

Pseudobulbar Affect

Clinical Picture and Diagnosis



What Is Crying?



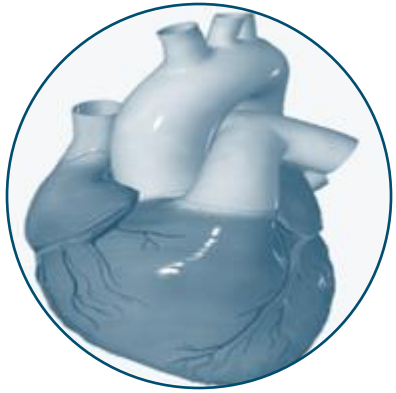
Why Do We Cry?

Crying is described as *“the shedding of tears, from the lacrimal apparatus ... Only humans cry with tears in response to emotional events”*¹

Crying can act as

- A communication tool²
 - Elicits helping behavior from others through verbal and nonverbal cues
- An emotional relief³
 - Considered cathartic and reduces tension in individuals
- An indicator of joy³
 - Can be associated with positive emotions and feelings of overwhelmed joy, elation, or gratitude

Historical Views of Crying



1500 BC

Tears were described as the byproduct of weakened materials in the heart turning into water¹

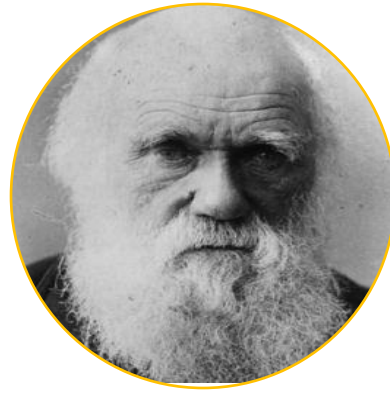
1600s

Emotions like love were believed to heat the heart, which generated water vapor to cool itself down. When the vapor cooled near the eyes, tears formed¹



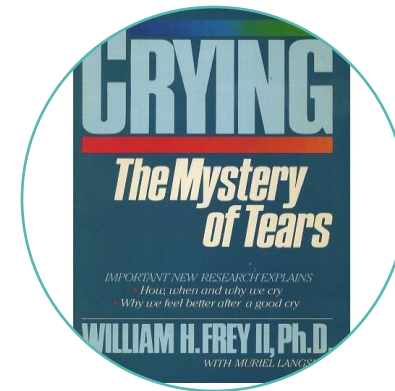
1800s

Charles Darwin described crying as a mere side effect of facial muscle contractions²



1985

William Frey hypothesized crying as a method to remove toxic substances in blood due to stress³



Present

While the reasons for why we cry are still up for debate, researchers conclude that crying is a very important form of communication⁴



The Neurocircuitry of Normal Laughing and Crying

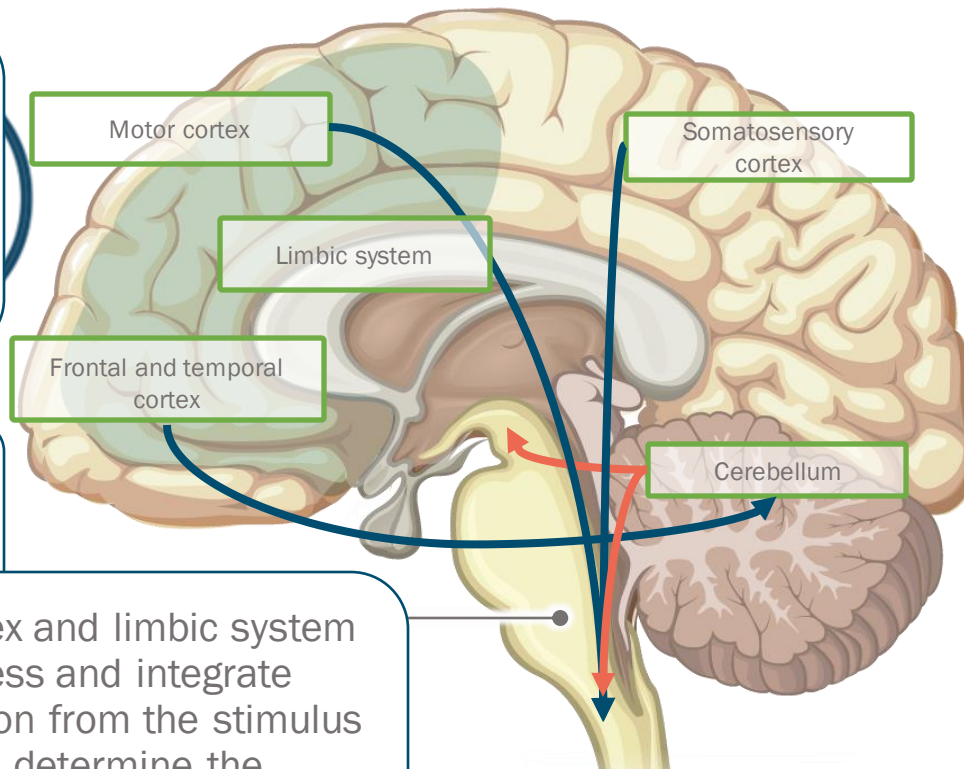
The cortico-pontine-cerebellar (CPC) network involves the¹:

- Cerebral cortex and limbic system
- Pons and other areas of the brain stem
- Cerebellum

The CPC network is responsible for emotional expression and may play a role in PBA²

Through the normal process, a stimulus results in

The cortex and limbic system process and integrate information from the stimulus and determine the appropriate emotional response^{1,2}



Areas in the brain stem integrate and relay this information to activate emotional motor systems—the somatic and visceral motor responses³

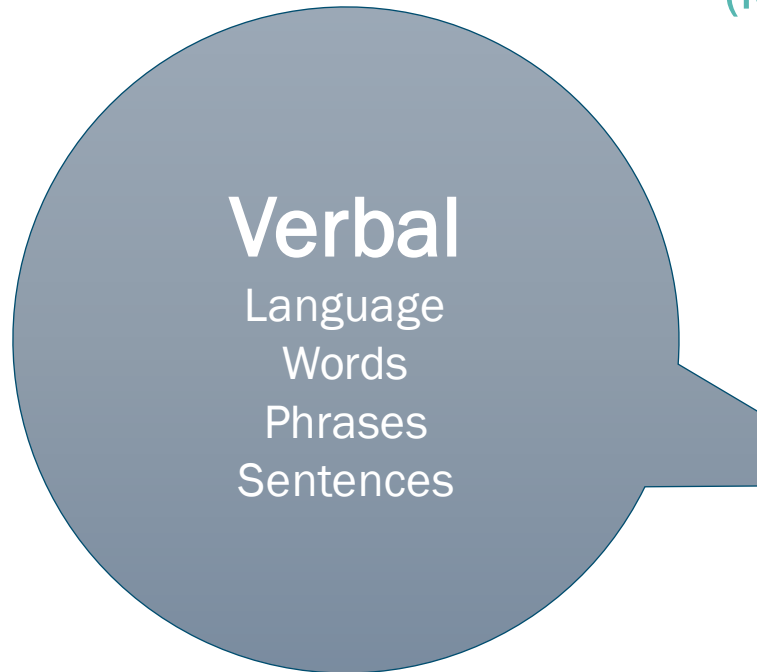
The cerebellum further modulates the response to ensure its appropriateness for the situation¹

➡ Emotional motor expression

➡ Cerebellar input

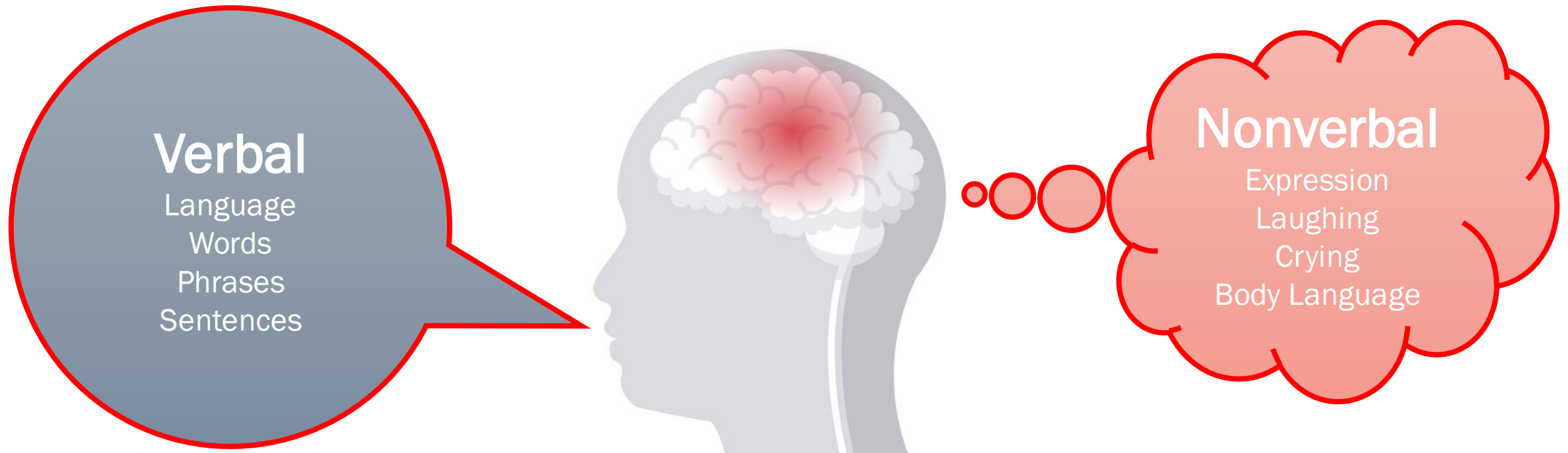
We Communicate Emotions in Several Ways

The two overarching ways of communication are verbal and nonverbal
(ie, communicating how we think and feel)^{1,2}



Injuries That Alter Brain Physiology May Affect How an Individual Communicates

Injuries to the brain can disrupt how a patient communicates emotions¹

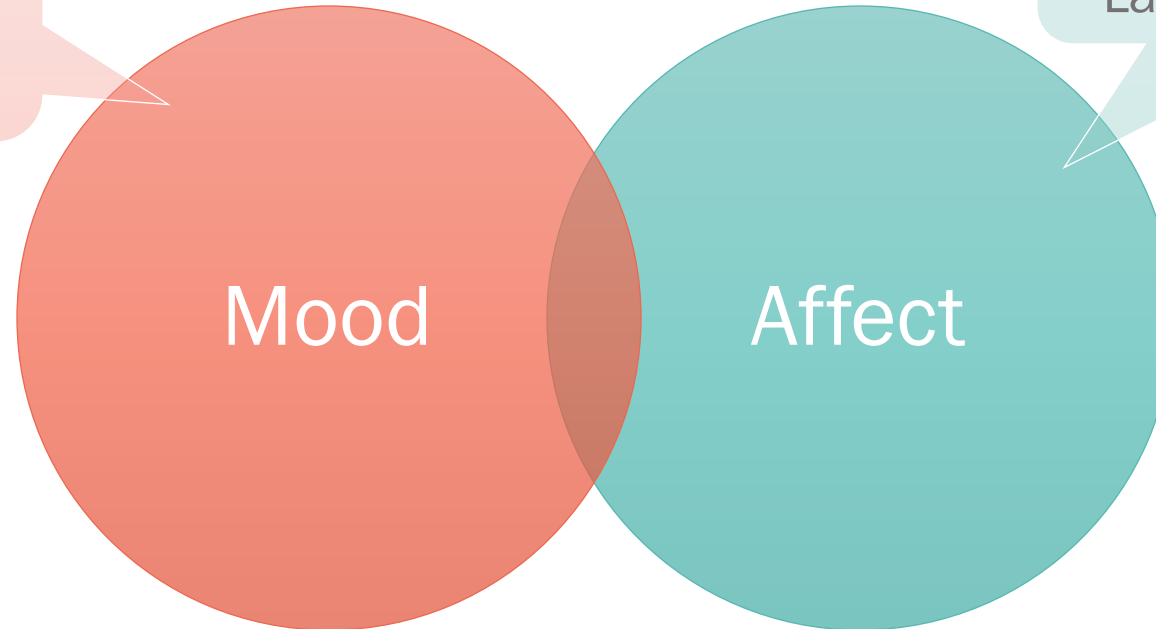


Patient affect that is incongruent to mood can be a distinguishing feature of pseudobulbar affect (PBA)²

What Is the Difference Between Mood and Affect?

Pervasive and sustained emotional state or “emotional baseline”

- **How we feel:** Sad, happy



Expression of how we feel at a given moment

- Laughing, crying

PBA: A Disease That Disrupts Emotional Expression



ARS Question

How familiar are you with PBA?

1. Not very
2. Somewhat familiar
3. Familiar
4. Very familiar

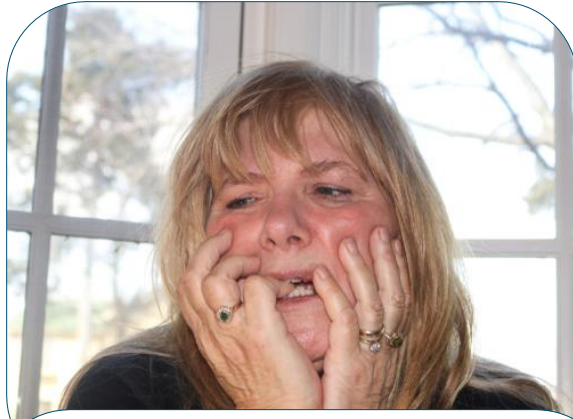
PBA Is...



- A neurologic disorder that involves frequent, sudden, and uncontrollable crying and/or laughing^{1,2}
- A condition that occurs secondary to neurologic disease or injury, including^{1,3,4}
 - Dementias, including Alzheimer's disease (AD)
 - Stroke
 - Traumatic brain injury (TBI)
 - Multiple sclerosis (MS)
 - Parkinson's disease (PD)
 - Amyotrophic lateral sclerosis (ALS)
 - Brain tumor
 - Hypoxia

PBA Is More Than What We See^{1,2}

A PBA diagnosis is not just what we see...



...but also what patients say.

“Once I start crying, I can’t seem to stop.”

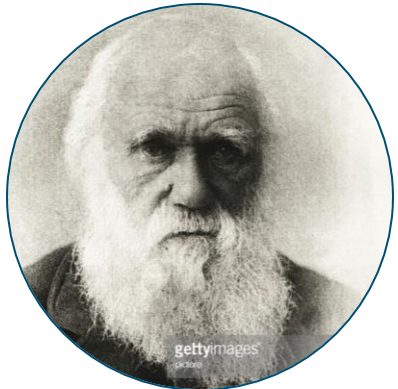
PBA is often categorized

“Something may be slightly funny, but I will just start laughing hard.”

episodes.

“I don’t really know why I’m crying.”

PBA Is Not New



1872

Charles Darwin describes the condition: "Certain brain diseases, such as hemiplegia, brain-wasting, and senile decay, have a special tendency to induce weeping"¹



1924

S.A.K. Wilson offers the first comprehensive clinical description of "pathological laughing and crying" (PLC) syndrome²



1969

K. Poeck suggests diagnostic criteria³



1993

R.G. Robinson publishes a rating scale for pathological laughter and crying following stroke⁴



2006

J. Cummings provides updated criteria clarifying the distinction between mood vs affect and suggesting stimuli may provoke PBA episodes⁵



1886

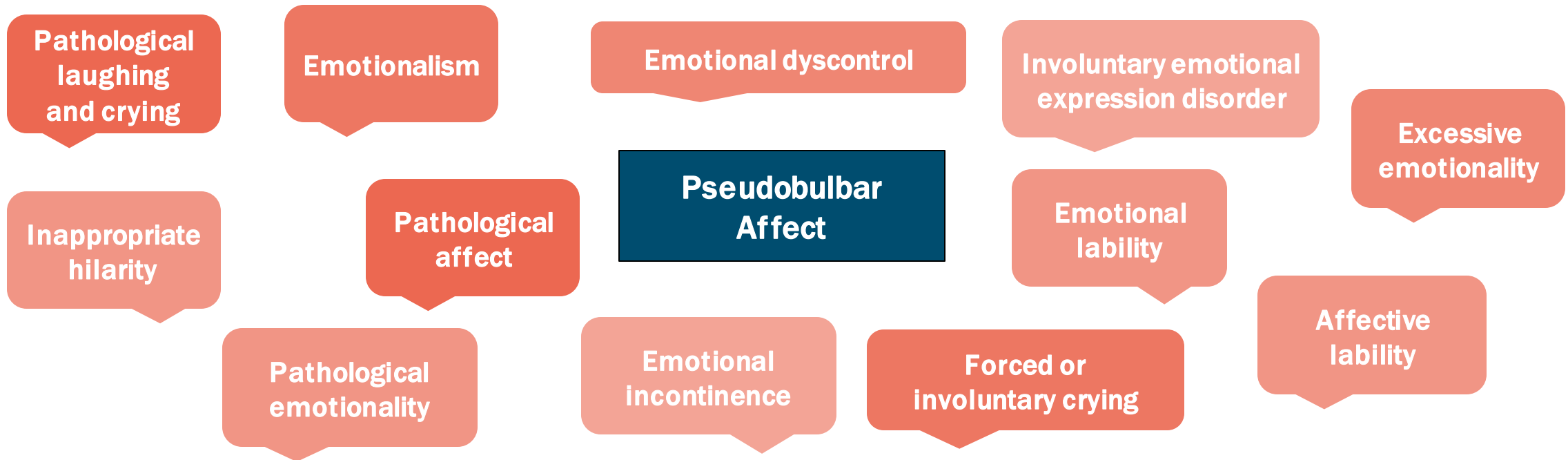
H. Oppenheim coins the term "pseudobulbar affect" to differentiate symptoms that would typically be associated with bulbar palsy¹

Image source: my.clevelandclinic.org/staff

1. Suave WM. *CNS Spectr.* 2016;21:37-43. 2. Wilson SAK. *J Neuro Psychopathol.* 1924;4(16):299-333. 3. Poeck K. Pathophysiology of emotional disorders associated with brain damage. In: Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology.* New York, NY: John Wiley & Sons, Inc.; 1969:343-367. 4. Robinson RG et al. *Am J Psychiatry.* 1993;150(2):286-292. 5. Cummings JL. *CNS Spectr.* 2006;11:1-7.

Terminology for PBA Has Been Inconsistent^{1,2}

- Many terms have been used to describe PBA, but these are not necessarily synonymous or interchangeable^a



^aThese terms are not always synonymous with pseudobulbar affect.

1. Cummings JL et al. *CNS Spectr.* 2006;11:6 (Suppl 6). 2. Miller A et al. *Exp Rev Neurother.* 2011;11(7):1077-1088.

PBA Is Characterized by...

1 Episodes of crying or laughing that are:

Sudden

“When I cry, it comes on without any warning”

Frequent

“She does it a number of times each week”

Uncontrollable

“I want to stop laughing, but I can’t”



PBA Is Characterized by...

- 2 Episodes that may or may not match a patient's feeling or stimulus¹

Crying or laughing may be:

Exaggerated—excessive or out of proportion to mood

“I can't help making so much noise when I cry...it's embarrassing.”

Incongruent—inappropriate or inconsistent with mood

“I cry over the slightest thing ... people have started to watch what they say around me.”

- The expressions of these characteristics of crying can vary substantially among PBA patients^{2,3}



ARS Question

Which of these phrases is rarely used to describe PBA episodes of laughing or crying?

1. Sudden
2. Predictable
3. Uncontrollable
4. Frequent
5. Exaggerated
6. Incongruent

Estimating the Prevalence of PBA

- The PBA Registry Series (PRISM) was designed to estimate the prevalence of PBA in a large sample of patients diagnosed with 6 neurological conditions known to be associated with PBA¹
 - At multiple US sites, investigators offered patients the opportunity to participate in the PRISM study if patients were ≥ 18 years of age and diagnosed with AD, ALS, MS, PD, stroke, or TBI
 - PBA symptoms were measured by the Center of Neurologic Study-Lability Scale (CNS-LS); CNS-LS score ≥ 13 identified presence of PBA symptoms
 - At the close of enrollment, 173 sites had enrolled 5290 patients
 - 34.0% with AD; 2.4% with ALS; 23.0% with MS; 15.2% with PD; 14.3% with stroke; 11.2% with TBI
- CNS-LS is a self-report assessment used to measure PBA symptom frequency and severity²
 - Validated in patients with MS and ALS
 - Score ≥ 13 suggests the presence of PBA symptoms and warrants further assessment

CNS-LS Is a Screening Tool to Measure PBA Symptoms

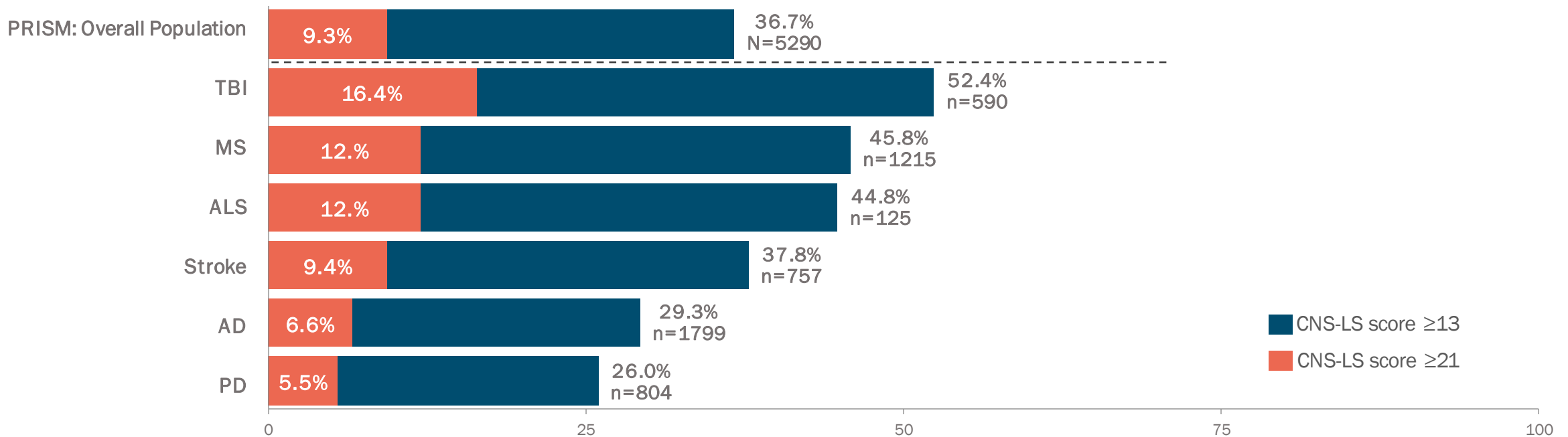
CNS-LS has been validated in ALS and MS patients^{1,2}

- In patients with ALS, a CNS-LS score of ≥ 13 correctly predicted a diagnosis of PBA for 82% of patients (N=99)¹
 - Sensitivity=0.84; specificity=0.81
- In patients with MS, a CNS-LS score of ≥ 13 correctly predicted a diagnosis of PBA for 78% of patients (N=90)²
 - Sensitivity=0.96; specificity=0.55
- A CNS-LS score of ≥ 17 correctly predicted 89% of PBA diagnoses in MS patients²
 - Sensitivity=0.94; specificity=0.83

PBA Symptoms Occur More Than You Think

- In the PRISM study (N=5290 enrolled), an estimated 37% of patients with 6 common underlying neurologic disorders* experienced symptoms of PBA (CNS-LS score ≥ 13 [†])

PBA Symptoms in Patients With Common Neurologic Conditions



*AD, ALS, MS, PD, stroke, or TBI.

[†]A CNS-LS score ≥ 13 is suggestive of PBA symptoms and merits further diagnostic assessment.

CNS-LS, Center for Neurologic Study-Lability Scale.

Brooks BR et al. *PLoS One*. 2013;8:e72232.

ARS Question

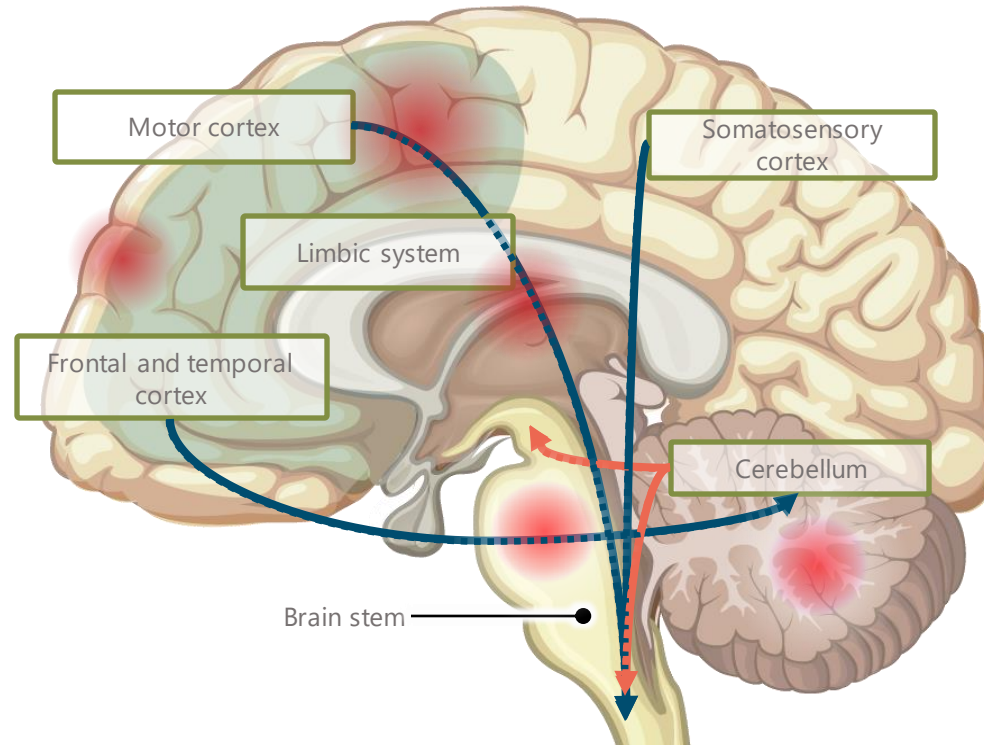
How many patients with PBA have you diagnosed or managed in the last year?

1. 0
2. 1-2
3. 3-4
4. 5-8
5. 9+

Pathophysiology of PBA— Involuntary Laughing and Crying

Brain lesions resulting from various neurological diseases or injuries may disrupt the function of the CPC¹

Damage to any part of one or more areas of the CPC can affect emotional expression^{1,2}



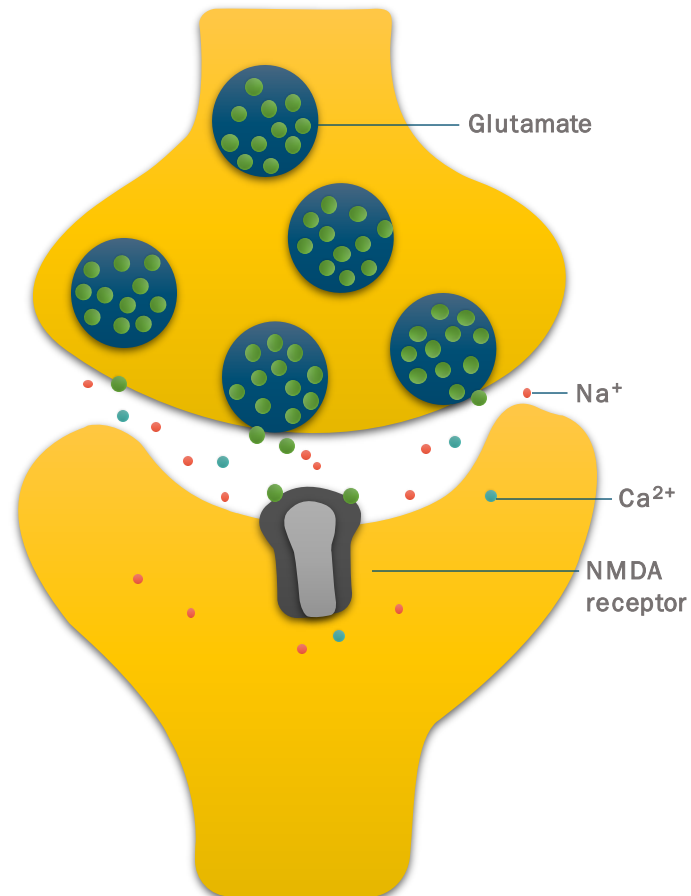
Disruption of neurotransmitter activity along the damaged pathways may contribute to PBA episodes²

➡ Emotional motor expression

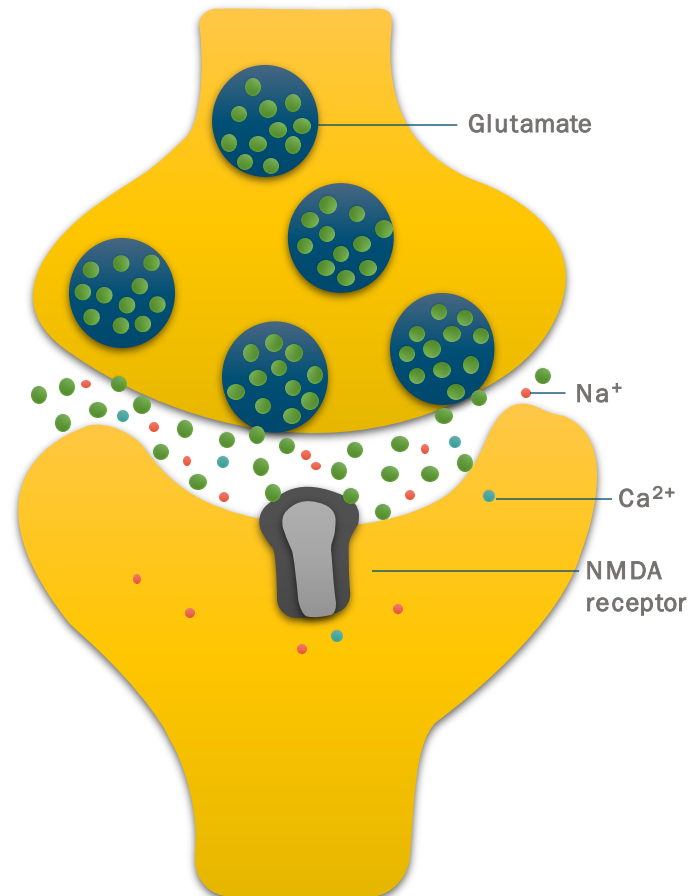
➡ Cerebellar input

PBA May Involve a Disruption of Normal Glutamate Signaling

Normal Glutamate Signaling:
Glutamate neurotransmitter receptors (eg, NMDA) facilitate multiple neurologic functions, including emotional expression^{1,2}



Abnormal Glutamate Signaling:
Brain lesions, cell damage, and other pathologies can lead to excess glutamate and excessive activation of glutamate receptors^{1,3}



As a result, abnormal neurotransmission and cell dysfunction can occur³

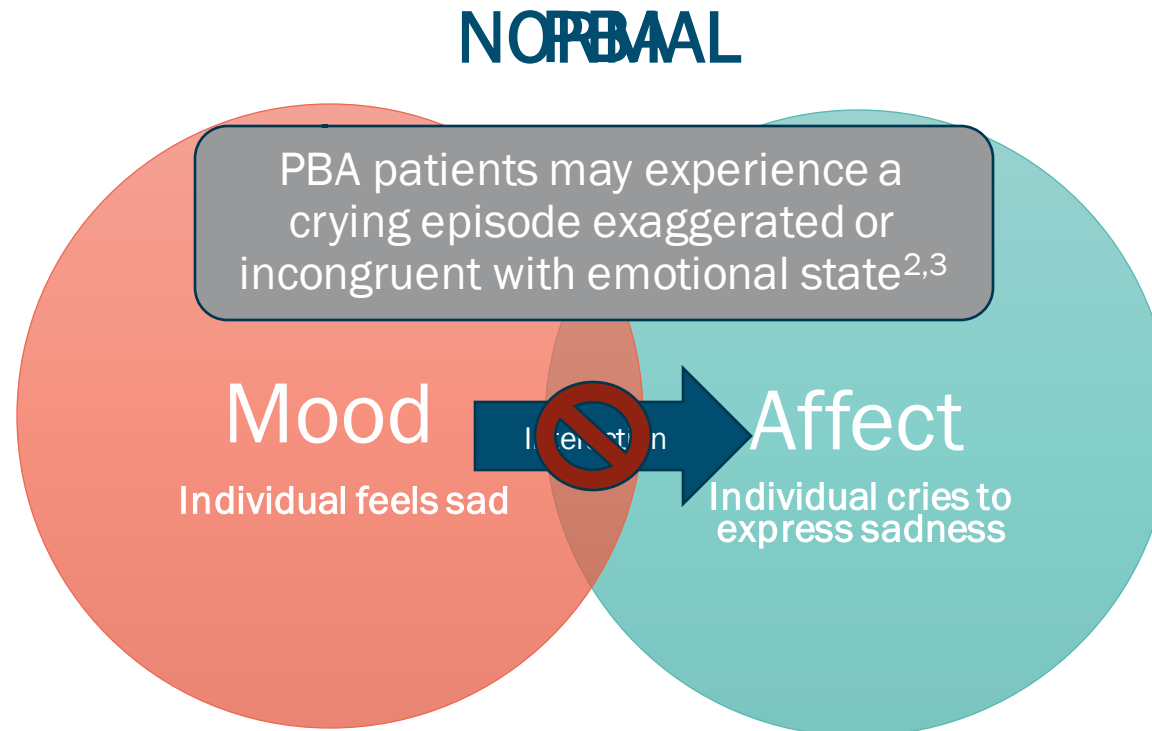
NMDA, N-methyl-D-aspartate; Ca²⁺, calcium; Na⁺, sodium.

1. Pankevich DE et al. *Inst Med Forum Neurosci Nerv Syst Disord*. 2011;74. 2. Lauterbach EC et al. *Neurosci Biobehav Rev*. 2013;37(8):1893-1916.

3. Nguyen L et al. *J Pharmacol Sci*. 2015;127(1):17-29.

PBA Episodes Are Disconnected From Mood and/or Exaggerated¹⁻³

With PBA, there is a disconnect between mood (how patients *feel*) and affect (how they *express* those feelings)^{1,2}



**PBA Is More
Burdensome Than
We May Realize**

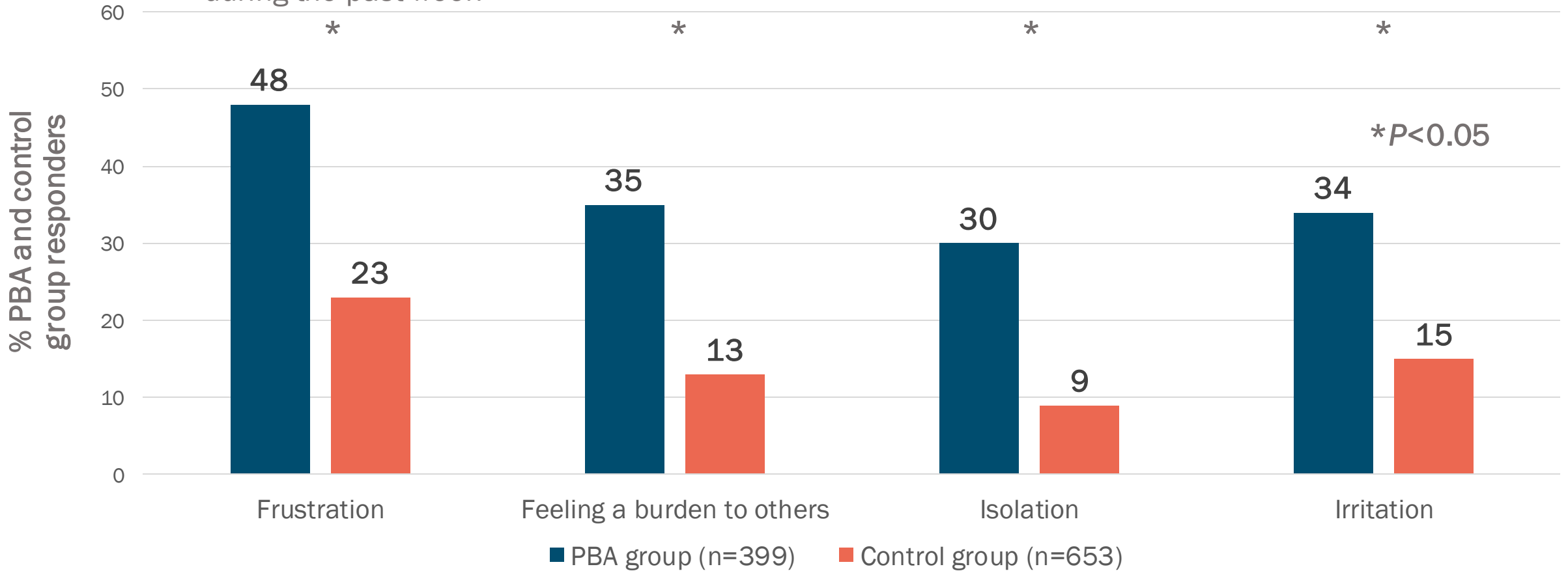


Understanding How Uncontrollable Crying and/or Laughing Affects Patients' Lives

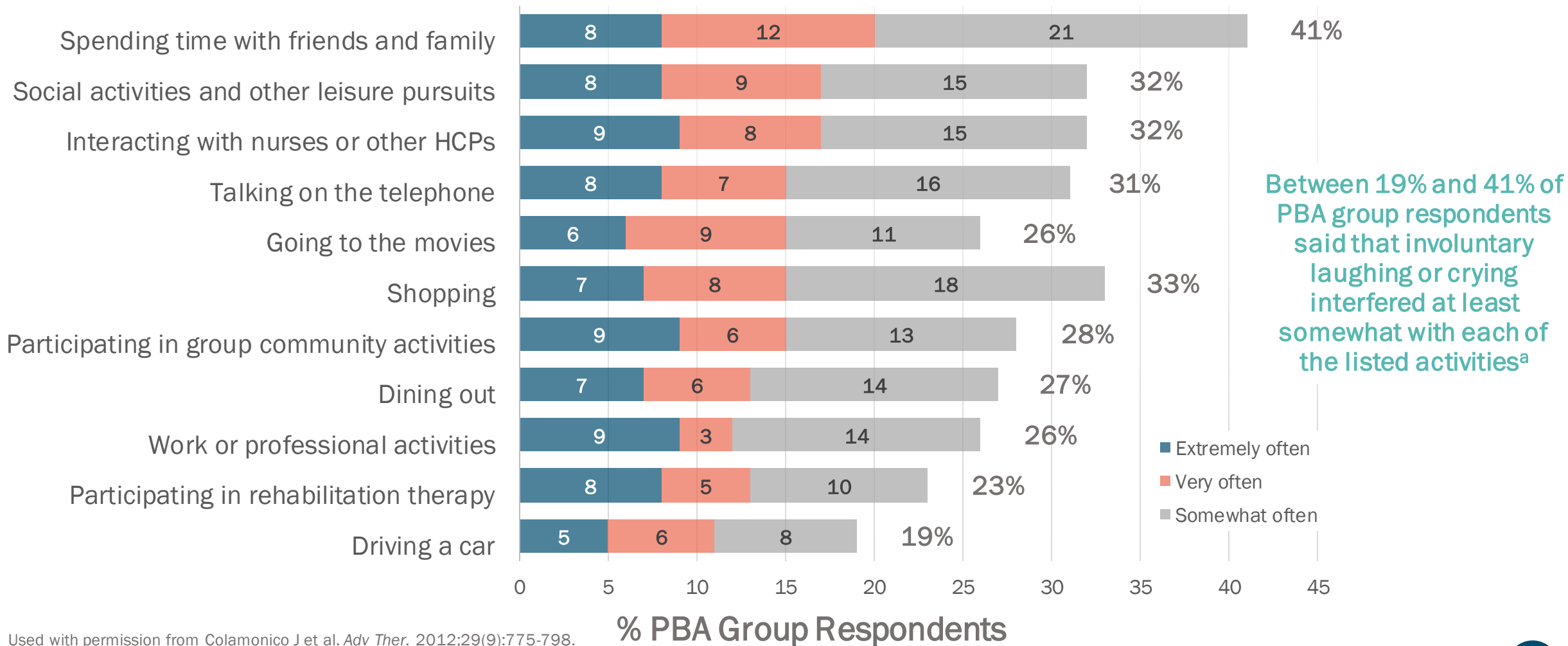
- An online US survey was conducted to estimate the effects of PBA symptoms on the health and functionality of patients
 - Compared measures of general health status, social and occupational function, quality of life (QOL) and other measures for patients with AD, ALS, MS, PD, stroke, and TBI with and without PBA symptoms
 - Survey sample included patients or primary caregivers who participated on a patient's behalf
 - PBA symptoms were defined as CNS-LS score ≥ 13 (PBA group)
 - 1052 respondents completed the survey; 37.9% met the criteria for inclusion in the PBA group

Impact of PBA Symptoms on Negative Feelings

- In a US survey, respondents in the PBA and control groups assessed their emotional state during the past week



Interference of PBA Symptoms With Patient Function

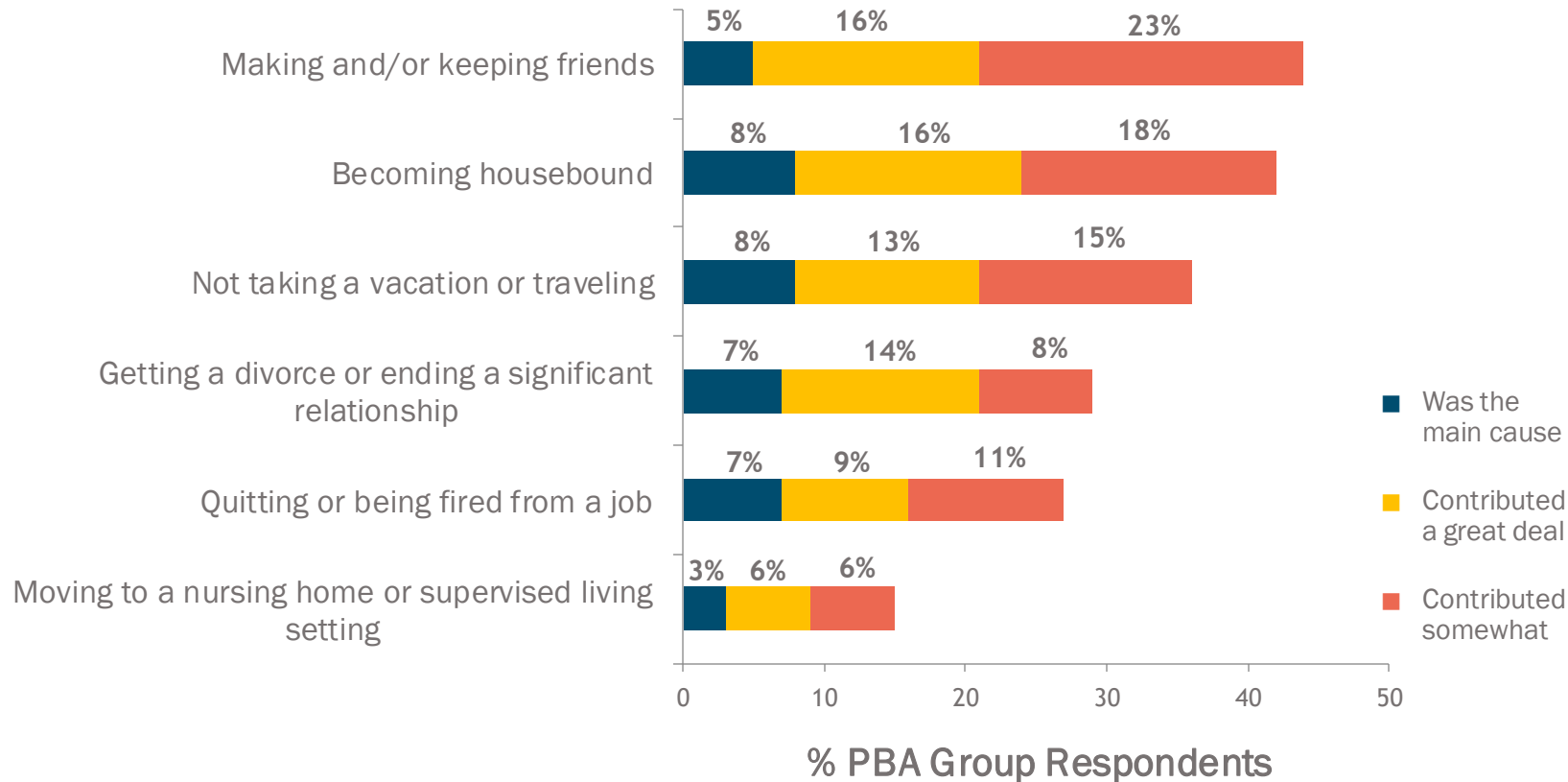


Used with permission from Colamonico J et al. *Adv Ther.* 2012;29(9):775-798.

^aPBA group respondents were asked to respond to the following question: "Please indicate, how often you would say the episodes of involuntary crying and/or laughing interfere with your [your patient's] participation in each of the following activities. If you [your patient] do [does] not participate in an activity, please select 'Does not apply to me [him/her].'" This question was completed only by PBA group members (n=280) who answered "yes" to the question, "Have you [has the patient you care for] ever experienced involuntary episodes of crying and/or laughing that were exaggerated or even contrary to how you [he/she] felt at the time?"

Impact of PBA Symptoms on Important Life Situations

“To what extent have your [your patient’s] involuntary episodes of laughing and/or crying ever contributed to the following life situations? Please select all situations that apply.”



- 9%-24.4% of respondents^a said that involuntary episodes of laughing and/or crying contributed “a great deal” to or “were the main cause” of distressing life situations^b

Average number of situations affected by PBA symptoms	
1 or more	63%
2 or more	47%
3 or more	35%

Used with permission from Colamonico J et al. *Adv Ther.* 2012;29(9):775-798.

^aPBA group respondents were asked to respond to the following question: “To what extent have your [your patient’s] involuntary episodes of laughing and/or crying ever contributed to the following life situations? Please select all situations that apply.” ^bThis question was completed only by PBA group members (n=280) who answered “yes” to the question “Have you [has the patient you care for] ever experienced involuntary episodes of crying and/or laughing that were exaggerated or even contrary to how you [he/she] felt at the time?”

Colamonico J et al. *Adv Ther.* 2012;29(9):775-798.

PBA Identification and Differentiation



PBA Is Not Easily Identified

- Patients and caregivers may not know that PBA is a distinct condition and fail to discuss symptoms with their HCPs^{1,2}
- PBA is often confused with other emotional and behavioral disorders (eg, bipolar disorder, anxiety, PTSD)¹



Is this ...

... *depression?*

... *anxiety?*

... *PTSD?*

... *stroke?*

... *Alzheimer's?*

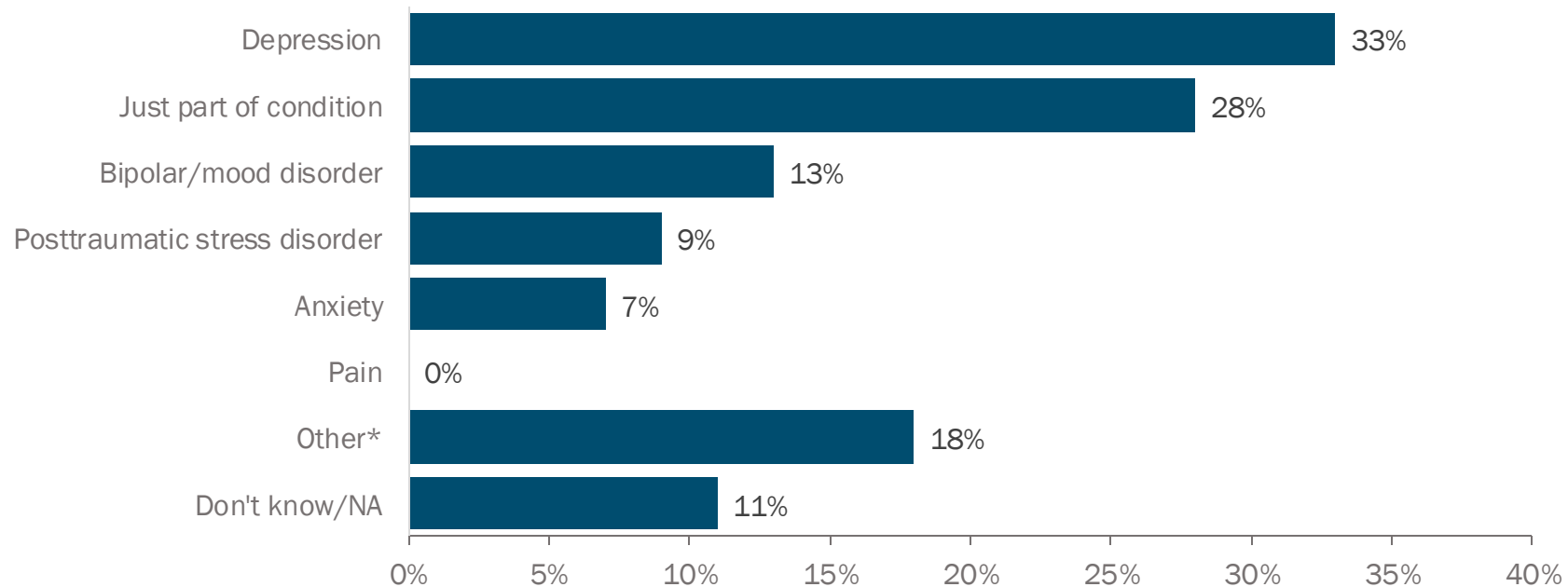
... *PBA?*

... *bipolar disorder?*

PBA Can Be Difficult to Diagnose

- In a US online survey, the majority of diagnoses received by patients who discussed their uncontrolled crying and/or laughing with a physician were depression or related to the patient's underlying illness^a
- Nearly 60% of patients with possible PBA symptoms who reported uncontrolled crying and/or laughing to a physician were not diagnosed with a disorder^b

Diagnoses Received Across All Disease Groups (N=227)



Reprinted with permission from Work SS et al. *Adv Ther.* 2011;28:586-601.

^aPatients were previously identified as having ALS, AD, MS, PD, stroke, or symptoms suggestive of TBI; ^bThe CNS-LS was used in this study as a measure of PBA frequency and severity. The CNS-LS has been validated in patients with MS and ALS. A CNS-LS score ≥ 13 is suggestive of PBA symptoms and merits further diagnostic assessment.

*Includes various personality disorders, psychotic disorders, "stress."

NA, not available.

Work SS et al. *Adv Ther.* 2011;28:586-601.

Differentiating PBA From Depression^{1,2}

- To help distinguish PBA from depression, identify the characteristics of crying^{1,*}

Crying

PBA

- Disproportionate to or inconsistent with how the patient feels
- Uncontrollable
- Happens frequently, suddenly, and may be brief

Depression

- Matches how the patient feels
- Mostly controllable; stops when mood changes
- Onset and duration defined by mood

ARS Question

Do you formally screen for PBA in your practice using an assessment tool such as the CNS-LS?

1. No
2. Occasionally
3. Regularly

ARS Question

Which patients do you typically screen for PBA?

1. All patients
2. Geriatric patients
3. Patients with known neurologic disorders
4. Other
5. None at all

Screening Can Be Simplified by Asking Key Questions

“Do you frequently cry but don’t feel depressed?”¹

“Do you frequently laugh when nothing is funny?”¹

“Do even little things make you feel like crying?”¹

“Do you have sudden, uncontrollable crying and/or laughing?”¹

“Do you laugh and cry and don’t know why?”¹

“Have you had involuntary episodes of crying and/or laughing that were exaggerated or contrary to how you felt at the time?”^{2*}

“Do you suffer from sudden laughter or crying that you cannot control?”¹

*This question asks about the hallmark features of PBA and is considered to have face validity as an initial screening question.

1. Data on file. Avanir Pharmaceuticals, Inc. 2. Colamonic J et al. *Adv Ther.* 2012;29:775-798.

CNS-LS Can Be Used to Screen for PBA Symptoms

Validated in both ALS and MS patients^{1,2}

- Center for Neurologic Study-Lability Scale (CNS-LS)¹⁻³
 - Self-report assessment made up of subscales for laughter and tearfulness
 - Score ≥ 13 suggests the presence of PBA symptoms and warrants additional assessment

**Center for Neurologic Study-Lability Scale (CNS-LS)
for Pseudobulbar Affect (PBA)**

The CNS-LS is a short (seven item), self-administered questionnaire that provides a quantitative measure of the perceived frequency of PBA episodes. The CNS-LS helps physicians accurately diagnose PBA. A CNS-LS score of 13 or higher may suggest PBA. Addressing PBA is an important component in the overall management of patients with underlying neurologic disease or injury.

Instructions: 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 one number for each item.

Patient name: _____ Date of assessment: _____

Applies never	Applies rarely	Applies occasionally	Applies frequently	Applies most of the time	
1	2	3	4	5	
Assessment questions					Answers
1.	There are times when I feel fine one 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 amused very easily or that I seem to become amused 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: _____					

Source: Moore SR, Gresham LS, Bromberg MB, et al. A self report measure of affective lability. *J Neurol Neurosurg Psychiatry*. 1997; 63:89-93.

PBA-0115-OTH-0416

1. Moore SR et al. *J Neurol Neurosurg Psychiatry*. 1997;63(1):89-93. 2. Smith RA et al. *Mult Scler*. 2004;10(6):679-685. 3. Smith RA et al. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2004;5(Suppl 1):99-102.

Summary

- PBA is characterized by frequent, sudden, and uncontrollable episodes of crying and/or laughing secondary to underlying neurologic conditions
- Symptoms of PBA are believed to be the result of dysfunction in widespread circuits connecting the frontal cortex to the brain stem and the cerebellum
- Despite its prevalence and impact on the daily life of patients, PBA may be mischaracterized and underdiagnosed. PBA may be mischaracterized as depression
- Screening patients or caregivers with several questions about PBA symptoms could lead to a discussion about further assessment and possible diagnosis

PBA Case Studies



Case study of a patient with Alzheimer's disease and PBA

Case study of a patient with history of stroke and PBA

Case study of a patient with TBI and PBA

Case Study of Patient With Alzheimer's Disease (AD) and PBA

History

- 70-year-old female with AD was referred to a neurologist for “frequent daily expressions of sadness, including episodic crying”
 - Episodes started approximately 6 months ago
 - Patient would call for help but then abruptly stop crying
 - Patient is unable to effectively communicate the reason for her episodes

Medical history

- Family has history of AD but no history of depression
- Patient has hypertension, well-controlled
- The patient experienced good health until her cognition and memory began to decline
 - Diagnosed with AD at 65
- Physical health continued to decline and she was enrolled in a long-term care facility

Case Study of Patient With AD and PBA (cont'd)

Neurologic examination

- Normal neurologic and cognitive exam
 - Further neurologic and psychologic evaluation were not available due to health status and poor cooperation of the patient
- Family members report no reason or cause for her episodes
 - Other than her deteriorating mental status, no changes reported in her home environment or social status

Case Study of Patient With Stroke and PBA

History

- 60-year-old female presents with sudden, frequent, uncontrollable episodes of crying
 - Episodes may last up to approximately 5 minutes, often with no provocation
- Patient often experiences episodes of exaggerated crying that is out of proportion/inappropriate to the situation or conversation

Medical history

- Two strokes at ages 49 and 58
- Medical history includes hypercholesteremia, hypertension, and diabetes
- Previously diagnosed with depression and has been prescribed an SSRI
 - Patient reports improvement in mood, but frequency of crying episodes remain unchanged
 - Patient administered a second SSRI with no noticeable change
- Following two rounds of SSRI treatment, the patient was diagnosed with treatment-resistant depression

PATIENT: "It just doesn't take much to get the tears flowing. Anything can set me off, but the worst crying episodes are when someone mentions something...anything...that is just slightly upsetting but my reaction is completely inappropriate. And I know it's inappropriate but I still can't stop!"

The worst part is my friends and family used to be concerned, but now it just seems to annoy them. I can tell they are careful about what they say to me now. It's embarrassing."

Case Study of Patient With Stroke and PBA (cont'd)

Mental status examination

- No compromise to executive function, recognition, language, or visuospatial functions
- During the exam, the patient experienced an episode of prolonged, exaggerated crying
 - Episode was triggered when the physician casually mentioned his favorite TV show had been cancelled
 - The patient was unable to compose herself for several minutes
 - The patient's husband explained that this episode is typical of what has been occurring, and that her crying episodes often last longer

Case Study of Patient With Traumatic Brain Injury (TBI) and PBA

History

- 35-year-old male presents to neurologist with “crying or laughing outbursts”
 - Episodes typically occur approximately 4-5 times a day, but occasionally skip a week or intensify both in frequency and duration for a couple of days
 - Episodes consist of unprovoked, exaggerated crying and the patient occasionally laughs at inappropriate times

Medical history

- Family history of depression
 - Both parents managed with antidepressants
- Patient is a Marine and combat veteran who was honorably discharged after serving in the Middle East
 - Denies history of skull trauma, but acknowledged he was exposed to numerous concussive blasts
 - Diagnosed with TBI
 - He has experienced episodes of anxiety, insomnia, and tinnitus

Case Study of Patient With TBI and PBA (cont'd)

Mental status examination

- No compromise to executive function, language, or visuospatial functions
- Mild impairment of recall, recognition, and attention

Imaging

- MRI appears normal

Case Study of Patient With TBI and PBA (cont'd)

Patient diagnosed with posttraumatic stress disorder

- Patient was prescribed an SSRI and benzodiazepine

6-month follow-up

- Episodes have not resolved
- Patient reports decrease in anxiety and insomnia, but complains of drowsiness and dizziness at times
- No decrease in the frequency of crying or laughing
 - Crying is still the most common outburst expression
- The patient denies feeling depressed, but acknowledges that the uncontrollable episodes are “affecting his life”