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ORIGINAL RESEARCH

Pseudobulbar Affect: an Under-recognized and Under-treated Neurological Disorder

Susan S. Work · Jennifer A. Colamonico · Walter G. Bradley · Randall E. Kaye

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ABSTRACT

Introduction: Pseudobulbar affect (PBA) is a neurologic syndrome of emotional affect disinhibition, characterized by uncontrollable, exaggerated, and often inappropriate emotional outbursts, which may cause severe distress, embarrassment, and social dysfunction. However, the US prevalence of PBA remains unknown. ***Methods:*** An online survey was conducted primarily to estimate the US prevalence of PBA in patients with the six most commonly associated conditions: Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, stroke, and traumatic brain injury. Invitations to participate were randomly sent online to adults (aged ≥18 years) registered in the Harris Poll Online Panel who were patients or belonged to a household with a patient diagnosed with one of the six conditions (identified through previous screening by Harris Interactive). Participants were screened for PBA using the Pathological Laughing and Crying Scale (PLACS) and the Center for Neurologic Study-Lability Scale (CNS-LS). PBA estimates were made using a cut-off score of ≥13 on the PLACS and two different cut-off thresholds on the CNS-LS, a lower one of ≥13 and a more rigorous one of ≥21. Existing US prevalence data for the six underlying conditions were used to estimate US prevalence of PBA. ***Results:*** Of 38,000 individuals invited to participate, 8876 responded (23%) and 2318 (26%) completed the questionnaire. Mean prevalence of PBA across all six conditions was 10.1%, 9.4%, and 37.5% with the PLACS ≥13, CNS-LS ≥21, and CNS-LS ≥13 thresholds, respectively. Using disease population estimates from government agencies and professional organizations, the estimated US population with PBA ranged from 1.8 to 7.1 million. Among patients who discussed their laughing and/or crying episodes with a physician, 41% were diagnosed, and about half received a medication for their episodes. ***Conclusions:*** The overall prevalence of PBA was estimated to be about 10% across these commonly associated

Susan S. Work (✉) · Randall E. Kaye
Avanir Pharmaceuticals, Inc., 101 Enterprise, Suite 300, Aliso Viejo, CA 92656, USA. Email: SWork@avanir.com

Jennifer A. Colamonico
Healthcare & Policy Research, Harris Interactive, 161 Sixth Avenue, 6th Floor, New York, NY 10013, USA

Walter G. Bradley
Department of Neurology, Miller School of Medicine, University of Miami, 1120 NW 14 Street, Miami, FL 33136, USA

underlying neurological conditions and appears to be under-recognized.

Keywords: Alzheimer's disease; amyotrophic lateral sclerosis; diagnosis; multiple sclerosis; Parkinson's disease; prevalence; pseudobulbar affect; stroke; traumatic brain injury; treatment

INTRODUCTION

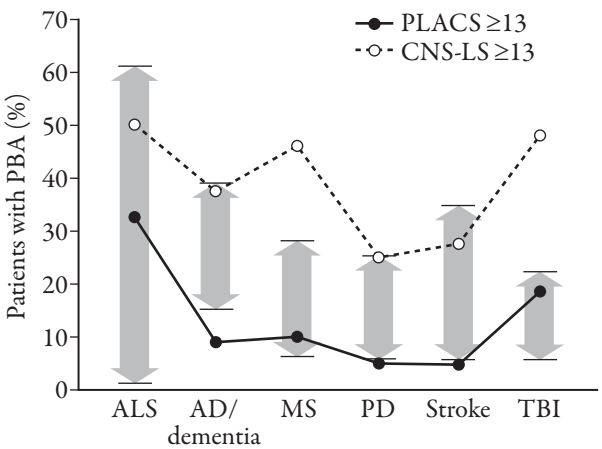
Pseudobulbar affect (PBA) is a neurologic syndrome of emotional affect disinhibition, characterized by frequent, uncontrollable emotional outbursts of crying and/or laughing that are usually exaggerated and inappropriate to the stimulus, and may be mood incongruent.[1-3] Some patients may also display outbursts of anger or frustration.[4] PBA occurs primarily in patients with neurologic conditions, stroke, or traumatic brain injury (TBI) and has been reported in patients with brain injury from numerous other causes, such as tumors, aneurysms, and herpes encephalitis.[3,5] Although its etiology is unclear, PBA is thought to be caused by the presence of brain lesions interfering with neural circuits and neurotransmitters that regulate voluntary and perhaps over-learned involuntary emotional expression.[2,3]

Clinical syndromes of abnormal emotional expression in patients with brain lesions or injury have been noted since at least the late 19th century and defined with varying terms and descriptions, including pathological laughter and crying (PLC), involuntary emotional expression disorder, and emotional lability.[1,6] Clinical case and study data have shown that PBA may cause severe distress, embarrassment, and social disability among patients.[3,7-10] In addition, studies have shown that patients with PBA or similar syndromes experience an increased incidence of depression,[11] impairments in executive function[12] and sexual function,[13] and ability to perform activities of daily living[14] compared with patients with the same underlying neurological disorder but without PBA.

However, the total prevalence of PBA in the USA remains unclear. Prevalence estimates for PBA in each of the six most commonly associated conditions – amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD)/dementia, multiple sclerosis (MS), Parkinson's disease (PD), stroke, and TBI – have differed considerably within each population[1,3] (Figure 1[5,10,11,15-32]). This variability is probably due to differences in the populations studied and in the criteria and methods used for identifying PBA.[1,3] Yet, no previous study has sought to estimate the prevalence of PBA across different disorders using similar criteria and methods of identification.

In addition, several researchers have observed that PBA is generally under-recognized,

Figure 1. Ranges of estimated prevalence for PBA and similar syndromes, such as emotional lability as variously defined and identified in published reports are indicated by the vertical gray arrows.[5,10,11,15-32] Prevalence rates determined in the present study with PLACS≥13 and CNS-LS≥13 are indicated by the transverse plot points. The prevalence rates determined with CNS-LS≥21 in the present study were very similar to those for PLACS≥13, and are not shown here to enhance visual clarity. AD=Alzheimer's disease; ALS=amyotrophic lateral sclerosis; MS=multiple sclerosis; PD=Parkinson's disease; TBI=traumatic brain injury.



misdiagnosed, and under-treated, although there are few data to quantify these observations.[1,3,8,33] We conducted an online survey among patients in the USA with six underlying conditions commonly associated with PBA – ALS, MS, stroke, AD/dementia, TBI, and PD – in order to prospectively estimate the overall prevalence of PBA and quantify the extent to which PBA is diagnosed and treated. Secondary goals were to investigate patterns of physician recognition, diagnosis, and treatment of PBA.

MATERIALS AND METHODS

Survey Overview

This stratified sample survey was designed and directed by the authors. Avanir Pharmaceuticals commissioned the study, which was conducted by Harris Interactive® (HI), a market research firm specializing in public opinion and consumer surveys (http://www.harrisinteractive.com). Both patients with PBA and caregivers were surveyed to ensure participation of more severely incapacitated patients.

Study Sample

The study sample was drawn from a nationally representative sample of more than 6 million US adults (aged 18 years and over), registered in the Harris Poll Online (HPOL). The HPOL includes 1.5 million subjects who have been screened by HI via a checklist for presence of chronic illnesses. To recruit patients with ALS, AD, MS, PD and stroke, HPOL panel members previously identified by HI as either having one of the above conditions, or being a primary caregiver for a household member with the condition were sent online invitations inviting them to participate in a survey about their "thoughts on and experiences with some important healthcare related topics." The online survey was fielded between September 20 and October 7, 2005.

As TBI is not part of the HI Chronic Illness Screener instrument, these patients were identified by sending survey invitations to panel members with chronic headaches, posttraumatic stress disorder (PTSD), or general disability. The survey asked these members if they had been diagnosed by a physician or other healthcare professional with TBI, defined as a head injury requiring hospitalization, which resulted from being knocked unconscious, having a skull fracture, or suffering other brain injury. The TBI patients in this sample thus represented a subset of relatively severe cases, as US data show that only about 16% of TBI survivors annually are hospitalized for their injury.[34] In addition, invitations were sent to a randomized national sample from the general HPOL to enhance the representativeness of the sample. Recruitment quotas were set for each underlying condition in order to have a large enough sample of each disease state for analysis (Table 1).

Study Measures

To identify PBA, participants were asked to complete the Pathological Laughing and Crying Scale (PLACS),[31] and the Center for Neurologic Study-Lability Scale (CNS-LS),[4,35] which includes an auxiliary subscale for episodes of anger/frustration. Patients and caregivers were asked the same questions, with caregivers answering based on their observations of the patient.

PLACS

The PLACS is an interviewer-rated instrument that measures the severity of PBA symptoms, and has been validated in stroke patients.[31] Eight items of the scale relate to laughing and eight to crying. The scale begins with two screening questions asking if the respondent

Table 1. Estimated prevalence of PBA within and across the six most commonly associated neurologic conditions.

Population	ALS	AD/dementia	MS	PD	Stroke	TBI	TOTAL
Desired sample quota	225	500	500	500	500	≥250*	2475
Invitations mailed	4343	5124	6723	5721	7013	9013†	37937
Survey total, *n*	40	499	504	449	500	326	2318
Patients/caregivers, *n*	25/15	49/450	418/86	254/195	415/85	273/53	1434/884
Patients/caregivers, %	63/37	10/90	83/17	57/43	83/17	84/16	62/38
Proportion of patients with PBA per scale/threshold criteria							
PLACS≥13, %	32.5	9.2	9.8	5.0	4.7	17.4	10.1
CNS-LS≥21, %	27.5	9.6	9.8	3.6	4.3	15.5	9.4
CNS-LS≥13, %	50.0	38.5	46.2	24.0	27.6	48.2	37.5
Margin of error at 95% confidence, %	15.5	4.4	4.4	4.6	4.4	5.4	2.0
Estimated US prevalence of underlying conditions							
US prevalence: Source 1‡	30,000	6,800,000 (4,000,000 AD)	400,000	1,000,000	5,400,000	5,300,000	18,930,000
US prevalence: Source 2§	17,928‖	747,000	179,280¶	597,600	1,942,200#	2,390,400	5,874,408
Estimated US prevalence of PBA							
PLACS≥13: Source 1:	9750	625,600	39,200	50,000	253,800	922,200	1,911,930
Source 2:	5827	68,724	17,569	29,880	91,283	415,930	593,315
CNS-LS≥21: Source 1:	8250	652,800	39,200	36,000	232,200	821,500	1,779,420
Source 2:	4930	71,712	17,569	21,514	83,515	370,512	552,194
CNS-LS≥13: Source 1:	15,000	2,618,000	184,800	240,000	1,490,400	2,554,600	7,098,750
Source 2:	8964	287,595	82,827	143,424	536,047	1,152,173	2,202,903

*As TBI is not included as part of the Harris Chronic Illness Panel, the potential sample pool was unknown and thus quota limits for TBI were difficult to anticipate; therefore, quota limits for TBI were set at 250 to 500.
†As TBI is not included as part of the Harris Chronic Illness Panel, TBI was identified by sending survey invitations to panel members with chronic headaches, posttraumatic stress disorder (PTSD), or general disability, and inquiring whether these members had been diagnosed by a physician or other healthcare professional with TBI, defined as a head injury requiring hospitalization, which resulted from being knocked unconscious, having a skull fracture, or suffering other brain injury. Therefore, a greater number of invitations were sent to these groups in order to identify a sufficient number of patients with TBI.
‡Source 1: Prevalence was derived from the following professional and government organization Web sites:
1. ALS: The ALS Association.[38]
2. AD/dementia: National Institute of Neurological Disorders and Stroke (NINDS).[39]
3. MS: National MS Society.[40]
4. PD: Parkinson's Disease Foundation.[41]
5. Stroke: American Stroke Association.[42]
6. TBI: Centers for Disease Control (CDC) and National Center for Injury Prevention and Control (NCIPC) estimate of Americans who currently have a long-term or lifelong need for help to perform activities of daily living as a result of a TBI.[43]
§Source 2: Prevalence was calculated from approximate point prevalence rates per 100,000 population (all ages) provided by Wallin and Kurtzke, 2004[44] multiplied by 2988, ie, the approximate total current USA population divided by 100,000. The number used for the total USA resident population (298,755,510) was derived from the Population Division of the United States Census Bureau.[45]
‖Motor neuron disease.
¶Rate for high-risk areas.
#Acute cerebrovascular disease and subarachnoid hemorrhage.
AD=Alzheimer's disease; CNS-LS=Center for Neurologic Study-Lability Scale; MS=multiple sclerosis; PBA=pseudobulbar affect; PD=Parkinson's disease; PLACS=Pathological Laughing and Crying Scale; TBI= traumatic brain injury.

has experienced laughing or crying episodes; if either question or both are answered "rarely or no," the following questions related to laughing or crying, or the rest of the scale, is not administered. Each item/symptom is scored for severity on a scale of 0 to 3 points (0=rarely or not at all, 3=frequently), and then totaled to obtain an overall score. In stroke patients, a PLACS cut-off total score of ≥13 (PLACS≥13) has been shown to distinguish individuals with PBA, with a sensitivity for clinically diagnosed PBA of 0.88, a specificity of 0.96, and a positive predictive value of 0.83 (*n*=67).[31] The PLACS has not been validated in other populations. For purposes of this survey, the PLACS questions were revised to allow for self-administration.

CNS-LS and Auxiliary Subscale

The CNS-LS is a self-report measure of PBA that has been validated in both ALS[4] and MS[35] patients. The CNS-LS consists of a subscale for laughter (four items) and one for tearfulness (three items), with each item scored on a five-point scale (1=applies never, 5=applies most of the time). In ALS patients (*n*=99), a cut-off score of 13 on the CNS-LS was found to successfully predict neurologists' diagnoses of PBA for 82% of patients, with a sensitivity of 0.84 and a specificity of 0.81; the CNS-LS also showed good test-retest reliability (0.88) and internal consistency (Cronbach's α coefficient=0.87).[4] In MS patients (*n*=90), a CNS-LS cut-off score of 13 correctly predicted 78% of physicians' diagnoses regarding PBA, with a sensitivity of 0.96 and a specificity of 0.55, while a cut-off score of 17 correctly predicted 89% of physicians' diagnoses, with a sensitivity of 0.94 and specificity of 0.83.[35] For this survey, a CNS-LS cut-off score of ≥13 (CNS-LS≥13) was used as previously validated, and a more conservative cutoff of ≥21 (CNS-LS≥21) was also used, based on mean CNS-LS baseline scores from clinical trials in patients with MS or ALS and PBA.[33,36]

An eight-item auxiliary subscale of the CNS-LS measures episodes of labile anger, frustration, and impatience that may have a syndromal association with laughing and crying episodes.[4] When combined with the seven items of the CNS-LS in ALS patients, the resulting 15-item scale showed an internal consistency of 0.92 and test-retest reliability of 0.88.[4] A score of ≥27 on the combined scale predicted physicians' diagnoses regarding PBA with a sensitivity of 0.74 and a specificity of 0.80.[4] A cut-off score of ≥15 on the auxiliary scale to identify patients with labile anger, frustration, and impatience, associated with or independent of crying/laughter, was used in this trial based on the reported auxiliary scale scores of patients with and without PBA[4] and additional clinical trial experience with this subscale communicated by R.A. Smith in a telephone conversation (March 2006).[37]

Prevalence Estimates

Prevalence estimates for each of the six underlying neurological conditions were derived from two sources: professional and government organizations that serve as resources for US disease-prevalence data (Table 1, Source 1[38-43]), and a standard neuro-epidemiological review textbook (Table 1, Source 2[44,45]).[44,46,47] These data were found to be divergent, indicating lack of consensus on these statistics, with estimates generated by professional and government organizations being generally higher than those from published research reports cited in the textbook. Therefore, it was deemed prudent and appropriate to present both sets of data. The percentage frequency of PBA for each condition according to the PLACS and CNS-LS scores was multiplied by the prevalence of each disease and summed to derive a total estimated prevalence of PBA in the USA.

Assessment of PBA Diagnosis and Treatment Patterns

With regard to management of PBA, respondents were asked what kind of physician is mostly responsible for their care; if they had discussed the symptoms with that physician; if a diagnosis had been given for sudden crying or laughing or both; and if the physician had prescribed medication for recent episodes of crying/laughing or anger/frustration.

Statistical Analysis

Weighting for Demographic Variables and Proportionality

To adjust for potential bias due to nonresponse and to ensure that the sample was representative of the US adult population in each disease group, patient data for four of the six underlying conditions were weighted.[48] Weighting factors were applied to match the age and gender proportions of respondents with each disease to national figures provided by the National Center for Health Statistics/National Health and Nutrition Examination Survey[49] and the National Center for Injury Prevention and Control/Centers for Disease Control and Prevention.[50] For example, because there was a low response rate among young male TBI patients, who make up a substantial portion of this population, responses from young male TBI patients were inflated to reflect their true proportion among TBI patients.

Demographic weighting targets were applied only to patients, as caregivers did not provide age and gender data for their patients. As 90% of AD respondents were caregivers, the number of AD patient respondents was too small to weight. Similarly, the number of ALS patient respondents was too small to weight, due to the low incidence of the condition. "Unweighted" respondents were assigned a demographic weight of 1. For prevalence estimates, a proportional weight was assigned to each respondent (in addition to the demographic weights for each condition, where applicable) based on the proportion of their condition among all six conditions combined (Table 1, Source 1[38-43]). For uniformity, all sample sizes are reported herein as unweighted numbers; however, all percentages calculated from participant responses are reported with weighting factors applied.

Margin of Sampling Error

With probability samples the size of this survey sample (n=2318), there is 95% certainty that the results have a sampling error of ±2%. Although the online sample does not meet the strict criteria of a probability sample, a similar margin of sampling error is expected here. Analysis of individual neurological conditions yields a larger sampling error due to smaller sample sizes (Table 1). The margin of error at the 95% confidence interval (CI) is approximately 4% to 6% for the various conditions, with the exception of the smaller ALS sample (n=40), for which the margin of error is about 16%.

Backfill of Missing Data

The original survey was missing a question from the PLACS scale regarding the frequency of laughing and/or crying episodes. Therefore, a recontact survey was conducted among respondents who were asked the PLACS questions, of whom 86% completed the missing questions. To backfill missing responses, the multiple imputation capabilities in the Statistical Analysis System 9.0 were used to estimate replacement values.[51] The Markov Chain Monte Carlo method in SAS PROC MI was used to create a single "imputation" for each missing item. Each imputed value was constrained to an integer value in the range of the original data (0-3).

RESULTS

Survey Population

A random sample of approximately 38,000 subjects (*n*=37,937) of the HPOL database who had previously been identified as having ALS, AD, MS, PD, stroke, or symptoms suggestive of TBI were invited to participate. The average time to complete the online survey was 9 minutes. Of the 8876 (23.4%) respondents, 6086 (68.6%) were ineligible to participate due to non-US residence, respondent age (<18 years), or not having been diagnosed with one of the six underlying conditions of interest. Of the 2790 eligible respondents, 2318 (83.1%) completed the questionnaire and were used in the final data set. An additional 179 (6.4%) did not finish the survey, and 293 (10.5%) were eliminated because the quota for their disease state had already been met (Table 1). The relative proportions of patients and caregivers in each group also varied widely, with caregivers comprising a high of 90% of respondents in the AD group, and a low of 17% in both the MS and stroke groups (Table 1).

PBA Prevalence

The CNS-LS scale with a cut-off score of ≥13 yielded larger estimates of PBA prevalence within and across the disease groups, compared with the higher CNS-LS threshold of 21 points (CNS-LS≥21) and the PLACS cutoff of ≥13, which produced similar rates (Table 1). The mean prevalence estimate of PBA across all six diseases was 10.1% as identified by a PLACS≥13 score; 9.4% with the CNS-LS≥21 score; and 37.5% with a CNS-LS≥13 cutoff. PBA prevalence estimates differed substantially among the six neurologic conditions evaluated, being highest in ALS and lowest in PD, regardless of the criteria used (Table 1).

US Population Estimates

Application of the PLACS≥13 and CNS-LS≥21 estimates for PBA to prevalence estimates from the US government and from professional organizations for the six underlying conditions yielded similar prevalence estimates for PBA, while the CNS-LS≥13 threshold derived markedly higher estimates (Table 1). The estimates of total US prevalence of PBA based on government data (Source 1[38-43]) were 1.9 million with PLACS≥13, 1.8 million with CNS-LS≥21, and 7.1 million with the CNS-LS≥13 threshold (Table 1). Using the lower prevalence data from the neuro-epidemiological review by Wallin and Kurtzke[44] (Source 2[44,45]), the estimates for total US prevalence of PBA were 0.6 million with PLACS≥13, 0.55 million with CNS-LS≥21, and 2.2 million with CNS-LS≥13 (Table 1).

Episodic Anger and Frustration Related to PBA

Among all respondents, 58.7% scored ≥15 on the anger/frustration subscale of the CNS-LS, ranging among disease groups from a high of 74.1% in those with AD to a low of 40.3% in the stroke group. Anger/frustration and laughing/crying episodes were often coexistent; a greater percentage (25.3%) of patients with scores of ≥15 for anger/frustration also experienced inappropriate laughing/crying episodes compared with the overall sample (16%). Moreover, most patients exceeding PLACS and CNS-LS threshold scores for laughing/crying also reported anger/frustration episodes; 90.5% of patients with a PLACS score ≥13, 95.8% of patients with a CNS-LS score ≥21, and 88.3% of patients with a CNS-LS score ≥13 also had a score of ≥15 for anger/frustration. However, 41.3% of respondents who scored <13 in the CNS-LS scored ≥15 on the anger/frustration subscale,

suggesting that anger/frustration episodes may be a primary manifestation of emotional lability in many patients, and that including these episodes in the definition of PBA would affect prevalence estimates. Caregivers reported a markedly higher percentage of ≥15 anger/frustration scores (72.7%) than did patients (47.6%).

Diagnosis of PBA

Of the 937 respondents who screened positive for PBA using CNS-LS≥13 and/or reported sudden episodes of crying and/or laughter, 637 (73.6% weighted) said they had discussed their episodes of laughing and/or crying with a physician. Of the respondents who discussed their sudden crying/laughter with a physician, 41% were given a diagnosis for the episodes (Table 2), which, as reported by the patients/caregivers, was most often depression, or that the symptoms were related to their underlying illness; however, no respondents reported a diagnosis of PBA, PLC, or related terminology (Figure 2).

Figure 2. Diagnoses received across all disease groups by patients who discussed their laughing and/or crying episodes with a physician and were given a diagnosis (total *n*=227). *Includes various personality disorders, psychotic disorders, "stress."

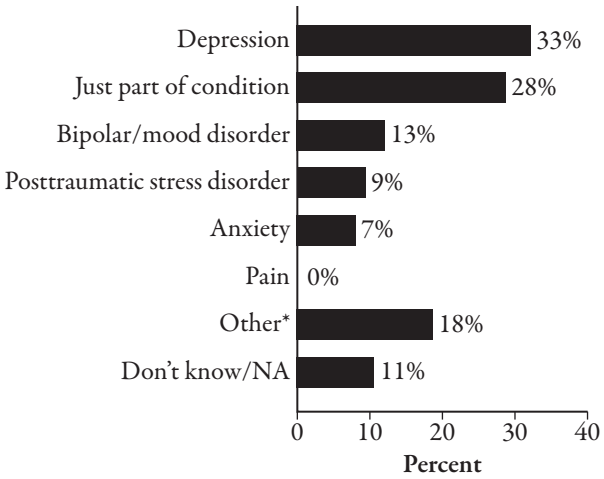


Table 2. Diagnosis and treatment in patients who discussed their sudden crying and/or laughing episodes with a physician.

Given diagnosis?	Total* (*n*=637)	ALS (*n*=21)	AD (*n*=171)	MS (*n*=121)	PD (*n*=97)	Stroke (*n*=96)	TBI (*n*=131)
Yes, %	41	38	37	29	23	35	51
No, %	59	62	63	71	77	65	49
Requested treatment?	**Total*† (*n*=671)**	**ALS (*n*=21)**	**AD (*n*=186)**	**MS (*n*=129)**	**PD (*n*=99)**	**Stroke (*n*=103)**	**TBI (*n*=133)**
Yes, %	46	52	39	37	39	45	55
No, %	54	48	61	63	61	55	45
Prescribed medication?	**Total*† (*n*=671)**	**ALS (*n*=21)**	**AD (*n*=186)**	**MS (*n*=129)**	**PD (*n*=99)**	**Stroke (*n*=103)**	**TBI (*n*=133)**
Yes, %	52	43	51	42	36	50	56
No, %	48	57	49	58	64	50	44

*Total weighted proportionally among all six conditions based on their prevalence in the general population.
†Includes patients who discussed laughing/crying and/or anger/frustration episodes with a physician.
AD=Alzheimer's disease; ALS=amyotrophic lateral sclerosis; MS=multiple sclerosis; PD=Parkinson's disease; TBI=traumatic brain injury.

Treatment of PBA

Of patients who discussed their episodes of involuntary crying and/or laughing with their physician (total *n*=671), 46% requested treatment and 52% were prescribed a medication (Table 2), including 85% of the patients who requested treatment and 24% of those who did not specifically request treatment. Among patients who did not request treatment, the most common reasons given were that "the recent episodes of crying and/or laughter do not significantly impair my quality of life" and "I have other conditions and/or health issues that I consider to be more important than my recent episodes of crying and/or laughter." Of all survey respondents (total *n*=2318), 40% were taking medications that have been reported to be potentially effective in reducing PBA symptoms, such as tricyclic antidepressants (8%), other antidepressants (31%), or antipsychotics (13%). Among patients with a score of ≥15 on the anger/frustration subscale, 53% reported receiving these medications. Among patients with a CNS-LS ≥13, 58% were receiving these medications, with 14.1%, 46.3%, and 21.4% receiving tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) or other nontricyclic antidepressants, or antipsychotics, respectively, indicating that for many patients, PBA symptoms were not sufficiently controlled by the medications prescribed (Table 3).

DISCUSSION

This is the first epidemiologic survey to assess the prevalence of PBA symptoms of involuntary laughing and crying using a single methodology across the six conditions with which PBA is most commonly associated. The survey results suggest that the total mean prevalence of PBA across these disease populations ranges from about 10%, when identified with either a PLACS score of ≥13 or a CNS-LS score of ≥21, to 37.5%, when identified by a CNS-LS score of ≥13 (Table 1). Depending on the specific scale and threshold score used to define PBA and the data source used to estimate the size of the US population afflicted with the six associated conditions, estimates of the PBA population range from a low of 0.55 million to 1.9 million (PLACS≥13/CNS-LS≥21) to a high of 2.2 million to 7.1 million (CNS-LS≥13) US cases. Considering that PBA occurs in other neurological conditions besides the six surveyed here,[3,5] and this survey did not systematically include institutionalized patients, the prevalence of PBA in the USA appears conservatively to be at least 0.5 million to 2 million.

This survey also showed that labile anger/frustration is present in more than half of patients with these underlying neurological disorders, and is more common in patients who also have PBA symptoms of inappropriate laughing and crying (88.3% of patients with CNS-LS≥13

Table 3. Medication use and percentage of patients with scores indicating pseudobulbar affect.

Concomitant medications	CNS-LS≥13 (*n*=857)	CNS-LS≥21 (*n*=195)	PLACS≥13 (*n*=217)
Any antidepressant or antipsychotic (*n*=922), %	58.0	69.6	72.7
Tricyclic antidepressants (*n*=185), %	14.1	27.8	35.1
Other antidepressants (*n*=734), %	46.3	55.6	45.5
Antipsychotics (*n*=218), %	21.4	37.3	42.2
No antidepressant or antipsychotic medication (*n*=1396), %	42.0	30.4	27.3

CNS-LS=Center for Neurological Studies-Lability Scale; PLACS=Pathological Laughing and Crying Scale.

also scored ≥15 on the CNS-LS lability subscale compared with 41.3% of those with CNS-LS <13). These findings are consistent with previous epidemiological data suggesting that episodes of anger and frustration, in addition to laughter and crying, are an important component of emotional lability in PBA.[4] In addition, the survey showed that recognition, diagnosis, and treatment of PBA are substantially suboptimal, with only about 40% of patients who discussed their episodes receiving a diagnosis (most often depression), and many patients remaining untreated or ineffectively treated.

These prevalence findings concur with previous data showing wide variance in PBA prevalence among the commonly associated underlying neurological conditions (Table 1) and within individual disease populations depending on methodology for identifying PBA (Figure 1[5,10,11,15-32]). Estimates of PBA prevalence in patients with ALS, for example, have ranged from 2% to 60%,[15,17,20] with expert consensus opinion accepting the estimate of "as many as 50%".[16] Indeed, a 2009 study of treatment outcomes in 5600 ALS patients found that 42% of patients were receiving treatment for PBA.[52] The present estimates of 27.5%, 32.5%, and 50% PBA prevalence in ALS patients identified with the CNS-LS≥21, PLACS≥13, and CNS-LS≥13 thresholds, respectively, are thus within the range of previously reported and clinically accepted estimates.

In patients with AD, the reported prevalence of nonspecific emotional lability has ranged from about 25% to 74%.[3,53,54] A study that identified PLC using a semi-structured interview based on Poeck's criteria for diagnosis of PBA, which require that the episodes are provoked by nonspecific stimuli, are uncontrollable, and do not reflect the subjective affective state or influence the prevailing mood,[55,56] found that 40 (39%) of 103 patients with AD screened positive for PBA.[22] Patients in this study were also given a comprehensive battery of psychological and cognitive tests (including the PLACS) to identify correlates of pathological affect. Respective PLACS scores were 0.0 and 1.8 in patients without pathological affect compared with 0.0 and 11.9 in patients diagnosed with pathological crying and 1.8 and 7.3 in patients diagnosed with mixed pathological affect. The prevalence of PBA in this trial is consistent with the estimate of 38.5% found in the present study using the CNS-LS≥13 threshold, and is about four times higher than both the 9.2% and 9.6% prevalence estimates using PLACS≥13 and CNS-LS≥21, respectively. In MS patients, estimates of PBA prevalence have ranged from 7% to 29%.[21,24,25,57] Feinstein et al.,[24] interviewed 152 consecutive outpatients with MS and identified a point prevalence for PLC of 9.9% (15/152) using the Poeck criteria. Patients were also interviewed using the PLACS; however, mean PLACS scores are provided for only 11 of the patients diagnosed with PLC who went on to participate in a case-control study; the mean PLACS score in these patients was 17 (range 10-23). The point prevalence in the study by Feinstein et al. was similar to that found for MS patients in our survey sample using a PLACS≥13 cutoff (9.8%), or CNS-LS≥21 (9.8%), while the rate shown using the CNS-LS≥13 (46.2%) was over four times higher (Table 1). This disparity could be related to the more restrictive criteria of Poeck used by Feinstein et al., compared with the CNS-LS≥13 cutoff, and may thus illustrate how more exclusive criteria can better define specific characteristics of PBA, but may also underestimate the prevalence of patients with involuntary and uncontrollable laughing and/or crying episodes, regardless of how they relate to context or inner mood.

Reported PBA prevalence rates in PD patients are typically lower than those in patients with ALS,

dementia, and MS and have ranged from 5.1% to 16.8%.[5,11,14,58] This survey also showed a lower prevalence of PBA in PD patients of 5% using the PLACS≥13 cutoff, while the CNS-LS≥21 yielded a lower estimate of 3.6%, and the CNS-LS≥13 threshold derived a markedly higher estimate of 24% (Table 1). In studies that used criteria similar to this survey for the detection of PBA in PD patients, one (*n*=193) reported a PBA prevalence of 7%, based on the Cummings criteria, which require that PBA episodes cause clinically significant distress or impairment in social or occupational functioning.[58,59] This study also found that CNS-LS cut-off scores of ≥13 and ≥17 yielded rates of 42.5% and 16.6%, respectively, of patients with "clinically significant PBA symptoms." Notably, a CNS-LS cutoff of ≥11 provided the maximum sensitivity (93%) and specificity (51%) when correlated with the Cummings criteria results. The inability to obtain both high sensitivity and specificity with the CNS-LS in this study would raise questions as to the validity of this scale in PD patients.[58] However, another study in patients with movement disorders (*n*=269), which used a CNS-LS≥17 cutoff, reported a 7.1% prevalence of PBA in a subgroup of patients with PD (*n*=168), almost the same rate as found with the Cummings criteria.[5] Therefore, both the 5% and 3.6% estimates based on PLACS≥13 cutoff, and CNS-LS≥21, respectively, in this survey appear to be conservative and consistent with prevalence estimates obtained using structured interviews.

Studies in stroke patients have reported prevalence of crying and laughing syndromes ranging from about 6% to 52%.[9,12,27-30,60] None of these studies used the CNS-LS or the PLACS to identify PBA, although the PLACS has been validated in stroke patients, and a score of 13 was found to identify patients with PBA (sensitivity=0.88, specificity=0.96, positive predictive value=0.83).[31] Several used the "Kim criteria" for emotional incontinence, which require that the patient has shown excessive and/or inappropriate laughter or crying or both, as compared with the premorbid state, on at least two occasions.[12,27,29,60] Three studies used the "House criteria" for emotionalism, described as tearfulness that is more frequent than before the stroke, sudden and uncontrollable, but without regard to appropriateness of the expression.[9,29,30] In this survey, the PBA prevalence in stroke of 4.7% and 4.3% found with the PLACS≥13 and CNS-LS≥21 criteria, respectively, are below even the lowest rate previously found in stroke patients, while the rate of 27.6% found with the CNS-LS≥13 cutoff is within the previously reported prevalence range identified in previous trials. Here again, in stroke patients as noted above for MS patients, it appears that the type or threshold of criteria used to define and identify PBA may result in significant differences in its estimated prevalence. This suggests that the choice of criteria for identification of PBA may rest, in part, with the purpose of the clinician or researcher, such as whether to maximize sensitivity in capturing patients experiencing uncontrollable laughing and crying episodes, perhaps for further evaluation, or place a greater emphasis on specificity in identifying a well-defined population with distinct characteristics. For example, based on their CNS-LS validation studies, Moore and colleagues suggested that a cut-off score of 13 on this scale (sensitivity 0.84, specificity 0.81) was most appropriate for general research purposes, while a less stringent CNS-LS cutoff of 11 (sensitivity 0.91, specificity 0.71) was considered appropriate for clinical screening of patients with troublesome laughing and/or crying episodes.[4]

Only two previous studies have reported PBA prevalence in TBI.[10,32] In one study, 16

(5.3%) of 301 hospitalized patients with TBI were identified as having PBA based simply on whether the patients were observed by clinicians to laugh or cry excessively in response to minimal stimulation.[32] The other study, which used criteria similar to that of Poeck to identify PBA, and the PLACS as a measure of PBA symptom severity, found that 10 of 92 (10.9%) hospitalized patients with TBI had PBA, and the mean (SD) PLACS score for these patients was 13.6 (4.6).[10] In comparison, the present survey found considerably higher PBA rates in TBI patients of 17.4% and 15.5% using PLACS≥13 and CNS-LS≥21 thresholds, respectively, and 48.2% with the CNS-LS≥13 cutoff.

Overall, PBA prevalence in this survey, as estimated using PLACS≥13 and CNS-LS≥21 thresholds, was consistent with or below that reported in other studies for five of the six individual disease populations surveyed (Figure 1). This survey found a higher PBA prevalence in TBI patients than previously reported; however, the previous data in this population are limited.[10,32] The CNS-LS≥13 cutoff generally yielded PBA rates above those found in previous studies, but produced a result similar to what is probably the most reliable previous estimate in AD patients, while the PLACS≥13 and CNS-LS≥21 results were well below that rate. These comparisons suggest that the total US prevalence estimates of approximately 0.5–2 million, based on the PLACS≥13 and CNS-LS≥21 thresholds, obtained in this survey, may be conservative, while the estimate of about 7 million based on the CNS-LS≥13 is probably high.

The considerable prevalence of PBA identified by these survey results highlight the need for improved recognition, diagnosis, and treatment. However, less than half (41%) of survey participants who discussed their inappropriate laughing and crying episodes with a physician were given a diagnosis, and in no case was the reported diagnosis PBA (Figure 2). It has been noted that PBA episodes may at times resemble crying spells in depression[61] and emotional lability in mania,[62] partly explaining the difficulty in diagnosis.

While this study also documented low rates of recognition and treatment of PBA, it should also be noted that no FDA-approved medications indicated for PBA were available until recently. Among medications reportedly used off-label for PBA,[3,63] there is some evidence of efficacy for SSRIs[64-66] and tricyclic antidepressants,[1,31] while antipsychotics may be effective in treatment of emotional lability[67] and anger/aggression.[68] However, about half of surveyed patients registering PBA symptoms were already receiving antidepressant or antipsychotic medications, indicating that these treatments may not be optimally effective in some patients.

Dextromethorphan/quinidine (Nuedexta™, Avanir Pharmaceuticals, USA), an uncompetitive N-methyl-D-aspartate receptor antagonist and sigma-1 receptor agonist,[63] was approved by the FDA in 2010 as the first medication indicated for treatment of PBA.[69] This agent has demonstrated efficacy in treating PBA in phase 3 clinical trials in patients with ALS or MS.[33,36,70]

Certain limitations of this study must be noted. It was undertaken on patients self-reported as having been diagnosed with one of the chronic diseases, ALS, AD, MS, PD, or stroke, or identified by directed screening for TBI. The Harris Chronic Illness Panels are household-based and do not include institutionalized groups, which could bias towards a less severely affected population. To minimize such bias, caregivers were included as a proxy for more functionally impaired patients; however, the survey methodology may have resulted in recruitment of a less severely affected population leading to potential underestimation of the overall disease

prevalence. The methodology used in this survey also limited the clinical details available for greater in-depth analysis of the prevalence results, and the amount of information available about the relationship of the specialty of the treating physician to diagnosis of PBA, which is of significance in regard to whether PBA was treated and how. Nevertheless, the methodology resulted in a large survey sample and produced important results and conclusions about PBA across the board in the USA, which could offer pointers to future in-depth studies that are needed.

In conclusion, this survey estimated the mean prevalence of PBA to be at least 10% and up to 38%, depending on the symptom threshold used for detection, across the six most common underlying neurological conditions associated with PBA. Based on US population estimates for these neurologic conditions, these survey data indicate a total US PBA prevalence of up to approximately 2 million people using a high symptom threshold to as high as 7 million using a lower symptom threshold. These data also highlight the need for greater awareness, recognition, and treatment of PBA. Additional studies are warranted to confirm the validity and reliability of the PLACS and CNS-LS, including the CNS-LS anger/frustration subscale, in all the most common underlying conditions associated with PBA and, perhaps, to refine these diagnostic criteria.

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