on emotions.
  - Facial expressions of emotions are universal. Gestures are culture-specific.
  - Emotions are not unique to humans, but found in other species too.
  - Explained why particular movements signal particular emotions. In this context he elucidated the principle of antithesis: a signal conveys a certain message because it is the opposite another signal.
The neuropsychiatric history of laughing and crying.
In 1886, Oppenheim and Siemerling made the connection between dysregulated emotions and pseudobulbar involvement.

Hermann Oppenheim (1858-1919)

Ernst Siemerling (1857–1931)
The neuropsychiatric history of laughing and crying

Charcot at the Salpetriere

Edouard Brissaud (1852 – 1909)
The neuropsychiatric history of laughing and crying
Edouard Brissaud

• “rire et pleurer spasmodique”
• Thalamic centre for laughter regulation
• PBA due to lesions of the anterior internal capsule or corticobulbar tract
  • Linked Parkinson’s disease to pathological changes in the substantia nigra.
  • Hemifacial spasm
• Was Marcel Proust’s doctor (Dr. du Boulbon)
The neuropsychiatric history of laughing and crying

Charles Frere (1852-1907)  

- “Fou rire prodromique” as a prelude to neurological symptoms:
  - Episodic chorea
  - Episodic aphasia and hemiparesis
  - Motor symptoms
- Gelastic epilepsy.
Terminology

• Pseudobulbar affect*
• Pathological laughing and crying
• Emotional incontinence
• Involuntary Emotional Expression Disorder
• Emotional lability
• Emotionalism
• Excessive emotionality
• Forced laughter or crying

*pseudo refer to the presence of bulbar sings like dysarthria and dysphagia in the absence of a bulbar (brainstem) lesion. The symptoms arise from an upper motor neuron lesion entailing disruption of the cortico-bulbar tracts that exert supranuclear control over the brain stem.
Phenomenology

- Mood = subjective feeling of sadness, irritability
- Affect = objective assessment of a person’s mood state.
- In a normal mental state examination, mood and affect are congruent.
- In an abnormal mental state, they may be congruent or incongruent.
- An example of an incongruent mental state occurs in pseudobulbar affect.
  - Mood and affect become disconnected.
  - Crying without sadness, laughter without happiness, laughter and crying intermingled without sadness or happiness.
Classic definition of pseudobulbar affect.
(Klaus Poeck, 1926 – 2006)
Classic definition of pseudobulbar affect.
(Klaus Poeck, 1926 - 2006)

- Response to non-specific stimuli.
- Absence of voluntary control of facial expression.
- Absence of a corresponding change in mood exceeding the period of laughing and crying.
- The expression of emotion does not lead to a sense of relief.

- Not the same as:
  - Emotional lability
  - Euphoria
  - Laughter and crying secondary to substance abuse, psychosis or histrionic behavior.
### Involuntary Emotional Expression Disorder

**Episodes of involuntary or exaggerated emotional expression that result from a brain disorder, including crying, laughing or related emotional displays.**

- Episodes represent a change from the person's usual emotional reactivity
- May be incongruent with the person's mood
- Independent or in excess of any precipitating stimulus

**The disturbance causes clinically significant distress or impairment in social or occupational functioning.**

**The symptoms are not better accounted for by another neurologic or psychiatric disorder**
(e.g. gelastic or dacrycystic epilepsy, facial dystonia, facial or vocal tics, facial dyskinesias, mania, depression, panic disorder, psychosis.

**The symptoms are not the direct effect of a substance**
(e.g. drug, alcohol, medication)

**Supportive observations:**

- Autonomic changes (e.g. flushing of the face)
- Pseudobulbar palsy signs (e.g. increased jaw jerk, exaggerated gag reflex, tongue weakness, dysarthria, dysphagia)
- Proneness to episodic anger

**Descriptive characteristics:**

- Sudden onset
- Typically brief
- Stereotyped

Fig. 1. Pathologic rage in a 16-year-old boy after subarachnoid hemorrhage from an aneurysm of the left posterior communicating artery. Note right facial weakness. (1–4) Rage attack when looking at the physician. (5) Change to a desperate screaming. (6) With furious cries, the patient snaps at a spatula held near his mouth. He would bite and snap at any object in a similar fashion. Note mixed expression with aggressive behavior (unpublished observations of the author).
# Distinguishing PBA from depression

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>PBA</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional expression</td>
<td>Crying, laughing, both</td>
<td>Crying</td>
</tr>
<tr>
<td>Emotional experience</td>
<td>Episodes independent of mood</td>
<td>Associated sadness</td>
</tr>
<tr>
<td>Duration</td>
<td>Brief (minutes)</td>
<td>Days to months</td>
</tr>
<tr>
<td>Voluntary control</td>
<td>None</td>
<td>Emotions can be controlled to a degree</td>
</tr>
<tr>
<td>Stereotypy</td>
<td>Episodes are stereotyped</td>
<td>Variable</td>
</tr>
<tr>
<td>Neurological disorder</td>
<td>Always present</td>
<td>May or may not be present</td>
</tr>
<tr>
<td>Pseudobulbar signs</td>
<td>May be present</td>
<td>Absent</td>
</tr>
<tr>
<td>Anger</td>
<td>May accompany episodes</td>
<td>Absent</td>
</tr>
<tr>
<td>Provocative stimulus</td>
<td>Non-specific, minimal, inappropriate to the situation</td>
<td>Specific mood related situations</td>
</tr>
<tr>
<td>Associated thought content</td>
<td>Frustration, anger, embarrassment</td>
<td>Hopelessness, guilt, worthlessness, thoughts of death, helplessness</td>
</tr>
<tr>
<td>Appetite/sleep/diurnal variation</td>
<td>No relationship</td>
<td>Changes</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>Not present</td>
<td>Common</td>
</tr>
</tbody>
</table>
Prevalence of Pseudobulbar Affect

- Amyotrophic lateral sclerosis: 2-60%
- Alzheimer’s disease: up to 7-25%.
- Multiple sclerosis: 7-29%
- Stroke: 6-52%
- Traumatic brain injury: 11% lifetime prevalence to 5% one year prevalence.
- Parkinson’s disease: 1-31%

- The main reason for these broad ranges is the definition of PBA.
The taxonomy of mental phenomena
Lumpers or splitters?

Kraepelin (1856-1926)  Griesinger (1817-1868)
## Table 1

### Summary of Poeck’s Criteria for Pseudobulbar Affect

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Emotional episodes are situationally inappropriate and can be precipitated by nonspecific stimuli.</td>
</tr>
<tr>
<td>2</td>
<td>There is no relation between the expressed emotional expression and the patient’s mood at the time of the episode.</td>
</tr>
<tr>
<td>3</td>
<td>The episodes are paroxysmal and the patient is unable to control the extent and duration of the episodes.</td>
</tr>
<tr>
<td>4</td>
<td>The expression of emotions does not lead to an internal sense of relief.</td>
</tr>
</tbody>
</table>

*Note. Adapted from Brooks et al. (2013) and Poeck (1969).*
Assessment of Pseudobulbar Affect
self-report scale and structured interview
Center for Neurologic Study-Lability Scale (CNS-LS) for pseudobulbar affect (PBA)

The CNS-LS is a short (seven-item), self-administered questionnaire, designed to be completed by the patient, that provides a quantitative measure of the perceived frequency of PBA episodes. The CNS-LS can help physicians accurately diagnose PBA. A CNS-LS score of 13 or higher may suspect PBA.

Patient’s name: ___________________________

Date of assessment: ________________

Using the scale below, please write the number that describes the degree to which each item applies to you DURING THE PAST WEEK. Write only 1 number for each item.

<table>
<thead>
<tr>
<th>Applies never</th>
<th>Applies rarely</th>
<th>Applies occasionally</th>
<th>Applies frequently</th>
<th>Applies most of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**Assessment questions**

1. There are times when I feel fine 1 minute, and then I’ll become tearful the next over something small or for no reason at all.
2. Others have told me that I seem to become absorbed very easily or that I seem to become absorbed about things that really aren’t funny.
3. I find myself crying very easily.
4. I find that even when I try to control my laughter, I am often unable to do so.
5. There are times when I won’t be thinking of anything happy or funny at all, but then I’ll suddenly be overcome by happy or happy thoughts.
6. I find that even when I try to control my crying, I am often unable to do so.
7. I find that I am easily overcome by laughter.

**Answers**

**Total Score:** ____________

The CNS-LS has been validated in ALS and MS patient populations. This questionnaire is not intended to substitute for professional medical assessment and/or policy.

APPENDIX 1. Pathological Laughter and Crying Scale (Patient Interview)

Ratings are based on clinical assessment. Initial probe questions are given for each item. However, further questions may be used for clarification. Write the number in the spaces provided which most accurately reflects clinical symptoms.

1. Have you recently experienced sudden episodes of laughter?
   ___ Rate the frequency of the episodes during the past two weeks.
   0. Rarely or not at all
   1. Occasionally
   2. Quite often
   3. Frequently

2. Have you recently experienced sudden episodes of crying?
   ___ Rate the frequency of the episodes during the past two weeks.
   0. Rarely or not at all
   1. Occasionally
   2. Quite often
   3. Frequently

If you have experienced sudden episodes of laughter, please answer the following (questions 3–10), otherwise skip to question 11.

3. Have these episodes occurred without any cause in your surroundings?
   ___ Rate the frequency with which the episodes have occurred without external stimuli in the past two weeks.
   0. Rarely or not at all
   1. Occasionally
   2. Quite often
   3. Frequently

4. Have these episodes lasted for a long period of time?
   ___ Rate the average duration of the episodes during the past two weeks.

5. Have these episodes been uncontrollable by you?
   ___ Rate the ability to control the episodes during the past two weeks.
   0. Rarely or not at all
   1. Occasionally
   2. Quite often
   3. Frequently

6. Have these episodes occurred as a result of feelings of happiness?
   ___ Rate the frequency with which the episodes have occurred as a result of happiness in the past two weeks.
   0. Rarely or not at all
   1. Occasionally
   2. Quite often
   3. Frequently

7. Have these episodes occurred in excess of feelings of happiness?
   ___ Rate the frequency with which the episodes have been disproportionate to the emotional state in the past two weeks.
   0. Rarely or not at all
   1. Occasionally
   2. Quite often
   3. Frequently

8. Have these episodes of laughter occurred with feelings of sadness?
   ___ Rate the frequency of association between the episode and the paradoxical emotion in the past two weeks. The sadness must precede or accompany the episode and not be a reaction to it.
### 9. Have these episodes occurred with any emotions other than happiness or sadness, such as nervousness, anger, fear, etc.?
- Rate the frequency of association between the episodes and emotions in the past two weeks. The emotions must precede or accompany the episode and not be a reaction to it.
  - 0. Rarely or not at all
  - 1. Occasionally
  - 2. Quite often
  - 3. Frequently

### 10. Have these episodes caused you any distress or social embarrassment?
- Rate the degree of distress or embarrassment caused by the episodes in the past two weeks.
  - 0. Rarely or not at all
  - 1. Occasionally
  - 2. Quite often
  - 3. Frequently

*If you have experienced sudden episodes of crying, please answer the following (questions 11-18).*

### 11. Have these episodes occurred without any cause in your surroundings?
- Rate the frequency with which the episodes have occurred without external stimuli in the past two weeks.
  - 0. Rarely or not at all
  - 1. Occasionally
  - 2. Quite often
  - 3. Frequently

### 12. Have these episodes lasted for a long period of time?
- Rate the average duration of the episodes during the past two weeks.
  - 0. Very brief
  - 1. Short (a few seconds)
  - 2. Moderate (less than 30 seconds)
  - 3. Prolonged (more than 30 seconds)

### 13. Have these episodes been uncontrollable by you?
- Rate the ability to control the episodes during the past two weeks.
  - 0. Rarely or not at all
  - 1. Occasionally
  - 2. Quite often
  - 3. Frequently

### 14. Have these episodes occurred as a result of feelings of sadness?
- Rate the frequency with which the episodes have occurred as a result of sadness in the past two weeks. The sadness must precede or accompany the crying and not be a reaction to it.
  - 0. Rarely or not at all
  - 1. Occasionally
  - 2. Quite often
  - 3. Frequently

### 15. Have these episodes occurred in excess of feelings of sadness?
- Rate the frequency with which the episodes have been disproportionate to the emotional state in the past two weeks.
  - 0. Rarely or not at all
  - 1. Occasionally
  - 2. Quite often
  - 3. Frequently

### 16. Have these episodes of crying occurred with feelings of happiness?
- Rate the frequency of association between the episode and the paradoxical emotion in the past two weeks. The happiness must precede or accompany the crying.
  - 0. Rarely or not at all
  - 1. Occasionally
  - 2. Quite often
  - 3. Frequently

### 17. Have these episodes occurred with any emotions other than sadness or happiness, such as nervousness, anger, fear, etc.?
- Rate the frequency of association between the episodes and emotions in the past two weeks. The emotions must precede or accompany the episode and not be a reaction to it.
  - 0. Rarely or not at all
  - 1. Occasionally
  - 2. Quite often
  - 3. Frequently

### 18. Have these episodes caused you any distress or social embarrassment?
- Rate the degree of distress or embarrassment caused by the episodes in the past two weeks.
  - 0. Rarely or not at all
  - 1. Occasionally
  - 2. Quite often
  - 3. Frequently
Pseudobulbar affect: Burden of illness

- N=1052 (399 with PBA and 653 without)
- stroke, multiple sclerosis, Parkinson’s and Alzheimer’s diseases, ALS, TBI.
- Those with PBA had worse quality of life, quality of relationships, less work productivity and greater work impairment.
- PBA considered a major cause for 24% of the sample becoming housebound.
- PBA considered a major cause for 9% of the sample being moved to a supervised living placement.

The neuroanatomy of laughing and crying
Quick anatomical refresher

- **Bulbar**
  - Pons
  - Medulla oblongata
  - Cerebellum

- **Brain stem**
  - Midbrain
  - Pons
  - Medulla oblongata

Quick anatomical refresher

Corticobulbar tract

Cortico-pontine-cerebellar tract

William James (1842 – 1910)

• If the hypothesis of the emotions “is ever to be definitively confirmed or disproved it seems it must be by asylum physicians and nervous specialists, for they alone have the data in their hands.”
The neuroanatomy of laughing and crying
Kinnier Wilson: the anatomy of laughter and crying

- Asymmetry of voluntary facial expression disappeared when the features were innervated under the influence of emotions. *Voluntary facial paresis*

- Volitional normality but emotional abnormality of facial movement. Typically unilateral. This involuntary facial paresis may show up in response to exertion. Can be induced by compressing the epigastric region which induces forcible (involuntary) thoracic respiration. *Emotional facial paresis*

- Three possibilities are considered:
  - Are the overwhelming laughter and tears activated by the appropriate stimuli?
  - Do they in turn induce the appropriate frame of mind?
  - Do they have they any emotional content at all?

- The stimuli are inadequate and inappropriate.

- Visible emotion does not correspond to the patient’s real feelings.

- It differs from legitimate emotional performance in its inevitability, its frequency, its uncontrollable character, the contradictory “cause” and “effect” and the extreme facility with which it is induced.
The neuroanatomy of smiling: volitional versus emotional

Normal volitional facial movements

‘Mimic’ palsy on the left when laughing
Edgar Allen Poe (1809-1849)

• “When I wish to find out how wise, or how stupid, or how good, or how wicked is anyone, or what are his thoughts at the moment, I fashion the expression of my face as accurately as possible in accordance with the expression of his, and then wait to see what thoughts of sentiments arise in my mind or heart, as if to match or correspond with the expression.”
Put on a happy face.

Gray skies are gonna clean up,
Put on a happy face;
Brush off the clouds and cheer up,
Put on a happy face.
Take off the gloomy mask of tragedy,
It's not your style
You'll look so good that you'll be glad
Ya' decide to smile!

Pick out a pleasant outlook,
Stick out that noble chin;
Wipe off that "full of doubt" look,
Slap on a happy grin!
And spread sunshine all over the place,
Just put on a happy face!

And if you're feeling cross and bitterish
Don't sit and whine
Think of banana split and licorice
And you'll feel fine
I knew a girl so glooming
She'd never laugh or sing
She wouldn't listen to me
Now she's a mean old thing

So spread sunshine all over the place
Just put on a happy face
Just put on a happy face
So, put on a happy face

From the musical: Bye Bye Birdie
Kinnier Wilson: the anatomy of laughter and crying

- Voluntary control: corticopontine, corticobulbar and corticospinal tracts.

- Involuntary control; Two pathways, one from the frontal lobe, the other from the sensory cortex which come together bordering on the third ventricle and run down near the midline to the medulla. Responsible for the emotional activation of the faciorespiratory system.

- Impair voluntary control and involuntary actions of the same mechanisms become apparent. There is a balance between these to mechanisms. The quivering lip of a child exemplifies this.

- Double control of faciorespiratory synkinesis: a) Voluntary, when we inhibit automatic movement, and b) Involuntary when that automatic movement is forced to give way to the expression of emotion.
Kinnier Wilson: the anatomy of laughter and crying

• Damage the top-down control exerted by the motor system and uncontrollable laughter or crying may follow. There is volitional facial weakness. PBA does not have to occur, however.

• Damage the postulated involuntary system, namely those systems originating in the frontal and sensory cortices and ending in the pons, an emotional paresis may occur.

• Wilson acknowledges that there are a number of unanswered questions, but he ends his 34 page article with this clinical observation: “Neurologists have occasion, every now and then, to observe cases in which laughter [is associated] with ataxia or dysmetria… the laughter of cerebellar patients not infrequently assumes a particular character.”
PBA and the cerebellum.

- 51 year old man with a stroke: primary manifestation was uncontrollable laughter and crying.
- MRI showed three lesions in the brainstem and two in the cerebellum.
- There were no other brain lesions.
- The lesions disrupted the cerebro-ponto-cerebellar projections disconnecting or disrupting circuits to telencephalic structures, i.e. the rest of the brain from the cerebellum.
Fig. 2 Lesions in patient C.B. The MRIs show the neuroanatomical correlates of the lesions in the cerebellum.
Fig. 3 The cerebellum is interconnected with telencephalic structures.
Why the cerebellum?

- Laughter and crying determined by perceptions of what is funny or sad.
- These stimuli are perceived or remembered within a particular cognitive/social context.
- These perceptions are then linked to the appropriate emotion by discrete brain regions such as the ventromedial frontal cortex, anterior cingulate cortex and amygdala.
- These sites in turn activate the effector sites that control the mechanics of laughter/crying, namely the motor cortex, premotor regions, hypothalamus and specific cranial nuclei.
- In healthy people, the initial external trigger, eg. a funny joke, attendance at a funeral, will engender an emotion that is appropriate to the social circumstances of the moment.
- The fine tuning of the emotional response that places the emotional reaction within a socially appropriate context is controlled by the cerebellum.
Why the cerebellum?

- Think of the cerebellum as a relay station receiving inputs from telencephalic structures that determine emotion and passing these signals on to the brain stem structures that control the physiological mechanics of laughter and crying. **But this connection is made only after ensuring that these emotions are socially appropriate.**

- In support of this disconnection hypothesis, the authors cite their patient’s cognitive results. These revealed executive function deficits (Tower of Hanoi Task) in the context of otherwise largely normal function.

- Performance on the Tower of Hanoi Task, like that of the Stroop Task, is associated with reciprocal communication between the prefrontal/anterior cingulate cortices and the cerebellum.
<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Score</th>
<th>Classification</th>
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</thead>
<tbody>
<tr>
<td><strong>Verbal reasoning</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Vocabulary</td>
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<td>Similarities</td>
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<tr>
<td>Arithmetic</td>
<td></td>
<td>9</td>
<td>Average</td>
</tr>
<tr>
<td>Digit Span</td>
<td></td>
<td>8</td>
<td>Average</td>
</tr>
<tr>
<td>Information</td>
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<td>Average</td>
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<td>Mildly impaired</td>
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<tr>
<td>Benton VRT No. errors</td>
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<td>Benton VRT CFT 30’ Recall</td>
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<td>5%</td>
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<td>Grooved Pegboard</td>
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<td></td>
</tr>
<tr>
<td>Right hand</td>
<td></td>
<td>16%</td>
<td>Low normal</td>
</tr>
<tr>
<td>Left hand</td>
<td></td>
<td>16%</td>
<td>Low normal</td>
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<td><strong>Executive functions</strong></td>
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</tr>
<tr>
<td>Tower of Hanoi Trial 2</td>
<td></td>
<td>65</td>
<td>Normal</td>
</tr>
<tr>
<td>Tower of Hanoi Trial 3</td>
<td></td>
<td>120</td>
<td>Impaired</td>
</tr>
<tr>
<td>Tower of Hanoi Trial 4</td>
<td></td>
<td>120</td>
<td>Impaired</td>
</tr>
</tbody>
</table>

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More evidence for frontal-cerebellar disconnections in PBA

Resting state fMRI analysis of pseudobulbar affect in Amyotrophic Lateral Sclerosis (ALS): motor dysfunction of emotional expression

Francesca Trojì, Federica Di Nardo, Giulia D'Alvano, Giuseppina Cialazzì, Carla Passaniti, Antonella Mangione, Minoo Sharbafshaaer, Antonio Russo, Marcello Silvestro, Mattia Siciliano, Mario Cirillo, Gioacchino Tedeschi, Fabrizio Esposito

Abstract
Pseudobulbar affect (PBA), referring to exaggerated or inappropriate episodes of laughing and/or crying without an apparent motivating stimulus, has been mainly attributed to bilateral degeneration of corticobulbar tracts. We aimed at exploring brain functional connectivity (FC) correlates of PBA in patients with amyotrophic lateral sclerosis (ALS), the most common motor neuron disease, frequently associated with PBA. Resting state functional MRI (RS-fMRI) independent component analysis (ICA) and seed-based analyses and voxel-based morphometry (VBM) whole-brain analysis were performed on 27 ALS patients (13 with PBA; 14 without PBA) and 26 healthy controls (HC), for investigating functional and structural abnormalities in ALS patients compared to HC and in patients with PBA compared to patients without PBA. Between-patient analysis revealed different FC patterns, especially regarding decreased FC in several areas of cognitive (default mode, frontoparietal, salience) and sensory-motor networks in patients with PBA compared to those without PBA. However, no significant differences were found in gray matter atrophy. Seed-based analysis showed increased FC between middle cerebellar peduncles and posterior cingulate cortex and decreased FC between middle cerebellar peduncles and left middle frontal gyrus in patients with PBA compared to patients without PBA. Our findings support the involvement of fronto-cerebellar circuits in regulating emotional expression in patients with ALS.
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.

**Setting:** 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 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
Multiple sclerosis and PBA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PLC Group, Mean (SD) (n=11)</th>
<th>Control Group, Mean (SD) (n=13)</th>
<th>χ² or t Test</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43.7 (8.3)</td>
<td>42.5 (5.3)</td>
<td>t=0.5</td>
<td>22</td>
<td>.7</td>
</tr>
<tr>
<td>Gender, F/M</td>
<td>4/7</td>
<td>4/9</td>
<td>χ²=0.1</td>
<td>1</td>
<td>.8</td>
</tr>
<tr>
<td>EDSS</td>
<td>6.4 (1.7)</td>
<td>6.2 (1.4)</td>
<td>t=0.3</td>
<td>22</td>
<td>.7</td>
</tr>
<tr>
<td>Pyramidal</td>
<td>4.0 (1.2)</td>
<td>3.5 (1.3)</td>
<td>t=0.9</td>
<td>22</td>
<td>.4</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>1.9 (1.6)</td>
<td>2.2 (1.5)</td>
<td>t=-0.5</td>
<td>22</td>
<td>.6</td>
</tr>
<tr>
<td>Brainstem</td>
<td>1.5 (1.6)</td>
<td>1.1 (1.2)</td>
<td>t=0.8</td>
<td>22</td>
<td>.4</td>
</tr>
<tr>
<td>Sensory</td>
<td>1.4 (1.6)</td>
<td>1.4 (1.1)</td>
<td>t=-0.04</td>
<td>22</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Bowel and bladder</td>
<td>1.5 (2.2)</td>
<td>1.2 (1.5)</td>
<td>t=0.4</td>
<td>22</td>
<td>.7</td>
</tr>
<tr>
<td>Visual</td>
<td>1.7 (1.8)</td>
<td>0.8 (1.1)</td>
<td>t=1.4</td>
<td>22</td>
<td>.2</td>
</tr>
<tr>
<td>Mentation</td>
<td>0.9 (0.9)</td>
<td>0.5 (0.5)</td>
<td>t=1.5</td>
<td>22</td>
<td>.2</td>
</tr>
<tr>
<td>Other</td>
<td>0.4 (0.5)</td>
<td>0.7 (0.6)</td>
<td>t=-1.4</td>
<td>22</td>
<td>.2</td>
</tr>
<tr>
<td>Duration of MS, y</td>
<td>10.4 (5.8)</td>
<td>12.2 (6.5)</td>
<td>t=-0.7</td>
<td>22</td>
<td>.5</td>
</tr>
<tr>
<td>Disease course</td>
<td>Relapsing-remitting 1</td>
<td>1</td>
<td>χ²=0.02</td>
<td>1</td>
<td>.9</td>
</tr>
<tr>
<td></td>
<td>Chronic-progressive 10</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PLC indicates pathological laughing and crying; EDSS, Expanded Disability Status Scale; and MS, multiple sclerosis.
## Table 2. Psychiatric Results for PLC and Control Subjects*

<table>
<thead>
<tr>
<th>Test Score</th>
<th>PLC Group, Mean (SD) (n=11)</th>
<th>Control Group, Mean (SD) (n=13)</th>
<th>t Test or Mann-Whitney U Test</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLACS score (range)</td>
<td>17.0 (10-23)</td>
<td>0 (0-12)</td>
<td>z=-4.2</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety score</td>
<td>8.5 (3.6)</td>
<td>6.8 (4.2)</td>
<td>t=0.9</td>
<td>21</td>
<td>.3</td>
</tr>
<tr>
<td>Depression score</td>
<td>7.1 (3.3)</td>
<td>7.5 (4.3)</td>
<td>t=-0.3</td>
<td>21</td>
<td>.8</td>
</tr>
<tr>
<td>GHQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety score</td>
<td>5.7 (2.4)</td>
<td>7.3 (4.1)</td>
<td>t=-1.1</td>
<td>21</td>
<td>.3</td>
</tr>
<tr>
<td>Somatic score</td>
<td>4.3 (2.5)</td>
<td>6.6 (4.2)</td>
<td>t=-1.5</td>
<td>21</td>
<td>.1</td>
</tr>
<tr>
<td>Social dysfunction score</td>
<td>10.1 (3.2)</td>
<td>10.6 (3.4)</td>
<td>t=-0.4</td>
<td>20</td>
<td>.7</td>
</tr>
<tr>
<td>Depression score</td>
<td>4.5 (5.2)</td>
<td>4.3 (5.6)</td>
<td>z=0.0</td>
<td></td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Total GHQ score</td>
<td>24.6 (9.9)</td>
<td>29.1 (14.4)</td>
<td>t=-0.8</td>
<td>20</td>
<td>.4</td>
</tr>
</tbody>
</table>

*PLC indicates pathological laughing and crying; PLACS, Pathological Laughing and Crying Scale; ellipses, not applicable; HAD, Hospital Anxiety and Depression Scale; and GHQ, General Health Questionnaire.
Pathological laughing and crying in MS: cognitive correlates

Pathological laughing and crying in multiple sclerosis: a preliminary report suggesting a role for the prefrontal cortex

A Feinstein*,1, P O’Connor2, T Gray2 and K Feinstein3

1Sunnybrook Hospital, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, University of Toronto, Canada; 2St. Michael’s Hospital, 30 Bond Street, Toronto, Ontario M5B 1W6, University of Toronto, Canada

As part of a wide ranging study investigating the prevalence, demographic and disease related characteristics of pathological laughing and crying (PLC) in multiple sclerosis (MS), a putative role for the prefrontal cortex was also explored. Eleven multiple sclerosis (MS) patients with carefully defined PLC were compared to a control group of 13 MS patients without PLC on various cognitive indices known to be sensitive to frontal lobe dysfunction. Although the two groups did not differ with respect to age, sex, physical disability, disease course, duration of MS, years of education, premorbid IQ, and depression, the PLC group performed more poorly on the Stroop test and a measure of verbal fluency. They also showed a trend to make more total errors on the Wisconsin Card Sort Test. The relevance of these findings to the pathogenesis of PLC is discussed, in particular whether the syndrome is, in part, mediated by dysfunction of the prefrontal cortex.

Keywords: multiple sclerosis; affect; mood; pathogenesis; psychometric; cognition
Frontally mediated cognitive tasks in PBA

<table>
<thead>
<tr>
<th>Task</th>
<th>PBA (n=11)</th>
<th>Non-PBA (n=13)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroop (secs)</td>
<td>44.7(12.1)</td>
<td>35.1(10.4)</td>
<td>p=.05</td>
</tr>
<tr>
<td>COWAT</td>
<td>28.1(8.10)</td>
<td>36.9(9.5)</td>
<td>p=.03</td>
</tr>
<tr>
<td>WCST-perseverative errors</td>
<td>17.5(12.2)</td>
<td>18.9(15.2)</td>
<td>p=.8</td>
</tr>
<tr>
<td>WCST-total errors</td>
<td>34.6(24.4)</td>
<td>29.7(16.6)</td>
<td>p=.5</td>
</tr>
<tr>
<td>WCST-categories completed</td>
<td>5.0(1.6)</td>
<td>5.4(1.0)</td>
<td>p=.5</td>
</tr>
</tbody>
</table>
PBA associated with more lesions in the following areas:

**Table:**

<table>
<thead>
<tr>
<th>Region</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global lesion volume</td>
<td>T2</td>
</tr>
<tr>
<td>Brain stem</td>
<td>T1</td>
</tr>
<tr>
<td>Medial inferior frontal L</td>
<td>T2</td>
</tr>
<tr>
<td>Medial inferior frontal R</td>
<td>T2</td>
</tr>
<tr>
<td>Medial superior frontal R</td>
<td>T2</td>
</tr>
<tr>
<td>Inferior parietal L</td>
<td>T2</td>
</tr>
<tr>
<td>Inferior parietal R</td>
<td>T2</td>
</tr>
</tbody>
</table>

**Abstract:** Pseudobulbar affect (PBA) is defined as episodes of involuntary crying, laughing, or both in the absence of a matching subjective mood state. This neuropsychiatric syndrome can be found in a number of neurological disorders including multiple sclerosis (MS). The aim of this study was to identify neuroanatomical correlates of PBA in multiple sclerosis (MS) using a case-control 1.5T MRI study. MS patients with (n = 14) and without (n = 10) PBA were matched on demographic, disease course, and disability variables. Correlated psychiatric disorders including depressive and anxiety disorders were absent. Hypo- and hyperintense lesion volumes plus measurements of atrophy were obtained and localized anatomically according to parcellated brain regions. Between-group statistical comparisons were undertaken with a set at 0.01 for the primary analysis. Discrete differences in lesion volume were noted in six regions: brainstem hypointense lesions, bilateral inferior parietal and medial inferior frontal hyperintense lesions, and right medial superior frontal hyperintense lesions. All significant higher in the PBA group. A logistic regression model identified four of these variables (brainstem hypointense, left inferior parietal hyperintense, and left and right medial inferior frontal hyperintense lesion volumes) that accounted for 70% of the variance when it came to explaining the presence of PBA. In conclusion, MS patients with PBA have a distinct distribution of brain lesions when compared to a matched MS sample without PBA. The lesion data support a widely-dispersed neural network involving frontal, parietal, and brainstem regions in the pathophysiology of PBA.

**Keywords:** multiple sclerosis - MRI - affect - mood
MRI data
Pseudobulbar Affect: Connecting the dots…
A mechanistic understanding on PBA: fitting the pieces together.

Pathological laughter and crying: insights from lesion network-symptom-mapping

Julian Klingbeil, Max Wawrzyniak, Anika Stockert, Max-Lennart Brandt, Hans-Ralf Schneider, Moritz Metelmann and Dorothee Saur
A mechanistic understanding of PBA: Lesion network-symptom-mapping

• Identified case reports of PBA associated with isolated lesions (n=70)
• Control group: stroke patients with isolated lesions and no PBA (n=270)
• Used normative connectome data (resting state fMRI n=100) to identify brain regions that were likely affected by diaschisis based on lesion location.
• The connectome maps neural pathways that underlie human brain function.
• Diaschisis (derived from Greek meaning “shocked throughout”) refers to a change in brain function linked to a distant structural brain abnormality.
• Identified a bilateral network characterized by positive and negative connectivity that differentiated people with and without PBA.
A mechanistic understanding of PBA: Lesion network-symptom-mapping

Positive connectivity
- Cingulate
- Temporo-medial cortices
- striatum
- Hypothalamus
- Mesencephalon
- Pons

Negative connectivity
- Primary motor cortex
- Primary sensory cortex

Periaqueductal grey in the brain stem controls and coordinated facial expression, respiration and vocalization.
The neuroanatomy of smiling: volitional versus emotional

Normal volitional facial movements
“Kodak smile”

Emotional palsy of the left side of the face when laughing
A mechanistic understanding of PBA: Lesion network-symptom-mapping

Emotional paresis (n=15)
- Preserved volitional facial movements
- Cannot trigger emotional facial movement
- Lesions predominantly map onto the positive PBA network

Volitional paresis (n=46)
- Preserved emotional facial movements
- Cannot voluntarily induce movements of smiling/crying
- Lesions predominantly map onto the negative PBA network.
A mechanistic understanding of PBA: Lesion network-symptom-mapping: A 2-hit model

A  The PLC network

B  'One hit' causing ...

C  Two-hit model of PLC

‘A combination of direct lesion and indirect diaschisis effects cause PLC through the loss of inhibitory cortical control of a dysfunctional emotional system.’
Exploration of the Neural Correlates of Ticklish Laughter by Functional Magnetic Resonance Imaging

Elise Wattendorf¹, Birgit Westermann², Klaus Fiedler¹, Evangelia Kaza³, Martin Lotze³ and Marco R. Celio¹

¹Anatomy and Program in Neuroscience, Department of Medicine, University of Fribourg, CH-1700 Fribourg, Switzerland,
²Department of Neurosurgery, University Hospital, University of Basel, CH-4031 Basel, Switzerland and ³Functional Imaging Unit, Diagnostic Radiology, University Hospital, University of Greifswald, D-17489 Greifswald, Germany

Address correspondence to Marco R. Celio, Anatomy and Program in Neuroscience, Department of Medicine, University of Fribourg, Rte A. Gockel 1, CH-1700 Fribourg, Switzerland. Email: marco.celio@unifr.ch.
Figure 4. Conjunction analysis and effect size. Increased significance of hypothalamic activation in response to T versus I and versus L (a: sagittal paramedian; b: axial; c: frontal; P < 0.005 [uncorrected]). Parameter estimates (beta values) that were derived from the peaks of activity confirmed a higher level in this region during T than during either I or L (bar graph). Activity is also apparent in the amygdala (Amy) and in the somatosensory area representing the foot (Foot). The statistical maps are superimposed on an MNI-normalized image of the brain. Error bars indicate the 90% confidence interval.
## Major Depression and Pseudobulbar Affect: Comparison of MRI variance

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depression</td>
<td>40%</td>
</tr>
<tr>
<td>Pathological laughing and crying</td>
<td>~ 75%</td>
</tr>
</tbody>
</table>
1. Treatment of pseudobulbar affect

TREATMENT OF PATHOLOGIC LAUGHING AND WEEPING WITH AMITRIPTYLINE
RANDOLPH B. SCHIFFER, M.D., ROBERT M. HERNDON, M.D., AND RICHARD A. RUDICK, M.D.

Abstract Patients with bilateral forebrain disease may commonly manifest the syndrome of pathologic laughing and weeping. We investigated the efficacy of low-dose amitriptyline in 12 patients in whom this syndrome was a consequence of multiple sclerosis. In a double-blind crossover study comparing amitriptyline with placebo, eight patients experienced dramatic and significant improvement with amitriptyline (P = 0.02). The mean dose of amitriptyline was 57.8 mg per day and did not exceed 75 mg per day in any patient. Concurrent measurements of depression showed no change during the study.

We conclude that amitriptyline is effective in the treatment of this disturbance of affective expression, and that this effect is distinct from the antidepressant effect of the medication. (N Engl J Med 1985; 312:1480-2.)

Table 1. Clinical Features of 12 Patients with Emotional Lability and Multiple Sclerosis.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Gen</th>
<th>Lability</th>
<th>Multiplc Sclerosis</th>
<th>Ambulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type</td>
<td>Duration</td>
</tr>
<tr>
<td>1</td>
<td>48/F</td>
<td>Laughing</td>
<td>1 yr</td>
<td>10 yr</td>
</tr>
<tr>
<td>2</td>
<td>33/F</td>
<td>Laughing</td>
<td>1 yr</td>
<td>7 yr</td>
</tr>
<tr>
<td>3</td>
<td>50/F</td>
<td>Mixed</td>
<td>1 yr, 6 mo</td>
<td>6 yr, 3 mo</td>
</tr>
<tr>
<td>4</td>
<td>41/F</td>
<td>Weeping</td>
<td>1 yr</td>
<td>14 yr</td>
</tr>
<tr>
<td>5</td>
<td>48/M</td>
<td>Weeping</td>
<td>6 mo</td>
<td>10 yr, 10 mo</td>
</tr>
<tr>
<td>6</td>
<td>34/F</td>
<td>Weeping</td>
<td>1 yr</td>
<td>11 yr</td>
</tr>
<tr>
<td>7</td>
<td>65/M</td>
<td>Weeping</td>
<td>1 yr, 6 mo</td>
<td>25 yr</td>
</tr>
<tr>
<td>8</td>
<td>33/M</td>
<td>Mixed</td>
<td>1 yr, 3 mo</td>
<td>11 yr</td>
</tr>
</tbody>
</table>

Responders *

<table>
<thead>
<tr>
<th>Nonresponders *</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>12</td>
</tr>
</tbody>
</table>

*According to consensus of clinical judgment.

Table 2. Response to Amitriptyline.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>No. of Episodes of Laughing or Weeping per Week</th>
<th>Order of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AT BASE LINE</td>
<td>DURING PLACEBO</td>
</tr>
<tr>
<td>Responder</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td>6</td>
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</tr>
<tr>
<td></td>
<td>7</td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Continuous</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>3/interview</td>
</tr>
</tbody>
</table>
2. Treatment of pseudobulbar affect

**Case Report**

**Treatment of Pathological Crying with Citalopram**

W. P. Kaschka, A. Meyer, K. R. Schier, W. Fröscher

1 University of Ulm, Department of Psychiatry I, Weissenau Psychiatric Hospital, Ravensburg, Germany
2 University of Ulm, Department of Neurology and Epileptology at the Weissenau Psychiatric Hospital, Department of Psychiatry I, Ravensburg, Germany

**Brain Injury**

Paroxetine versus citalopram treatment of pathological crying after brain injury

Ulrich Muller, Toshiya Murai, Thomas Bauer-Wittmud & D. Yves Von Cramon

**Case Report**

Mirtazapine Treatment for Pathological Laughing and Crying After Stroke

Sung-Wan Kim, MD,† Il-Seon Shin, MD, PhD,‡ Jee-Min Kim, MD, PhD,§ So-Yeon Lim, MD,* Su-Jin Yang, MD, PhD,* and Jin-Sang Yoon, MD, PhD†

**Journal of Clinical Movement Disorders**

DOI 10.1186/s40734-015-0023-6

**CASE REPORT**

Pseudobulbar laughter as a levodopa off phenomenon exacerbated by subthalamic deep brain stimulation

P. K. Chattha, P. E. Greene and Ritesh A. Ramdhan
A mechanistic explanation for antidepressant efficacy in PBA.
Serendipity in medicine

• Serendipity is one of the many factors that may contribute to drug discovery, ie., penicillin, lysergic acid diethylamide, meprobamate, chlorpromazine, imipramine, iproniazid, sildenafil, chlordiazepoxide and AVP-923.

• Dialogues Clin Neurosci. 2006;8:335-344.

• Mechanism of Action of AVP
• AVP is an oral formulation of dextromethorphan hydrobromide (an uncompetitive NMDA receptor antagonist and sigma-1 agonist) and quinidine sulphate (a CYP450 2D6 inhibitor).
• Regulates excitatory neurotransmission in two ways.
  • Presynaptic inhibition of glutamate release via sigma-1 agonist activity
  • Postsynaptic glutamate response modulation via uncompetitive low-affinity NMDA antagonist activity.
3. Treatment of pseudobulbar affect

AVP-923

Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine

A randomized trial

B.R. Brooks, MD; R.A. Thaised, PhD; S.H. Appel, MD; W.G. Bradley, DM, FRCP; R.K. Olney, MD; J.E. Berg, RA; L.E. Pope, PhD. and R.A. Smith, MD, for the AVP-923 ALS Study Group.

Abstract—Background: Patients with ALS commonly exhibit pseudobulbar affect. Methods: The authors conducted a multicenter, randomized, double-blind, controlled, parallel, three-arm study to test a defined combination of dextromethorphan hydrobromide (DM) and quinidine sulfate (Q) (AVP-923) for the treatment of pseudobulbar affect in ALS. Q inhibits the rapid first-pass metabolism of DM. The effects of AVP-923 (30 mg of DM plus 30 mg of Q) given twice daily for 28 days were compared with those of its components. Patients were evaluated on days 1, 15, and 28. The primary efficacy variable was the change from baseline in the Center for Neurologic Study Lability Scale (CNS-LS) score. Secondary efficacy variables were laughing/crying episode rates and changes in Visual Analog Scales for Quality of Life (QOL) and Relationships (QOR). Efficacy was evaluated in intention-to-treat subjects who were not poor metabolizers of DM (n = 66 for AVP-923, n = 39 for DM, and n = 34 for Q). Safety was assessed in all randomized subjects (n = 140). Results: AVP-923 patients experienced 3.5-point greater improvements in CNS-LS than DM patients (p = 0.001) and 3.3-point greater improvements than Q patients (p < 0.001). AVP-923 patients exhibited lower overall episode rates, improved QOL scores, and improved QOR scores (p < 0.02 for all endpoints). Adverse effects were mostly mild or moderate; treatment-related discontinuation was 24% for AVP-923, 6% for DM, and 9% for Q. Conclusions: AVP-923 palliates pseudobulbar affect in ALS. Overall benefits of treatment are reflected in fewer episodes of crying and laughing and improvements in overall quality of life and quality of relationships.

Table 2 Efficacy assessments: ITT cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AVP-923</th>
<th>DM</th>
<th>Q</th>
<th>AVP-923 vs DM</th>
<th>AVP-923 vs Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS-LS</td>
<td>7.4</td>
<td>0.6</td>
<td>4.1</td>
<td>0.9</td>
<td>3.7</td>
</tr>
<tr>
<td>QOL</td>
<td>24.1</td>
<td>2.5</td>
<td>11.2</td>
<td>3.6</td>
<td>12.2</td>
</tr>
<tr>
<td>QOR</td>
<td>22.6</td>
<td>2.4</td>
<td>6.6</td>
<td>3.4</td>
<td>8.6</td>
</tr>
</tbody>
</table>

DM vs AVP-923 Q vs AVP-923

<table>
<thead>
<tr>
<th>Episode rate</th>
<th>Ratio</th>
<th>95% CI</th>
<th>Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>1.89</td>
<td>1.23-2.90</td>
<td>2.13</td>
<td>1.44-3.16</td>
<td>0.004</td>
</tr>
<tr>
<td>Crying</td>
<td>1.98</td>
<td>1.20-3.27</td>
<td>3.32</td>
<td>2.06-5.33</td>
<td>0.007</td>
</tr>
<tr>
<td>Laughing</td>
<td>1.49</td>
<td>0.87-2.54</td>
<td>1.63</td>
<td>1.00-2.67</td>
<td>0.142</td>
</tr>
</tbody>
</table>
4. Treatment of pseudobulbar affect

Randomized, Controlled Trial of Dextromethorphan/Quinidine for Pseudobulbar Affect in Multiple Sclerosis

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Objective: To evaluate the efficacy and safety of DMI/Q (capsules containing dextromethorphan [DM] and quinidine [Q]) compared with placebo, taken twice daily, for the treatment of pseudobulbar affect over a 12-week period in multiple sclerosis patients.

Methods: A total of 150 patients were randomized in a double-blind, placebo-controlled study to assess pseudobulbar affect with the validated Center for Neurologic Study-Lability Scale. Each patient also recorded the number of episodes experienced between visits, estimated quality of life and quality of relationships on visual analog scales, and completed a pain rating scale.

Results: Patients receiving DMI/Q had greater reductions in Center for Neurologic Study-Lability Scale scores than those receiving placebo (p < 0.0001) at all clinic visits (days 15, 29, 57, and 85). All secondary end points also favored DMI/Q, including the number of crying or laughing episodes (p ≤ 0.0077), quality of life (p < 0.0001), quality of relationships (p = 0.0001), and pain intensity score (p = 0.0271). DMI/Q was well tolerated; only dizziness occurred with greater frequency than with placebo.

Interpretation: Results in multiple sclerosis patients were similar to those of a previous study in amyotrophic lateral sclerosis, demonstrating that DMI/Q may be beneficial in treating potentially disabling pseudobulbar affect in a variety of neurological disorders.

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Fig 2. Improvement in Center for Neurologic Study-Lability Scale (CNS-LS) score from baseline by study day. Values shown are least squares means, adjusting for baseline levels and center effects. AVP-923 was the study code number for DMI/Q (capsules containing dextromethorphan [DM] and quinidine [Q]).
Pseudobulbar affect: timing of response to treatment

- **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 |
Conclusions

• Laughter and crying can occur without corresponding subjective mood states in a number of neurological diseases.
• The diagnosis may be overlooked and the phenomenology incorrectly attributed to a primary psychiatric illness like depression.
• It arises in response to widespread, abnormal brain activity involving both voluntary (motor) and involuntary (emotional) neural pathways that become dysfunctional.
• It can significantly disrupt quality of life.
• It can generally be well treated with a choice of pharmacologic interventions.
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