

Pseudobulbar affect: When patients laugh or cry, but don't know why



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Disruption of neural circuitry undermines voluntary control of affect

Pseudobulbar affect (PBA) is a disorder of affective expression that manifests as stereotyped and frequent outbursts of crying (not limited to lacrimation) or laughter. Symptoms are involuntary, uncontrolled, and exaggerated or incongruent with current mood. Episodes, lasting a few seconds to several minutes, may be unprovoked or occur in response to a mild stimulus, and patients typically display a normal affect between episodes.¹ PBA is estimated to affect 1 to 2 million people in the United States, although some studies suggest as many as 7 million,^{1,2} depending on the evaluation method and threshold criteria used.³

Many terms have been used to describe aspects of PBA (*Table 1*⁴ and *Box, page 58*⁵⁻¹⁰). This abundance of often conflicting terminology is thought to have impeded efforts to categorize emotional expression disorders, determine their prevalence, and evaluate clinical evidence of potential therapeutic options.¹¹

Where to look for pseudobulbar affect

PBA has been most commonly described in 6 major neurologic disorders:

- Alzheimer's disease
- amyotrophic lateral sclerosis (ALS)
- multiple sclerosis (MS)
- Parkinson's disease
- stroke
- traumatic brain injury (TBI).

Disclosures

Dr. Caplan has served as a consultant to Avanir Pharmaceuticals, an independent subsidiary of Otsuka America, Inc., manufacturer of the formulation of dextromethorphan/quinidine discussed in this article. Drs. Frock and Williams report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

Of these disorders, most studies have found the highest PBA prevalence in patients with ALS and TBI, with lesser (although significant) prevalence in Parkinson's disease (Table 2, page 59).^{1,12} These "big 6" diagnoses are not a comprehensive list, as many other disease states are associated with PBA (Table 3, page 59).¹²⁻¹⁴

As PBA has become better defined and more widely recognized, additional sequelae have been described. PBA's sporadic and unpredictable nature and the potential embarrassment and distress of public outbursts may lead to an agoraphobia-like response.¹⁵ People with PBA report a significantly worse subjective assessment of general health, quality of life, relationships, and work productivity compared with people with similar primary underlying diagnoses without PBA.¹⁶

2 Pathways: 'Generator' and 'governor'

Despite the many and varied injuries and illnesses associated with PBA, Lauterbach et al¹⁰ noted patterns that suggest dysregulation of 2 distinct but interconnected brain pathways: an emotional pathway controlled by a separate volitional pathway. Lesions to the volitional pathway (or its associated feedback or processing circuits) are thought to cause PBA symptoms.

To borrow an analogy from engineering, the emotional pathway is the "generator" of affect, whereas the volitional pathway is the "governor" of affect. Thus, injury to the "governor" results in overspill, or overflow, of affect that usually would be suppressed.

The emotional pathway, which coordinates the motor aspect of reflex laughing or crying, originates at the frontotemporal cortex, relaying to the amygdala and hypothalamus, then projecting to the dorsal brainstem, which includes the midbrain-pontine periaqueductal gray (PAG), dorsal tegmentum, and related brainstem.

The volitional pathway, which regulates the emotional pathway, originates in the dorsal and lateral frontoparietal cortex, projects through the internal capsule and midbrain

Table 1
The study of PBA has yielded a long list of descriptive terms

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
PBA: pseudobulbar affect
Source: Reference 4

basis pedunculi, and continues on to the anteroventral basis pontis. The basis pontis then serves as an afferent relay center for cerebellar activity. Projections from the pons then regulate the emotional circuitry primarily at the level of the PAG.¹⁰

Lesions of the volitional pathway have been correlated with conditions of PBA, whereas direct activation of the emotional pathway tended to lead to emotional lability or the crying and laughing behaviors observed in dacrystic or gelastic epilepsy.¹⁰

The pivotal nature of the regulation occurring at the PAG has guided treatment options. Neurotransmitter receptors most closely associated with this region include glutamatergic *N*-methyl-D-aspartate (NMDA), muscarinic M1 to M3, γ -aminobutyric acid (GABA)-A, dopamine D2, norepinephrine α -1 and α -2, serotonin 5-HT1B/D, and sigma-1 receptors. Volitional inhibition of the PAG is mediated by acetylcholine and GABA balance at this location.¹⁰

When to screen for PBA

Ask the right question. PBA as a disease state likely has been widely under-reported, under-recognized, and misdiagnosed (typi-

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PBA's unpredictable nature and potential embarrassment of public outbursts may lead to an agoraphobia-like response



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Pseudobulbar affect

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A single question might best refine the likelihood that a patient has PBA: 'Do you ever cry for no reason?'

Box

From Darwin to IEED, nomenclature has evolved over time

Charles Darwin⁵ was among the first to acknowledge the correlation between neurologic insult and dysregulated emotional expression, writing in 1872 that "certain brain disease, such as hemiplegia, brain-wasting, and senile decay, have a special tendency to induce weeping."

In 1886, Oppenheim and Siemerling⁶ proposed the terms "pseudobulbar affect" (PBA) and "pseudobulbar palsy" (a separate and distinct state that includes dyscontrol of facial muscles, resulting in dysarthria, dysphagia, and dysphonia) in their descriptions of patients with bilateral forebrain injury that appeared to mimic brainstem dysfunction.

Wilson⁷ in 1924 proposed that pathological laughing and crying (PLC)

was related to motor disinhibition resulting from bilateral corticobulbar lesions that disengaged a brainstem "faciorespiratory center" from cortical levels of control. In 1963, Poeck et al⁸ proposed diagnostic criteria for PLC.

More recently, Cummings et al⁹ proposed "involuntary emotional expression disorder" (IEED) in 2006 as an umbrella term for disorders having "involuntary outbursts or crying and/or laughing" as a primary feature. To distinguish more sufficiently between purely affective etiologies of these features (PBA) and disorders that include dysfunction of both mood and affect, Lauterbach et al¹⁰ divided IEED into 2 subtypes: PLC and emotional lability.

cally, as a primary mood disorder).⁹ Three factors underscore this problem:

- Patients do not specifically report symptoms of affective disturbance (perhaps because they lack a vocabulary to separate concepts of mood and affect)
- Physicians do not ask patients about separations of mood and affect
- Perhaps most importantly, PBA lacks a general awareness and understanding.

Co-occurring mood disorders also may thwart PBA detection. One study of PBA in Alzheimer's dementia found that 53% of patients with symptoms consistent with PBA also had a distinct mood disorder.¹⁷ This suggests that a PBA-specific screening test is needed for accurate diagnosis.

A single question might best refine the likelihood that a patient has PBA: "Do you ever cry for no reason?" In primary psychiatric illness, crying typically is associated with a specific trigger (eg, depressed mood, despair, anxiety). A patient's inability to identify a trigger for crying suggests the pathological separation of mood and affect—the core of PBA, and worthy of further investigation.

Clinical rating scales that correlate to disease severity appear to be the most effective in identifying PBA. The PRISM study, to date the largest clinic-based study of PBA symptoms, used the Center for Neurologic Study-Liability Scale (CNS-LS) to gauge the

presence and severity of PBA symptoms.¹ A 7-question, patient self-administered tool, the CNS-LS is graded on a 5-point Likert scale. A score ≥ 13 has high sensitivity and specificity for diagnosis of PBA, compared with physician diagnosis.

Another option, the 16-question Pathological Laughing and Crying Scale, is a clinician-administered screening tool. Again, a score ≥ 13 is consistent with symptoms required for a PBA diagnosis.

Treating PBA symptoms

Until recently, most pharmacotherapeutic interventions for PBA were based on off-label use of tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs). From 1980 to 2010, only 7 of 22 case reports or trials of TCAs or SSRIs for PBA were randomized, double-blind, and placebo-controlled. Five had 12 to 28 patients, and 2 had 106 and 128 patients, respectively. Only 1 controlled trial included a validated symptom severity scale, and none included a scale validated for PBA.¹⁸

In particular, imipramine and nortriptyline were studied for managing PBA in patients with stroke; amitriptyline, in patients with MS; and various SSRIs, in patients with stroke.¹¹ Response of PBA symptoms to antidepressant therapy was greater in all placebo-controlled trials than response to placebo.¹⁸ As seen in pharmaco-

Table 2

Prevalence of PBA in the 6 most common underlying disease states

	CNS-LS ≥ 21 (%) [consistent with moderate or severe PBA]	CNS-LS ≥ 13 (%) [consistent with symptoms of PBA]	N
Traumatic brain injury	16.4%	52.4%	590
Amyotrophic lateral sclerosis	12.0%	44.8%	125
Multiple sclerosis	12.0%	45.8%	1,215
Alzheimer's dementia	9.4%	37.8%	1,799
Stroke	6.6%	29.3%	757
Parkinson's disease	5.5%	26.0%	804
Average	9.3%	36.7%	5,290

CNS-LS: Center for Neurological Study-Liability Scale; PBA: pseudobulbar affect
 Source: References 1,12

therapy of depression, the lower burden of adverse effects and overall better tolerability of SSRIs resulted in their preferred use over TCAs. In some cases, the side effects of TCAs can be leveraged for therapeutic gain. If insomnia is a problem, a nighttime dose of a TCA could ameliorate this. Similarly, if a patient has sialorrhea, the anticholinergic effect of a TCA may show some benefit.¹⁹

Dextromethorphan plus quinidine.

Dextromethorphan has long been of interest for a variety of neurodegenerative diseases. Studies of its efficacy were largely unsuccessful, however, because rapid metabolism by cytochrome P450 (CYP) 2D6 prevented CNS penetration.²⁰ Quinidine is an avid inhibitor of CYP2D6, even at very low dosages. Adding quinidine to dextromethorphan limits metabolism, allowing dextromethorphan to accumulate to a plasma concentration sufficient to penetrate the CNS.¹² In 2010, the combination agent dextromethorphan hydrobromide (20 mg)/quinidine (10 mg) (DM/Q) became the first treatment to receive FDA approval for managing PBA.¹¹

Mechanism of action. The exact mechanism of DM/Q in PBA remains unknown. Dextromethorphan is an agonist of sigma-1 receptors and a relatively specific noncompetitive antagonist of NMDA receptors. It also has been shown to modulate glutamate

Table 3

Other disease states and injuries that have been associated with PBA

Acute demyelinating encephalomyelitis
Central pontine myelinolysis
Cerebral aneurysms
Cerebral arteriovenous malformations
Cerebral palsy
Cerebral tumors
Chemotherapy
Corticobasal degeneration
Deep brain stimulation
Frontotemporal dementia
Herpes encephalitis
Huntington's disease
Lipid storage diseases
Neurosyphilis
Normal pressure hydrocephalus
Primary lateral sclerosis
Progressive supranuclear palsy
Wilson's disease

PBA: pseudobulbar affect
 Source: References 12-14

and serotonin neurotransmission and ion channel function.²⁰ Sigma-1 receptors are concentrated in the brainstem and parts of the cerebellum that are thought to coordinate motor emotional responses. Agonism of sigma-1 receptors on glutamatergic neurons has been proposed to limit release of glutamate from the presynaptic neuron

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Response of PBA symptoms to antidepressant therapy was greater in all placebo-controlled trials than response to placebo



Pseudobulbar affect

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Compared with placebo, DM/Q use was associated with significantly reduced daily episodes of PBA at 2, 4, 8, and 12 weeks

Related Resource

• Bush D, Klein L (directors). Beyond laughter & tears: A journey of hope. Madpix Films, W20 Films; 2016.

Drug Brand Names

Amitriptyline • Elavil	Imipramine • Tofranil
Dextromethorphan hydrobromide (20 mg)/quinidine sulfate (10 mg)	Moxifloxacin • Avelox
• Nuedexta	Nortriptyline • Pamelor

while also limiting downstream transmission of glutamatergic signal in postsynaptic neurons.

Clinical trials. Two large trials have demonstrated efficacy of DM/Q in PBA. STAR was a 12-week, double-blind, placebo-controlled trial with 326 patients diagnosed with ALS or MS who showed PBA symptoms (CNS-LS score ≥ 13). Compared with placebo, DM/Q use was associated with significantly reduced ($P < .01$) daily episodes of PBA at 2, 4, 8, and 12 weeks.²⁰ The effect was rapid, with 30% fewer PBA episodes after the first week ($P < .0167$). At 12 weeks, 51% of patients on DM/Q had been symptom-free for at least 2 weeks.

The PRISM II study examined the efficacy of DM/Q in managing PBA in 102 individuals with dementia, 92 with stroke, and 67 with TBI. After 30 and 90 days, CNS-LS scores were significantly reduced ($P < .001$) compared with baseline scores.²⁰

Prescribing information. Dextromethorphan—typically in the form of cough syrup—has been implicated as a substance of abuse. A placebo-controlled trial demonstrated that co-administering quinidine with dextromethorphan limits measures of positive reinforcement, such as euphoria and drug liking. This suggests

that quinidine may be used to reduce abuse of dextromethorphan.²⁰ As such, the abuse potential of DM/Q appears to be low.

The most common adverse effects reported with DM/Q are diarrhea, dizziness, and cough.¹² Notably, patients who received DM/Q in the STAR trial were more likely to report dizziness than those receiving placebo (10.3% vs 5.5%), but patients receiving placebo were more likely to fall.^{21,22}

Package labeling warns that DM/Q causes dose-dependent QTc prolongation.²¹ Quinidine can be associated with significant QTc prolongation when dosed at antiarrhythmic levels, although mean plasma concentrations found with the 10 mg of quinidine in the approved DM/Q formulation are 1% to 3% of those associated with typical dosages used in antiarrhythmic therapy. Electrophysiology studies of quinidine 10 mg dosed every 12 hours have demonstrated a mean QTc increase at steady state of 6.8 milliseconds, compared with 9.1 milliseconds for a reference control (moxifloxacin).^{12,21}

Although this would seem to indicate a relatively low risk of clinically significant QTc prolongation at these ultra-low dosages of quinidine, it may be advisable to obtain an initial pre-dose and post-dose ECG and longitudinally monitor the QTc interval in patients with conditions that predispose to cardiac arrhythmias. Because quinidine inhibits CYP2D6, use caution when prescribing and monitoring other medications metabolized by this pathway.

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Bottom Line

Pseudobulbar affect (PBA) is characterized by paroxysmal affective outbursts that are (1) out of proportion to, and out of context with, patients' mood state and (2) outside of their control. PBA is caused by brain illnesses and injuries that disrupt neural circuitry that underpins the volitional control of affect. FDA-approved dextromethorphan and quinidine in combination has demonstrated significant reduction in PBA symptoms.

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Clinical Point

The most common adverse effects reported with DM/Q are diarrhea, dizziness, and cough

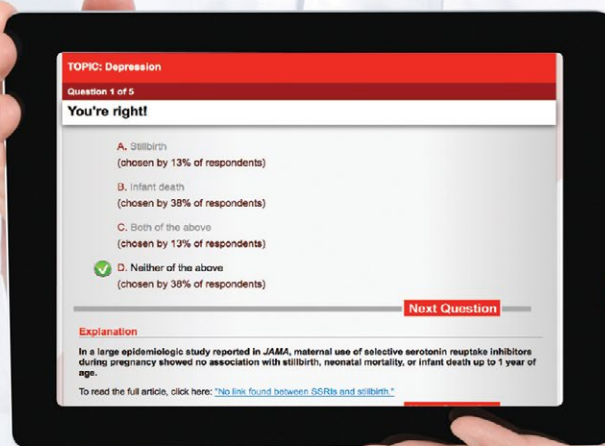
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