ADDING INSULT TO INJURY: THE CHALLENGE OF PSEUDOBULBAR AFFECT
Learning Objectives

• Recognize the neuropathology hypothesized to underlie PBA

• Implement evidence-based treatment strategies for patients with PBA
Pseudobulbar Affect Disorder (PBA)

- PBA is characterized by uncontrollable, inappropriate laughing and/or crying
- Patients with PBA often have:
  - Increased risk of depression and anxiety
  - Decreased quality of life
  - Impaired social interaction (due to embarrassment)

Occurs in the context of brain injury, including TBI, stroke, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS)

A Rose By Any Other Name Is...Distracting

- Affective lability
- Emotional dyscontrol
- Emotional dysregulation
- Emotional incontinence
- Emotional lability
- Emotionalism
- Excessive emotionality
- Forced laughter or crying
- Inappropriate hilarity
- Involuntary emotional expression disorder
- Labile affect
- Pathological affect
- Pathological laughter and crying
- Pathological weeping
- Pseudobulbar crying

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Need for PBA Guidelines

- Inconsistent use of terminology results in debate and confusion
- Involuntary Emotional Expression Disorder (IEED) is a medically accurate and unifying term
- For differential diagnosis of IEED, most important step is distinguishing crying as part of IEED versus crying in the context of a depressed mood
- In the literature on IEED, a distinction has been made between mood (defined as internal state) and affect (defined as external physical manifestations of emotion)
- This is confounded by labeling some mood disorders (e.g., bipolar, MDD) as affective disorders

Involuntary Emotional Expression Disorder (IEED)

• Core clinical feature of IEED is involuntary outbursts of crying/laughing
• Emotional outbursts have shared common features:
  - Outbursts are stereotyped
  - Mood incongruent, with an intensity out of proportion to the stimulus
  - Episodic, with a return to baseline upon conclusion
• Episodes of IEED may be accompanied by signs of pseudobulbar palsy (PBP): hyperactive jaw, facial reflexes, dysarthria
• Autonomic, respiratory, and vocal changes may occur in IEED
• Bulbar involvement in any disorder is followed by deterioration of the voice, difficulties in phonation, mastication, articulation, and respiration
• Affect changes, especially episodic anger

Symptoms of Disordered Emotional Expression

- Pathological laughing
- Pathological crying
- Labile affect
- Irritability
- Temper
- Disinhibition
- Aggression
- Impulsivity
- Unpredictable and rapidly changing emotions

Potential psychiatric conditions with disordered emotional expression due to dysfunction of the same brain circuits underlying pseudobulbar affect: loss of top-down control of bottom-up emotional drives

- Traumatic brain injury (symptoms of emotional dyscontrol beyond pathological laughing and crying)
- Dementia (neuropsychiatric and behavioral symptoms of dementia, especially agitation, and not just pathological laughing and crying)
- PTSD (symptoms of impulsivity and self-harm)
- Borderline personality disorder (symptoms of impulsivity and self-harm)
- Major depression, depression with mixed features, and bipolar depression, especially treatment-resistant; suicidality

Miscellaneous impulsive compulsive disorders:
- Impulsive violence
- Intermittent explosive disorder
- Impulsive gambling, binge eating, Internet use
- Impulsive/compulsive substance abuse
- Impulsive attention deficit hyperactivity disorder (ADHD)
- Oppositional defiant disorder (ODD)
- Disruptive mood dysregulation/ temper tantrums

PBA Registry Series (PRISM) Data

Brooks BR et al. PLOS One 2013;8(8):e72232.
<table>
<thead>
<tr>
<th>Table 2 Diagnostic criteria for pseudobulbar affect</th>
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<tbody>
<tr>
<td><strong>Poeck (1969)</strong></td>
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<tr>
<td>The emotional response is situationally inappropriate</td>
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<tr>
<td>The patient’s feelings and the affective response are not closely related</td>
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<tr>
<td>The duration and severity of the episodes cannot be controlled by the patient</td>
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<tr>
<td>Expression of the emotion does not lead to a feeling of relief</td>
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<tr>
<td><strong>Cummings (2006): necessary elements of the episodes</strong></td>
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<tr>
<td>A change from previous emotional responses</td>
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<tr>
<td>Inconsistent with or disproportionate to mood</td>
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<tr>
<td>Not dependent on a stimulus, or excessive relative to that stimulus</td>
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<tr>
<td>Cause significant distress or social/occupational impairment</td>
</tr>
<tr>
<td>Not accounted for by another psychiatric or neurologic disorder</td>
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<tr>
<td>Not due to a drug</td>
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Distinguishing Between PBA and Depression

- PBA is often underrecognized, misdiagnosed, and undertreated
  - Only 40% of individuals who discuss PBA symptoms with a clinician are diagnosed
- PBA is a disorder of affect (the expression of mood), not mood itself
- Often mistaken for depression
  - Duration of PBA episode is shorter (seconds vs. weeks)
  - Crying is not congruent with subjective mood
  - Other symptoms of depression (e.g., fatigue, anhedonia, hopelessness, guilt) are not associated with PBA
  - PBA generally responds faster to pharmacotherapy
- Can be comorbid with major depressive disorder (MDD), making it difficult to diagnose
- Ictal laughing and crying can also be signs of complex partial epilepsy
  - Usually accompanied by alterations in consciousness

Distinguishing Between PBA and Depression

PBA
- Brief episodes (seconds to minutes)
- Sudden, abrupt, no wind down
- Uncontrollable
- Exaggerated reaction or independent of mood

Crying

Depression
- Tonic mood (last weeks to months)
- Ongoing sadness or diminished interest
- Crying not well characterized
- Emotional expression matches patient’s mood
Distinguishing Between Bipolar Disorder and PBA

• PBA may be associated with bipolar disorders, especially with rapid cycling or mixed mood episodes

• Laughing or crying episodes are briefer

• No disturbances between episodes

  • Mood, cognition, and behavior show sustained changes in bipolar disorders

Screening for PBA: CNS-LS

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 suggest 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>
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</table>

Assessment questions

1. There are times when I feel fine 1 minute, and then I’ll become fearful the next over something small or for no reason at all.
2. Others have told me that I seem to become annoyed very easily or that I seem to become annoyed 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 funny 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.

Total Score:

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

Neurobiology of PBA

- Involves the cortico-pontine-cerebellar circuit
  - Includes motor, limbic, and association cortices
  - Descending pathways to brainstem, basis pontis, and cerebellum
    - The basis pontis is a convergence point for descending input to the cerebellum

- Pseudobulbar affect:
  - Inhibition from sensory cortices to motor and limbic cortices is reduced
  - Results in disinhibition of the cerebellar gate-control

PBA Pathophysiology

- Involves neural network of frontal lobes, limbic system, brainstem, cerebellum, or interconnecting white matter tracts of this network
- Cerebellum appears to play a much greater role than was previously hypothesized
- Cerebellum - key role in modulating emotional responses, based on input from cerebral cortex
- Disruption of the corticopontine–cerebellar circuits results in impairment of this cerebellar modulation
- Variety of neurotransmitters are involved: NE, DA, 5-HT, glutamate, and acetylcholine
Gate-Control Theory of Emotional Expression

Contextual information sent from cortex

Emotionally congruent response scaled and produced by cerebellum

• Golgi cells are thought to perform gating function on cerebellar output

• Axons from Purkinje cells project to deep cerebellar nuclei

• Parallel fibers transmit info from granule cells to Purkinje cells

• Granule cells receive input from pontine nuclei (via mossy fibers)

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Neurobiology of PBA

- Neurotransmitters/neuromodulators involved may include:
  - 5HT
  - Glutamate
  - Norepinephrine
  - Dopamine
  - Acetylcholine
  - GABA
  - Adenosine
  - Corticotropin-releasing hormone
  - Corticosteroids

Hypothesized Mechanisms of Dextromethorphan Action

- These receptors/systems are all implicated in the function of the brainstem and descending pathways relevant to PBA

- Agonist at sigma-1 receptors

- Blocks NMDA glutamate receptors

- Inhibits serotonin and norepinephrine reuptake

Why Quinidine?

- Quinidine inhibits the cytochrome P450 2D6 enzyme that metabolizes dextromethorphan, increasing the bioavailability of dextromethorphan 20-fold

Dextromethorphan-Quinidine in PBA Associated with Multiple Sclerosis

CNS-LS: Center for Neurologic Study–Lability Scale
AVP-923: Code name for dextromethorphan-quinidine

Dextromethorphan-Quinidene in PBA Associated with Amyotrophic Lateral Sclerosis

Low-Dose Dextromethorphan-Quinidine in PBA Associated with MS or ALS

Treatment Options for PBA

• Antidepressants:
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Tricyclic Antidepressants (TCAs)
• Can help reduce the frequency and severity of PBA episodes
• Typically prescribed at lower doses than for depression
• Evidence supporting the efficacy of these agents is limited and further research is needed
• Dextromethorphan hydrobromide/ quinidine sulfate (Neudexta) is the only FDA-approved medication designed specifically to treat PBA

Summary

• Pseudobulbar affect may result from damage to brain circuitry that includes motor, limbic, and association cortices as well as descending pathways to the brainstem, basis pontis, and cerebellum.

• Effective differential diagnosis should result in improved treatment for PBA.

• Numerous neurotransmitter/neuromodulator systems may be disrupted in pseudobulbar affect.

• Dextromethorphan-quinidine is the only agent FDA-approved for the treatment of pseudobulbar affect.

• The efficacy of dextromethorphan in the treatment of pseudobulbar affect is hypothetically related to its actions on sigma-1 and NMDA receptors as well as serotonin and norepinephrine reuptake transporters.