Pseudobulbar affect (PBA), also known as pathological laughter and crying, affects approximately 2 million Americans. The causes of PBA are complex, but it is believed to result from the alteration of neuronal pathways, primarily in the frontal lobe of the brain, which control emotions. Symptoms suggestive of PBA commonly occur in individuals diagnosed with Parkinson disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), traumatic brain injury (TBI), and stroke. Pseudobulbar affect (PBA) was first recognized in the 19th century; however, despite being extensively described before 1940, PBA is perceived as a relatively “new” disease today. In 1886, Oppenheim and Siemerling discussed individuals with lesions along the brainstem’s descending pathways with inflated emotional behavior. The behavior was described as “spasmodic explosive outbursts of laughter or weeping” and was termed “pseudobulbar affect.” One of the oldest descriptions of pathological laughing and crying is described by French surgeon, Ambroise Paré, during the 16th century.

PBA has been labeled emotional lability, emotional incontinence, involuntary emotional expression disorder, emotional dysregulation, emotionalism, or pathological laughing and crying. The patient’s laughter or crying does not always coincide with the mood or intensity of the experience the patient describes, the current social situation, or stimuli; PBA may also be elicited without a stimulus. Patients with PBA may have an appropriate response that is more intense, recurring, and hyperbolic. These responses may also be uncharacteristic of the patient, such as excessive crying in a patient who rarely cried prior to the onset of PBA. PBA is often misdiagnosed as a psychiatric disorder, such as depression, or underrecognized in patients with conditions whose symptoms mimic those of PBA. Unlike patients diagnosed with mood disorders, those with PBA have unsustained, explosive, and irregular emotional responses.

PBA occurs most commonly among patients who have PD, multiple sclerosis, amyotrophic lateral sclerosis or AD or have experienced a traumatic brain injury, stroke and other neurological diseases that damage the central nervous system. Patients and caregivers report experiencing embarrassment and a decreased quality of life, which
may lead to disruptions in their social lives, including isolation and loss of employment. It is a significant national health issue in the United States, occurring in greater numbers of individuals than those affected by PD, MS, or ALS alone.12-14

**Parkinson Disease**

In the United States, an estimated 1 million individuals, which is more than the combined number of patients who have been diagnosed MS or ALS, have a PD diagnosis. Worldwide, that number is 10 million. Every year in the United States, roughly 60,000 individuals are diagnosed with PD, not including the thousands who remain undiagnosed. PD is a chronic and progressive movement disorder with symptoms that persist and worsen over time. The symptoms and degree to which one experiences these are highly individualized, but symptoms typically include tremors of the hands, arms, legs, jaw, and face; bradykinesia, or slowness of movement; rigidity or stiffness of the limbs and trunk; and postural instability or impaired balance and coordination. There is currently no cure, although most patients are managed with medication and/or surgery.

Like PBA, the cause of PD is unknown, although research has facilitated a better understanding of this disease. PD involves the malfunction and death of vital neuronal cells in the brain, primarily the substantia nigra where neurons produce dopamine, the neurotransmitter that controls movement and coordination. As PD progresses, the amount of dopamine produced in the brain decreases, leaving a person unable to control movement.

The combined direct and indirect costs of PD, including treatment, Social Security payments, and lost income from an inability to work, are estimated to be nearly $25 billion per year in the United States alone. According to the PBA Registry Series (PRISM) trial, which will be described in greater detail later in this supplement, roughly 26% of patients with a PD diagnosis have symptoms suggestive of PBA.1

**Multiple Sclerosis**

MS is a chronic inflammatory and neurodegenerative disease that is a consequence of an abnormal response of the body’s immune system, which directs an immune-mediated process against the central nervous system. Targets include, but are not limited to, the nerve fibers in the brain, spinal cord, and optic nerves. This immune attack is also waged against the fatty myelin substance that covers the nerve fibers, resulting in scarring (or sclerosis). Although the cause is unknown, activation of the disease is hypothesized to be triggered by environmental causes in genetically susceptible individuals. MS affects approximately 400,000 people in the United States and adversely affects quality of life (QOL), employment, social relationships, and patients’ productivity.15,16 The total all-cause healthcare costs associated with MS, including direct and indirect costs, in the United States ranges from $8528 to $52,244 per patient per year, which equates to $20.8 billion for all patients annually.27 According to the PRISM trial results, approximately 46% of patients diagnosed with MS have symptoms suggestive of PBA.1

**Amyotrophic Lateral Sclerosis**

ALS, also known as Lou Gehrig disease, is a progressive neurological disease that mainly involves neurons responsible for controlling voluntary muscle movements such as swallowing, breathing, talking, and walking. When symptoms begin in the arms or legs, it is referred to as limb-onset ALS. Other individuals first notice speech or swallowing problems, which is termed bulbar-onset ALS.

The deterioration, degeneration, and death of motor neurons extending from the brain to the spinal cord and to muscles throughout the body cause the symptoms of ALS. These usually include muscle weakness or stiffness, with later progression to loss of strength in all muscles under voluntary control.

The CDC has estimated that between 14,000 and 16,000 Americans have ALS, which is a much smaller economic impact than PD or MS in comparative numbers. Regardless of the prevalence, ALS is severely debilitating for those diagnosed with the disease. Although the cause is unknown, several potential risk factors for ALS include being male, white, and between the ages of 60 and 69 years. Because military veterans are twice as likely to develop ALS, the hypothesis that environmental toxins may trigger the disease has facilitated the recognition of ALS as a service-connected disease by the US Department of Veterans Affairs. According to the PRISM trial results, roughly 45% of patients diagnosed with ALS also have symptoms suggestive of PBA.1

**Alzheimer Disease**

AD is the most common form of dementia, which is a general term for memory loss and other cognitive capacity that impacts daily life. AD accounts for up to 80% of dementia cases. AD is not considered a normal part of aging and is a progressive disease that worsens over time. Although current medication therapy does not cure or prevent AD from progressing, these agents can temporarily slow the worsening of dementia symptoms and improve QOL for those with AD and their caregivers. There are roughly 5.5 million Americans living with AD dementia in 2017, with most of these patients 65 years or older, and this number is growing quickly. Although the cause is unknown, several potential risk factors for AD include being 65 years or older, female, and black and/or Hispanic.28

Elderly patients with dementia have twice as many annual hospitalizations as elderly patients without dementia.29 Additionally, patients with dementia who have Medicare are more likely than patients without dementia to have other chronic disorders.30 The total annual payments (health, long-term, and hospice care) for people with AD or other dementias are slated to rise from $259 billion in 2017 to in excess of $1.1 trillion by 2050. This astounding increase contains more than a 4-fold growth in Medicaid and Medicare government spending and out-of-pocket spending.31
Traumatic Brain Injury and Stroke

The diagnosis of PBA in patients with brain injury resulting from a TBI and stroke is challenging and often misdiagnosed.\textsuperscript{20} Brain injuries resulting from TBI and stroke were also considered in the PBA patient spectrum in PRISM. According to the PRISM trial results, roughly 53\% and 38\% of patients diagnosed with these conditions, respectively, have symptoms suggestive of PBA.\textsuperscript{1}

TBI is described as, “an alteration in brain function, or other evidence of brain pathology, caused by an external force.”\textsuperscript{31} TBI caused by combat, sports, and minor accidents may have harmful results and lead to a reduction in brain reserve and protection against various brain disorders with late onset.\textsuperscript{22} In a single game, National Football League (NFL) players may be hit 30 to 50 times in the head.\textsuperscript{22} This may result in subdural hematomas, decreased cognition, and death.\textsuperscript{22} A highly publicized result of TBI in professional football players is chronic traumatic encephalopathy (CTE), a condition believed to be caused by tau tangles in the brain.\textsuperscript{23} Symptoms of CTE include changes in mood and behavior, headaches, Parkinsonism, and a decrease in coordination.\textsuperscript{23}

Currently, there is debate around the link between CTE and dementia, particularly in those with concussions, and a lack of clinical criteria to diagnose CTE.\textsuperscript{23,25} As a reason to question these postulations, skeptics cite “samples of convenience” used as case reports to derive the clinical and pathological CTE data, samples from athletes whose autopsies were requested because the person experienced neuropsychiatric symptoms as opposed to a randomly sampled group.\textsuperscript{23,25,26} However, results of a study by Mez et al of 202 American football players showed a diagnosis of CTE in 87\% of players from all levels of football and 99\% in NFL players.\textsuperscript{22} The authors noted further investigation is warranted, as CTE is not a rare disease, and the sample was one of convenience derived from donors.

Incidence and Prevalence

It is estimated that up to 2 million Americans have PBA with some sources suggesting that up to 7 million individuals in the United States exhibit symptoms suggestive of PBA.\textsuperscript{18,22} Despite this large population, there is new recognition that PBA is both underdiagnosed and undertreated.\textsuperscript{1} The varying individualized symptoms associated with PBA complicate efforts to further determine prevalence.\textsuperscript{1,4,29}

PRISM was created to collect prevalence data from patients with symptoms due to common neurological disorders in a large, representative sample of the US population.\textsuperscript{1} The registry was designed to collect information from 10,000 patients at 500 sites nationwide with the following 6 conditions: PD, MS, ALS, AD, TBI, or stroke.\textsuperscript{1} A total of 5290 patients enrolled in the PRISM registry.\textsuperscript{1} The characteristics of PRISM patients are listed in Table 1.\textsuperscript{1} The lowest average age was in the TBI and MS groups, roughly 48 years.\textsuperscript{1} A mean of 6.7 years was recorded as the time since the diagnosis of the underlying primary neurological condition, but this item was only recorded for 50.6\% of the sample.\textsuperscript{1}

The presence of PBA symptoms was defined as a Center for Neurologic Study-Lability Scale (CNS-LS) score ≥13.\textsuperscript{1} A CNS-LS score ≥21 was also evaluated to determine the prevalence of PBA in patients with more severe and recurrent symptoms.\textsuperscript{1,35,29} The CNS-LS was the first validated tool used to measure symptoms of PBA by self-report.\textsuperscript{1,16} It is divided into subscales used to measure crying (3 items) and laughter (4 items).\textsuperscript{1,31} Each item is scored from 1 (applies never) to 5 (applies most of the time), and the cumulative scoring may range from 7 to 35.\textsuperscript{1,31} The CNS-LS and an 11-point QOL scale assessing the impact of neurological disorders was completed by either the patient or the patient’s caregiver.\textsuperscript{1}

A total of 36.7\% of patients had CNS-LS scores ≥13 and 9.3\% had CNS-LS scores ≥21.\textsuperscript{1} Patients with PD (26.0\%) had the smallest group with CNS-LS scores ≥13 and TBI patients the highest, at 52.4\%. Higher CNS-LS scores were associated with lower QOL scores.

The prevalence of neurological diagnoses in patients ≥65 years in the PRISM trial was greatest in most categories, with the exception of ALS, MS, and TBI. The percentage breakdown is as follows: AD = 1660 (34.0\%), PD = 639 (21.0\%), MS = 1215 (23.0\%), ALS = 54 (1.8\%), stroke = 476 (15.6\%), and TBI = 107 (3.5\%).\textsuperscript{1} Although more females were enrolled in the registry, males were represented in a higher percentage in the ALS and PD populations.\textsuperscript{1} The differences in prevalence by age are unclear, but do not appear to be explained by a difference in the relative percentage of underlying neurological conditions between younger and older patients.\textsuperscript{1}

### Etiology

There has been more focus on PBA recently, especially since the FDA approval for a medication specific for this condition.\textsuperscript{22} Despite earlier

<table>
<thead>
<tr>
<th>TABLE 1. PRISM Patient Characteristics\textsuperscript{1}</th>
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</thead>
<tbody>
<tr>
<td>Total number of patients (N)</td>
</tr>
<tr>
<td>Average age (years)</td>
</tr>
<tr>
<td>Age 65 or older</td>
</tr>
<tr>
<td>Age 75 or older</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Neurological conditions</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
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uses of dextromethorphan with quinidine, little was understood about this emotional lability, the associated reflexive episodes of laughter and tearfulness, and the proposed mechanism by which these compounds were effective in controlling these symptoms.8 The pathways related to PBA are multifaceted and thought to result from disruptions of neural networks that control the generation and regulation of motor output of emotions.9 PBA is associated with brain injury or a neurological disease or disorder that alters normal neuronal control and affect likely linked to frontal lobe function and other areas of the brain, such as the brainstem and cerebellum.2 Brain lesions located mostly in the frontal lobes and descending pathways to the brainstem, basis pontis, and cerebellum, which encompass systems thought to be involved in motor control of emotional expression, are linked to PBA.2 One of the original hypotheses regarding the pathophysiology of PBA proposed that there was a disruption of the cortical inhibition to an upper brainstem center followed by release of lower bulbar nuclei that coordinate the motor response connected with laughing and crying.10 An additional hypothesis is that a dysfunction in the connection between the cerebellum and cerebral cortex leads to a disruption in emotional regulation.6,14

### Risk Factors

The underlying mechanisms associated with developing PBA are not fully understood. PBA is associated with brain injury and neurological disorders, many of which are associated with demographic predictors but otherwise have unknown origin; however, TBI and stroke are often preventable. The leading known causes of TBI in adults 65 years and older are falls and motor vehicle crashes.25 When addressing fall prevention in the elderly, identifying risk factors and patient education is key. Risk factors include issues with shoes and/or feet, poor vision, postural dizziness, gait and balance problems, psychoactive medications, lower body weakness, and home safety. Healthcare providers should educate patients about these risks and modify medications, if applicable; prevent hypotension; optimize vision; monitor for foot problems, and promote the importance of home safety.36,37 Wearing motorcycle helmets and seat belts and avoiding alcohol-impaired driving can decrease the risk of motor vehicle-associated TBI.11 Cardiovascular risk factors affect cognition as we age and are major contributors to the risk for conditions such as AD and stroke.16 According to the American Heart Association (AHA) and American Stroke Association, individuals can take actions to promote optimal brain health. These actions, termed the AHA’s Life’s Simple 7, include ideal health factors and behaviors that include, but are not limited to, controlling weight, blood pressure, blood glucose, and total cholesterol, and smoking cessation. Physical activity 4 or more times per week for more than 75 minutes with vigorous intensity and 150 minutes with moderate intensity and a healthy diet consisting of mainly fruits and vegetables, fish, and fiber-rich whole grains, with limited consumption of sodium and sugar-sweetened items, account for the suggested ideal health behaviors.38,39

### Clinical Presentation

PBA episodes are generally perceived to be unprovoked and out of proportion to the mood the patient is experiencing. The degree of emotional response is often considered extreme and unable to be voluntarily suppressed by the patient. Tearfulness is reported to be a more common PBA manifestation than laughter.4 PBA (especially crying-predominant PBA) has been reported to be more prevalent in women with ALS.40 Criteria common to PBA seen in TBI were reported by Poeck and Cummings et al, but others have also cited associated findings (Table 2).19,20

### Table 2: Reported Criteria Associated With PBA Manifestations6,20

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes are not congruent to the situation and may be triggered by nonspecific stimuli.</td>
<td>The patient’s emotional expression and current mood do not closely correlate and patient does not experience any relief while expressing the affects and episodic changes in mood correlating to the episodes. Difficulty in controlling episodes and episodes that build up and resolve in a stepwise manner.</td>
</tr>
<tr>
<td>Episodes not in line with or extremely exaggerated compared with the patient’s current mood and occur in an inappropriate situation or with an involuntary attribute at onset.</td>
<td>The necessity of a “wait-out” period for the patient to return to his or her prior activity. This usually takes anywhere from a few seconds to minutes.</td>
</tr>
<tr>
<td>Episodes are different from the patient’s usual emotional response, may be inconsistent with or in excess of the patient’s current mood, and are independent or in excess of inciting stimuli. Spontaneous or exaggerated expressions of emotion.</td>
<td>Disturbances caused by repetitive episodes result in social or occupational functional impairment or significant clinical distress. The symptoms are not elicited by a direct effect of a substance. No other psychological or neurological disorders account for the patient’s symptoms.</td>
</tr>
</tbody>
</table>

PBA indicates pseudobulbar affect.
Symptoms
Untreated PBA can be very distressing and embarrassing and can cause anxiety and social dysfunction, thus negatively affecting day-to-day functions, relationships, overall QOL, and patient productivity, as well as increasing the caregiver burden. The symptoms can be severe, with persistent, incessant episodes having an abrupt unpredictable onset. Some patients describe the feeling associated with the onset of a PBA episode as comparable to the start of a seizure; the duration of an outburst can be a few seconds to several minutes and may occur several times a day.

Symptoms suggestive of PBA in nursing homes present in 17.5% of residents with neurological conditions and 9% of residents overall.46 Symptoms suggestive of PBA were observed in an estimated 45% and 70% of patients diagnosed with dementia or HIV-dementia, respectively.44 More research to validate the findings (especially in patients with HIV-dementia) and more refined screening tools should be developed for patients who exhibit PBA symptoms.

Frequently co-occurring psychiatric disorders, especially depression (35%), can present with symptoms similar to PBA.3 PBA and depression must be considered separate conditions and treated accordingly. Symptoms such as fatigue, anorexia, insomnia, and feelings of hopelessness and guilt are not linked with PBA. Depressive symptoms classically last weeks to months, but a PBA episode only lasts seconds or minutes. Also, crying, as a symptom of PBA, might be unrelated or inflated relative to the patient’s mood, but crying is consistent with subjective mood in depression.

Impact
The cost of PBA includes not only financial aspects, but also those associated with the patient’s QOL. In a study by Palmgren et al that examined data from a large US national healthcare insurer, the annual weighted costs of hospitalizations were $12,394 per patient.43 Additionally, the annual weighted costs of emergency department visits were $1664 per patient.43

Although we understand there is a financial impact, there are also QOL impacts on the patients.45 When interpreting the QOL scale used in PRISM, the higher the score, the greater the negative impact (more adverse).1 Patients with PBA symptoms reported significantly worse mean QOL scores due to neurological conditions. QOL scores were the worst for all categories (PD, MS, ALS, AD, TBI, and stroke) and statistically significant for all but ALS (likely due to the small sample size). The QOL scale rated the impact on a scale of 1 (not at all) to 10 (strongly affected), all patient self-reported in response to “How has your neurological condition affected your quality of life?” (Table 3).

Similar to the QOL reported in the overall patient sample, patients ≥65 years with PBA symptoms had significantly higher mean scores for the impact of a neurological condition on QOL (6.3 for CNS-LS ≥13 vs 4.6 for CNS-LS <13; P <.0001, 2-sample t-test).1 The QOL impact parallels the findings from other studies, including the MOS 36-item short-form health survey (SF-36).44

Burden of Impact
Patients with PBA are aware of social norms and the inappropriateness of their responses. Thus, they are embarrassed by the inability to control these involuntary outbursts.4 This may lead to subsequent restriction of social interactions and a lower QOL.5 Subsequently, relationships may suffer, resulting in loss of those relationships, including divorce, and patients may become homebound.30

A study assessing the burden of illness across multiple measures and areas of function in patients suffering from PBA, such as social, occupational, and relationship problems, reported an example of how PBA affects patients.1,80 Results showed that patients and caregivers with PBA were less likely to be employed, likely due to a decrease in productivity at and outside of work and absenteeism from work.30 Patients with PBA are challenged by the underlying disorder as well as the accompanying emotional changes, thus often resulting in even more anxiety, depression, and other comorbid psychiatric illness and impairment compared with their non-PBA peers in the community.90 Another study evaluated the adverse impact of PBA symptoms and suggested that the symptoms alone, regardless as to whether they also had a posttraumatic stress disorder diagnosis, led to greatly decreased QOL and considerably increased healthcare costs.45

Caregivers experience a substantial burden when caring for patients with PBA. Compared with caregivers of patients with the same underlying neurological conditions without PBA, they experience a significantly increased illness burden.30 They feel uncertainty and embarrassment and lack the tools to handle these unpredictable outbursts. This can lead to even greater reduction in an already impaired degree, because of the underlying neurological disorder, of socialization, isolation, and lower QOL indices.90 We know that from other neurological conditions, such as dementia,

### TABLE 3. Quality-of-Life Scores of Patients With PBA Symptoms Categorized by Underlying Neurological Condition

<table>
<thead>
<tr>
<th>Neurological Condition</th>
<th>CNS-LS ≥13 (suggestive of PBA)</th>
<th>CNS-LS &lt;13 (not suggestive of PBA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI 52.4% (n = 590)</td>
<td>6.8</td>
<td>4.7</td>
</tr>
<tr>
<td>MS 45.8% (n = 1215)</td>
<td>7</td>
<td>5.2</td>
</tr>
<tr>
<td>ALS 44.8% (n = 125)</td>
<td>6.4</td>
<td>5.8</td>
</tr>
<tr>
<td>Stroke 37.8% (n = 757)</td>
<td>6.7</td>
<td>4.5</td>
</tr>
<tr>
<td>AD 29.3% (n = 1799)</td>
<td>6.4</td>
<td>4.3</td>
</tr>
<tr>
<td>PD 26% (n = 804)</td>
<td>6.4</td>
<td>5.2</td>
</tr>
</tbody>
</table>

AD indicates Alzheimer disease; ALS, amyotrophic lateral sclerosis; CNS-LS, Center for Neurologic Study-Lability Scale; MS, multiple sclerosis; PBA, pseudobulbar affect; PD, Parkinson’s disease; TBI, traumatic brain injury.
that behaviors that cannot be controlled by caregivers are often the catalyst for earlier unnecessary institutionalization.5 Elderly participants with varying degrees of cognitive impairment were more likely to have a shorter time to nursing home placement if they exhibited symptoms of behavioral, psychological, or poor physical health.6 Support for both the patients with PBA and their caregivers is essential in decreasing their burden of care and decline in health.

Conclusion

PBA is often unrecognized and misdiagnosed. Patients with PBA experience episodes of spontaneous or exaggerated laughter and/or crying that are disproportionate to or inappropriate for the current situation. It is often mistaken for mental health conditions such as depression and hidden by the symptoms of the commonly associated diseases ALS, TBI, MS, stroke, and AD. Both patients and caregivers often feel embarrassed, experience reduced QOL, and require support to help manage PBA. Raising awareness of PBA through the education of healthcare professionals, patients, families, caregivers, and the public may result in increased recognition and better management of PBA.

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Authorship information: Analysis and interpretation of data; concept and design; critical revision of the manuscript for important intellectual content; drafting of the manuscript; supervision.

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