

# The epidemiology and pathophysiology of pseudobulbar affect and its association with neurodegeneration

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**Abstract:** Pseudobulbar affect is a disorder resulting from neurologic damage manifesting as sudden, stereotyped affective outbursts that are not reflective of internal emotion. A literature review was completed to examine the current understanding of the epidemiology, characterization, diagnosis, pathophysiology, and treatment of pseudobulbar affect. This review revealed that it is common in neurodegenerative disorders but is poorly recognized, placing significant impacts on patients and their families. The disorder appears to result from a disruption of the cortico-limbic-subcortical-thalamic-pontocerebellar network involved in emotional expression and regulation with resulting disruptions of neurotransmitter systems. Effective treatment is available with agents such as selective serotonin reuptake inhibitors and dextromethorphan combined with quinidine, but further well-designed comparative studies are needed. Advances in technology such as neuroimaging may enhance knowledge about the pathophysiology of this disorder, and help guide future interventions.

**Keywords:** pseudobulbar affect, pathological laughing and crying, neurodegenerative disease, pathophysiology, epidemiology, treatment

## Introduction

Pseudobulbar affect (PBA) is a disorder seen in a wide variety of neurologic illnesses, but is particularly common in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), multiple sclerosis (MS), and various dementias.<sup>1,2</sup> It is characterized by stereotyped, involuntary outbursts of affect or objective emotional expressions (such as crying or laughing) that are excessive or incongruent with the individual's subjective emotional experience or mood.<sup>1-10</sup> In essence, neurologic damage leads to an uncoupling of the subjective experience of emotion or mood from the objective behaviors of emotion or affect that involve motor and autonomic responses.<sup>1,11</sup> Given that the objective expression of emotion normally reflects the subjective experience of emotion, given that clinicians are generally unaware of PBA as an entity, and given that the disorder is frequent in individuals with severe neurodegenerative disorders with multiple other comorbidities, it is not surprising that PBA is thought to be under diagnosed or misdiagnosed.<sup>12-14</sup> Varied nomenclature creates additional confusion. The multiple names denoting PBA or related diagnoses are listed in Table 1.<sup>2,5,10</sup> To further characterize the epidemiology, pathophysiology, diagnosis, and treatment of PBA, a comprehensive literature review of pediatric and adult publications was completed.

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**Table 1** Alternative names for pseudobulbar affect

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Pseudobulbar laughing or crying
Pathologic weeping or crying or laughing
Pathologic emotionalism or emotionality
Pathological affect
Organic emotionalism
Involuntary emotional expression disorder
Inappropriate hilarity
Forced laughter or crying
Excessive emotionality
Emotionalism
Emotional lability
Emotional instability
Emotional incontinence
Emotional dysregulation
Emotional dyscontrol
Compulsive laughing or crying
Affective lability
Affective instability
Affective incontinence

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## Epidemiology

The occurrence of PBA has been reported in a multitude of neurologic illnesses including, but not limited to, ALS,<sup>15–19</sup> PD and other movement disorders,<sup>13,20–22</sup> MS,<sup>23–37</sup> stroke,<sup>38–54</sup> various types of dementia and other neurodegenerative disorders,<sup>55–62</sup> traumatic brain injury (TBI),<sup>63–66</sup> central nervous system tumors,<sup>67–81</sup> neurogenetic syndromes,<sup>82–94</sup> and viral cerebellitis.<sup>95</sup> Rarely, certain therapeutic interventions have also reported PBA as a side effect of treatment. Case reports exist of pathologic laughing as a side effect of paroxetine,<sup>96</sup> sumatriptan,<sup>97</sup> and ziprasidone,<sup>20</sup> as well as deep brain stimulation, particularly of the subthalamic nucleus.<sup>98–102</sup> However, as will be discussed in this review, some consider medication side effects as an exclusionary criteria for PBA given their usual reversibility and lack of structural neurologic damage.<sup>1</sup>

The reported prevalence of PBA varies greatly depending on the underlying neurologic illness, the methodology of the study, and the diagnostic criteria used to identify cases. A recent online, stratified survey of a nationally representative sample attempted to establish the prevalence of PBA in the United States and specifically the prevalence of PBA in Alzheimer's dementia, ALS, MS, PD, stroke, and TBI.<sup>14</sup> The estimated prevalence in the US population varied depending on the scale and threshold score used to identify cases, but ranged from a low estimate of 0.55 million to a high estimate of 7.1 million. In the six neurologic conditions surveyed, overall prevalence was 10% to 38% depending on the threshold score used. Limitations of the study included a low response rate, use of scales not validated for some of

the identified populations, and reliance on respondents to report their neurologic diagnoses accurately. Estimates of prevalence for specific diseases from this study and other studies indicate that true prevalence in neurodegenerative disorders may range from 2%–60% in ALS,<sup>2,7,10,14</sup> 5%–17% in PD,<sup>5,13,14</sup> 7%–29% in MS,<sup>2,7,10,14</sup> and 10%–74% in Alzheimer's dementia.<sup>2,5,10,14</sup> The prevalence in nondegenerative disorders also shows a broad range of 6%–52% in stroke,<sup>2,7,10,14</sup> and 5%–11% in TBI.<sup>2,5,7,10,14,66</sup>

Comorbidity is often seen in those with PBA. It is associated with cognitive impairment in MS,<sup>103</sup> and depression in PD and other movement disorders.<sup>13,21</sup> There is also an association with anxiety.<sup>2,66</sup> Aside from structural neurologic disease, there are no consistently associated risk factors for PBA, although an isolated study indicates that premorbid, illicit drug use predisposes to PBA.<sup>66</sup> The valence of affective outbursts may be different depending on the laterality of lesions and gender.<sup>104</sup> Pathologic crying may be more prevalent in women and those with left-sided lesions, while pathologic laughing may be more prevalent in men and those with right-sided lesions.<sup>104</sup>

Quality of life is significantly affected by PBA with apparent detrimental effects on rehabilitation, occupational functioning, social functioning, and quality of relationships.<sup>5,13,105</sup> This finding is particularly important for progressive neurologic disorders where quality of life is a primary focus of care. A study of patients with movement disorders showed well-being subscores on the 39-question PD questionnaire were significantly lower for those with PBA.<sup>13</sup> Additionally, those with PBA were more likely to be taking an antidepressant.<sup>13</sup> A recent survey of patients with various neurologic illnesses showed that those with PBA scored significantly lower on the work productivity and impairment questionnaire, quality of life questionnaires, and quality of relationship questionnaires compared with controls, even when disease severity and other confounding factors were controlled.<sup>105</sup> PBA was the main reason for becoming housebound for 24% of respondents, and produced significant caregiver burden.<sup>105</sup> Stigma may also prevent ALS patients with PBA from discussing their symptoms.<sup>106</sup> Patient and family education is recommended for effective management and to reduce stigma.<sup>2</sup>

## Pathophysiology

The pathophysiology of PBA is likely varied and best conceptualized as a focal or diffuse disruption in the complex neurocircuitry or neurochemistry involved in the inhibition of emotional expression.<sup>11,107–115</sup> One of the

original hypotheses about PBA came from Wilson,<sup>115</sup> who proposed that there was disruption of the cortical inhibition to an upper brainstem center followed by release of lower bulbar nuclei that coordinate the motor responses associated with laughing and crying. Thus, this theory is often called the “release hypothesis.” Postmortem and imaging studies in patients with PBA seem to support this theory.<sup>11,107,111,113</sup> Other support comes from the anatomic location of lesions or activity involved in disorders related to PBA such as “fou rire prodromique,” whereby involuntary emotional expression relates to an apoplectic event,<sup>3,11,54,79,108,111,116</sup> or gelastic or dacrystic seizures where involuntary laughter or crying is part of a seizure.<sup>68,71,80,85,117–124</sup> More recently, lesions of cerebro–pontocerebellar circuitry have been implicated in PBA.<sup>11,107–110</sup>

At the neurotransmitter level, there is also likely to be dysfunction involved in PBA as evidenced by neuroimaging<sup>107,114</sup> and based on pharmacologic therapies that will be discussed further, later in this review. Serotonin deficiency, dopamine deficiency, glutamate excess, and sigma type one ( $\sigma$ -1) receptor abnormalities have all been implicated.<sup>107,113,114</sup> Serotonin may be involved in the modulation of emotional expression via ascending serotonergic pathways from the raphe nuclei to the hippocampus, lateral septum and striatum, and frontal cortex.<sup>107</sup> Further supporting a serotonin deficiency hypothesis, a 2004 single-photon emission computed tomography study of poststroke patients with and without pathological crying showed significantly lower binding ratios of the presynaptic serotonin transporter in the midbrain and pons of those with pathological crying.<sup>114</sup> The authors theorize a latent vulnerability that is uncovered after neurologic damage.<sup>114</sup> The effectiveness of serotonergic agents for the treatment of PBA provides support for this hypothesis.<sup>10</sup> Dopamine functions in the brain to modulate the signal-to-noise ratio of information processing circuits, and too little or too much dopamine disrupts the optimal processing of salient stimuli.<sup>107</sup> Although there is less evidence to support a dopamine deficiency or excess is a contributor to PBA, it is theorized that nonsalient sensory stimuli trigger automatic motor responses in the form of affective outbursts.<sup>107</sup> Individual reports of successful treatment of PBA with dopaminergic agents like levodopa support this theory.<sup>10</sup> Glutamate is the primary excitatory neurotransmitter in the brain, and is proposed to contribute to neurotoxicity in some degenerative disorders such as ALS where PBA is often seen.<sup>17</sup> Excess excitatory glutamate activity in the specific circuits described above is also theorized to contribute to inappropriate

affective outbursts. Modulation, but not complete blockade of N-methyl-D-aspartate (NMDA) receptors through noncompetitive antagonism is thought to reduce the excitatory activity while still allowing for desired activity.<sup>10</sup> The  $\sigma$ -1 receptors in the brain are thought to have multiple neuromodulatory functions and possibly an intracellular amplifying or sensitizing role.<sup>107</sup> Also,  $\sigma$ -1 receptors are densely distributed in areas theorized to be disrupted in PBA.<sup>107</sup> The endogenous ligands for these receptors may include gonadal steroids, but some serotonergic and NMDA receptor antagonists also have affinity for these receptors.<sup>107</sup> This could explain the effectiveness of apparently different pharmacologic agents, but it is unclear; variations in one neurotransmitter often have consequent impacts on the levels of other neurotransmitters.

In summary, as Rabins and Arciniegas<sup>107</sup> have proposed, PBA is theorized to come from a disruption in a complex cortico-limbic-subcortico-thalamic-pontocerebellar network, which is often related to lesions in descending corticobulbar fibers that inhibit emotional motor networks, lesions in brainstem and cerebellum white matter pathways that modulate emotion expression, and multiple abnormalities in neurotransmitter function.

## Characterization and diagnosis

The varied nosology and lack of consensus about diagnostic criteria has created confusion around the diagnosis of PBA. However, proposed diagnostic criteria are as follows:<sup>1</sup> paroxysmal episodes of laughing, crying, or other emotional outbursts that are linked to brain damage of some sort and represent a departure from the affected person’s affective baseline. Outbursts are sudden, involuntary, uncontrollable, last for seconds or minutes, and are incongruent with or out of proportion to the provoking stimulus, mood or internal state with a quick return to the prevailing mood thereafter. Outbursts are often stereotyped. The outbursts cause distress or dysfunction, and are not accounted for by another disorder or drug effect. Suggestive features include concurrent autonomic changes, pseudobulbar palsy, and episodic anger.

The differential diagnosis of PBA includes certain psychiatric disorders, certain neurologic disorders with mood or affect disturbance, or individuals within the normal spectrum.<sup>1,125–127</sup> Mood disorders such as depression or bipolar disorder may present with some affective lability, but affect is congruent with mood and episodes last days or weeks not seconds or minutes. Anxiety disorders such as posttraumatic stress disorder or panic disorder can present with episodic

displays of affect coupled with autonomic reactivity, but the individual will have an internal sense of anxiety. However, as pointed out above, PBA may be comorbid with disorders such as depression or anxiety, and the diagnosis of one does not exclude the other.<sup>2,13,21,66</sup> Psychotic disorders such as schizophrenia may present with incongruent or odd affect, but the diagnosis is clear based on the other presenting symptoms such as hallucinations, delusions, or disorganized behavior over a period of time. Personality disorders with affective dysregulation such as borderline personality disorder may show sudden and shifting affect, but this is congruent with the internal sense of unstable mood. Alcohol or psychoactive substance intoxication may present with emotional expressions inappropriate to the situation, but this is mood congruent. Witzelsücht is a disorder of mood associated with brain tumors, and more rarely TBI, stroke, or dementia, where patients experience inappropriate situations as genuinely funny or mirthful. Their inappropriate mirth may be mistaken for PBA. Similarly, those with MS may be misdiagnosed with PBA when they experience euphoric moods that appear inappropriate to their circumstance, but mood and affect are congruent. Neurologic disorders of affect may also be mistaken for PBA. As referenced above, seizure activity or aura can present with sudden episodes of laughter or crying in gelastic or dacrystic epilepsy. Risus sardonius from tetanus infection is a tetanic activation of facial expression resembling laughing, but is unlike PBA otherwise. Finally, essential crying is a normal propensity toward weeping in a small number of individuals, but does not cause impairment. Mood and affect are congruent in essential crying.

Typically, PBA is not the index symptom of a patient's presentation and is accompanied by symptoms and signs suggestive of the underlying neurologic abnormality.<sup>125</sup> If this is not the case, a complete examination and work-up is indicated considering the diagnostic criteria and differential diagnoses discussed above. This work-up would include a thorough history screening for functional impairment, psychosocial impact, and comorbidities, a physical exam, and indicated investigations based on the likely underlying neurologic disorder.

Multiple scales have been created and validated for screening, diagnostic clarity, research purposes, and monitoring of therapeutic response in PBA. The Center for Neurologic Study–lability scale (CNS-LS) is a self-report measure used to screen for PBA, as a research measure, and to monitor response to treatment.<sup>1,12,125–128</sup> It has been validated in ALS<sup>12</sup> and MS<sup>128</sup> with good criterion and construct

validity, sensitivity and specificity, test-retest reliability, and internal consistency. The pathological laughter and crying scale (PLACS) is an interviewer-administered questionnaire that can evaluate the severity of symptoms and response to treatment over time.<sup>1,125–127,129</sup> It has been validated in stroke,<sup>129</sup> TBI,<sup>66</sup> and Alzheimer's disease<sup>130</sup> with good sensitivity and specificity, test-retest reliability, and inter-rater reliability. The PLACS also includes two questions about distress or embarrassment. The emotional lability questionnaire is an adaptation of the PLACS for use specifically in ALS.<sup>131,132</sup> It has not been validated in other populations but seems to have internal and construct validity for ALS.<sup>131,132</sup>

## Treatment

Although PBA is likely related to specific disruptions of a complex cortico-limbic-subcortico-thalamic-pontocerebellar network, treatments are often targeted more globally. Multiple pharmacotherapies have been effective for the treatment of PBA.<sup>133–137</sup> The majority of medications are used off-label, with evidence from case reports, case series, small open-label trials, and small randomized, placebo-controlled trials.

Antidepressants have been classically used to reduce the frequency and severity of symptoms.<sup>138</sup> Within the class of antidepressants, selective serotonin reuptake inhibitors (SSRIs) are some of the most commonly used medications. There are case reports or series, and a small crossover, double-blind, placebo-controlled trial showing the effectiveness of citalopram.<sup>139–142</sup> Sertraline has been shown to be effective for treatment in a case report and case series, and in double-blind, randomized, placebo-controlled trials.<sup>143–145</sup> Case series and small open-label trials have supported the effectiveness of fluoxetine, paroxetine, and fluvoxamine.<sup>146–151</sup> There is also evidence for tricyclic antidepressants treatment of PBA in a small double-blind, placebo-controlled, crossover trial using amitriptyline in MS patients;<sup>152</sup> a small double-blind, placebo-controlled trial using nortriptyline;<sup>129</sup> and some evidence for the use of imipramine.<sup>153</sup> Additionally, there are case reports for the selective noradrenergic reuptake inhibitors venlafaxine,<sup>154</sup> duloxetine,<sup>155</sup> and reboxetine.<sup>156</sup> The action of serotonergic or noradrenergic agents appears independent of antidepressant effect and occurs more quickly than the antidepressant effects of these medications, indicating a distinct mechanism of treatment related to serotonin, or other effects on dopamine or  $\sigma$ -1 receptors.<sup>133–137</sup>

There is less evidence for the use of other agents such as the mood stabilizer and antiepileptic lamotrigine,<sup>157,158</sup>

the atypical antipsychotics quetiapine<sup>159</sup> and aripiprazole,<sup>160</sup> and the dopaminergic agents levodopa and amantadine.<sup>161,162</sup> The theoretical underpinnings of the mechanisms of action are unclear.<sup>133–137</sup>

The only US Food and Drug Administration-approved agent for the treatment of PBA is dextromethorphan/quinidine (DM/Q).<sup>163–167</sup> DM is a noncompetitive antagonist of the NMDA glutamate receptor and was discovered to be effective for PBA while being tested as a treatment to slow the neurotoxicity and progression of ALS.<sup>163–167</sup> Unfortunately, it was found to be ineffective for slowing the progression of ALS. Of note, DM/Q is also a  $\sigma$ -1 agonist.<sup>163–167</sup> The mechanism of action for PBA is not completely clear, but is theorized to be related to the  $\sigma$ -1 agonist action of DM. These receptors are densely distributed in areas related to emotional expression including limbic and motor regions of the brain as well as the brainstem and cerebellum.<sup>166–168</sup> DM is quickly metabolized by cytochrome P450 2D6 isoenzyme, and thus inhibition of this enzyme by Q is helpful to maintain therapeutic levels of DM for treatment.<sup>163–167</sup> Two relatively large, randomized, placebo-controlled, double-blind studies of patients with MS and patients with ALS or MS have shown DM/Q to be efficacious.<sup>163,165</sup>

Comparatively, the medications above have different benefits and risks of use. For example, SSRIs are relatively well-tolerated and safe, with less impact on the corrected cardiac QT interval, fewer medication interactions than that of DM/Q, fewer cardiac and anticholinergic side effects than tricyclic antidepressants, and have indications for comorbidities such as depression and anxiety.<sup>167,169</sup> However, SSRIs have their own risk profile such as an increased risk of bleeding amongst those with ischemic stroke, although mortality does not appear to be impacted.<sup>170</sup> Overall, DM/Q fared well in safety and tolerability trials.<sup>163,164</sup> It behooves the clinician to use the relative benefit and side effect profile to help patients and their families make appropriate treatment decisions.<sup>167</sup>

In addition to pharmacologic studies, there is support from small case series for cognitive and behavior therapy for PBA<sup>171,172</sup> and an alternative treatment technique called hwan-gryunhaedogtang, a traditional Chinese medicine approach to address imbalances in the mind and body.<sup>173</sup>

## Summary and future directions

In summary, PBA is a disorder resulting from neurologic damage manifesting as sudden, stereotyped affective outbursts that are not reflective of mood. This condition

is common in neurodegenerative disorders. It is poorly recognized, variably characterized, and causes significant distress and dysfunction for patients and their families. Although the biological underpinnings are unclear and likely multiple, there appears to be a disruption of the cortico-limbic-subcortico-thalamic-pontocerebellar network involved in emotional expression and regulation. Neurologic damage likely impacts neurotransmitter systems, and thus pharmacologic treatments are often used to modify neurotransmitters accordingly. Although the exact mechanism of action of pharmacologic treatments is unknown, agents such as SSRIs and DM/Q may be indicated depending on the needs of the individual patient.

The limitations of studies to date include the lack of consensus on diagnostic criteria and terminology, small sample sizes, varied populations presenting with PBA, inconsistent methods used between studies for finding cases, measuring symptoms and response, lack of assessment of comorbidity, lack of long-term data, and lack of comparative studies between the various available pharmacologic agents.<sup>1,2,5,7,11</sup>

It is hoped that identification and treatment of PBA is improved with a consensus on diagnostic criteria allowing for better identification of cases and larger sample sizes for studies. Future studies should identify those with PBA within specific patient populations, particularly amongst neurodegenerative disorders where PBA is more common, to better understand the variations within specific disease processes and guide specific treatments accordingly. Wider validation and use of available screening, diagnostic, and monitoring tools such as the CNS-LS, the PLACS, and the emotional lability questionnaire would provide further case identification, interstudy and intrastudy consistency, comparisons amongst various neurologic diseases, and accurate evaluation of response to treatments. Similarly, assessment of comorbidity using other diagnostic tools for depression, anxiety, cognitive functioning, and psychosocial impact would improve the quality of research in the field. All of the above would be best carried out with a long-term trajectory to monitor patients over the course of their illness. Future neuroimaging studies and advances in technology may further elucidate the exact anatomical, neurotransmitter, and cellular level disruptions in those with PBA. This may also help to inform and refine treatment options.<sup>11</sup>

Outside of pharmacologic interventions, there are multiple future avenues for novel treatments. Cognitive and behavioral therapies, other psychotherapies, and alternative

medicine treatments have not been well evaluated and warrant further attention based on preliminary studies.<sup>171–173</sup>

## Disclosure

The authors report no conflicts of interest in this work.

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