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CME Review Article

Recognizing and Treating Pseudobulbar Affect

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- Recognize PBA within the context of neurological disorders
- Implement evidence-based treatment strategies for patients with PBA

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Recognizing and treating pseudobulbar affect

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Pseudobulbar affect, thought by many to be a relatively newly described condition, is in fact a very old one, described as early as the 19th century. It refers to those who experience inappropriate affect, disconnected from internal state, or mood, generally thought to be the result of an upper motor neuron injury or illness. One possible explanation for this condition's relative obscurity is the dearth of treatment options; clinical medicine is not typically in the habit of identifying conditions that cannot be modified. Now, however, there is good evidence for the treatment of pseudobulbar affect, and even a therapy approved for use by the U.S. Food and Drug Administration (FDA). As a result, appropriate identification and subsequent management of pseudobulbar affect is more important than ever. This article purports to summarize the origins of pseudobulbar affect, most current hypotheses as to its physiopathology, clinical identification, and evidence for management.

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Introduction

Affect, or the external manifestation of one's internal state, is often taken for granted and given little credit for the immensely complex task it is. Multiple, interconnected regions of the brain are involved in the appropriate expression of affect, utilizing executive function in the prefrontal cortex, control of movement in the motor cortex, and even coordination through the cerebellum, all working together with the brainstem (the "bulb") to generate appropriate affect, such as laughter, crying, and tears, which, for most people, is as natural as, well, laughing. But for many people who suffer from a wide variety of neurological conditions, affect is not so natural, instead presenting with involuntary and inappropriate expressions of emotion that are at best confusing and at worst embarrassing to the point of severe social and professional dysfunction. While described with many names over the years, this syndrome is now most appropriately referred to as pseudobulbar affect (PBA).

As with many illnesses, the phenomenon is not new. Charles Darwin described the phenomenon as early as 1872, writing "certain brain diseases, such as hemiplegia, brain-wasting, and senile decay, have a special tendency to

induce weeping."¹ In a later example, Pierre Marie described "emotional lability" in 1892 as occurring with amyotrophic lateral sclerosis (ALS).² The use of the term "pseudobulbar" by Oppenheim and Siemerling in 1886 was an attempt to differentiate the cause of symptoms that would typically be associated with bulbar palsy (including dysarthria, dysphagia, slurring, dysphonia, etc.), but without any lower motor neuron lesions. Many other names have been used, including pathological laughing and crying, involuntary emotional expression disorder, affective lability/emotional lability, supranuclear bulbar palsy, even at some point "the laughing sickness," but now all these terms are unified under PBA.³

For all its interesting history, however, PBA continues to prove challenging to diagnose, leading to under-recognition, and thus continued disability for those afflicted. Particularly because PBA can be effectively treated, its recognition and diagnosis are even more urgently required; proper diagnosis has the potential to save patients years of symptoms that are disabling in all aspects of life, as well as a multitude of increasingly invasive and ineffective treatment trials for other suspected disorders that may not exist. PBA is often mischaracterized as a psychiatric condition, such as major depressive disorder, bipolar spectrum disorder, or post-traumatic stress disorder. While none of these conditions is mutually exclusive with PBA, neither will the treatments typically used to address them be very likely to improve the symptoms of affective dysregulation, thus

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unnecessarily giving the appearance of treatment resistance or residual symptoms.

The purpose of this article is to facilitate the early recognition, diagnosis, and ultimate treatment of PBA by summarizing what is known to date about its prevalence, potential etiology, and diagnostic considerations. Furthermore, PBA increasingly appears to be neither rare, nor simply an interesting neurological curiosity, but instead a rather common condition associated with a very diverse set of underlying conditions. Therefore its diagnosis and treatment might be better addressed when it is sought in a wide variety of medical settings, including not just the neurologist's office, but also the rehabilitation facility, the primary care setting, and of course the office where almost anyone presenting with dysregulation of affect will most commonly be referred: that of the psychiatrist.

Pathophysiology of Pseudobulbar Affect

The pathophysiology of PBA is not well understood. In recent years, however, some neuroanatomic correlates have provided clues leading to a more unified theory of how PBA arises. The most current theory of PBA was proposed by Parvizi *et al.*,⁴ who hypothesizes that it arises from disruption of the cortico-pontine-cerebellar circuit. In this theory, the expression of affect is modulated by multiple cortical areas, with afferent connections between the motor cortex, prefrontal cortex, and cerebellum through the basis pontis. Thus any condition, either through degenerative disorder or trauma, that disrupts these connections can result in dysregulated affect.⁴ Additional data have emphasized the importance of the cerebellum in this circuit, as well as the somatosensory cortex, which has an inhibitory role modulating the motor and prefrontal cortices for affective control. Recent understanding of the cerebellum has elucidated that it coordinates much more than just motor function. The cerebellar cortex also has very important roles in cognition, empathy, and modulation of affect. It has been suggested that certain cerebellar lesions may result in affective dysmetria, much as other cerebellar lesions result in limb dysmetria, with the sufferer therefore overshooting targets when reaching for objects.⁵

Other work further validates the above noted neuroanatomic correlates in PBA, and further suggests that any disruption in the cortico-pontine-cerebellar circuit, regardless of mechanism, has the potential to give rise to disturbance in affect. In a study of PBA symptoms post-stroke, it was found that the most frequently injured areas in patients with post-stroke pathological laughing and crying included the pons, basal ganglia, and subcortical white matter. Nearly all those with symptoms had bilateral lesions and most had multiple lesions.⁶ It is also noted that post-stroke anger proneness, described as a separate

condition from pathological laughter and crying or PBA, was very closely related to symptoms of laughing and crying in this cohort, raising the question of whether or not anger outbursts or other affective displays could also be included with laughing and crying in the symptoms of PBA.

In a 2013 case report, a patient undergoing chemotherapy presented with acute and dramatic pseudobulbar symptoms 2 days following an infusion. Her symptoms included involuntary crying spells without sadness or provocation as well as involuntary inappropriate laughter, up to 4 times a day. Symptoms peaked by the fourth day following infusion, and then resolved by the sixth day, suggesting a transient effect of the chemotherapy disrupting corticobulbar tracts.⁷

In 1995, a review of cases involving resection of vermian tumors in children revealed a significant incidence of PBA as well as mutism following the resections, which is consistent with the notion that single lesions in the cerebellum can give rise to PBA.⁸

In 2014, primary lateral sclerosis was shown to be very commonly associated with PBA, while not being particularly associated with cognitive impairment. PBA was noted to be associated with impaired cortico-ponto-cerebellar tracts secondary to primary lateral sclerosis.⁹

A 2015 case report described persistent PBA following acute disseminated encephalomyelitis, a rare inflammatory demyelinating disorder.¹⁰

These and other published studies and case reports illustrate that disruption of cortico-pontine-cerebellar tracts can occur by a variety of mechanisms, including toxic effects (consider chemotherapy or substance abuse), acute inflammatory syndromes, traumatic brain injury ranging from mild to severe, tumors, aneurysm, stroke, and surgery just to name a few. These facts should encourage any practitioner to expand the categories of illness that they think may be an underlying cause of PBA.

Prevalence of Pseudobulbar Affect

The most recent data on possible prevalence of PBA across several conditions came from the PBA Registry Series, the results of which were first published in 2013. In this study, 5290 subjects were included, all of whom were diagnosed with 1 of 6 neurological conditions: Alzheimer's dementia, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, stroke, or traumatic brain injury. All subjects completed a Center for Neurologic Study-Lability Scale (a standardized screening questionnaire for PBA, CNS-LS) to screen for PBA symptoms, with a score of 13 as the minimum for symptom significance and 21 as a measure of greater symptom significance. The total prevalence across the entire study population was 36.7% with CNS-LS ≥ 13 and 9.3% ≥ 21 . Different neurological conditions had

different prevalence, with Alzheimer's dementia at 29.3% and 6.6%; amyotrophic lateral sclerosis at 44.8% and 12%; multiple sclerosis at 45.8% and 12%; Parkinson's disease at 26.0% and 5.5%; stroke at 37.8% and 9.4%; and traumatic brain injury with the highest prevalence of 52.4% and 16.4%, respectively.¹¹ It is very important to note that the study focused on the above noted 6 conditions for the registry, but does not suggest that PBA occurrence is limited to those conditions.

In a recent study of veterans with possible traumatic brain injury, about 70% of those who screened positive for traumatic brain injury also had CNS-LS scores of 13 or greater, suggesting possible PBA. This study included originally included 33,487 veterans of Operation Iraqi Freedom, Operation Enduring Freedom, and Operation New Dawn, 14% of whom screened positive for traumatic brain injury. Out of those with traumatic brain injury, 46% were also diagnosed with posttraumatic stress disorder, 26% with major depressive disorder, and 17% with anxiety disorders, also suggesting a high degree of co-occurrence of these disorders with traumatic brain injury and PBA. Of particular note, prior to this study, most work regarding traumatic brain injury and PBA was focused on more severe injury, while this population was predominantly injured by blast (84%) and classified as "mild" (89%).¹² The notion of PBA being associated with mild traumatic brain injury expands the population at risk dramatically.

It is safe to say that currently, most published work serves to highlight the difficulty in estimating the prevalence of PBA, particularly in light of difficulties with diagnosis and possible differences in likelihood in the context of different underlying conditions. Adding to the confusion is the difficulty in consistently diagnosing some of the underlying conditions themselves, with conditions such as mild traumatic brain injury and post-concussive syndromes not being particularly well understood. Large registry studies such as the PBA Registry Series certainly have the potential to contribute to increasing clarity on the matter.

Challenges in Diagnosis of Pseudobulbar Affect

The first challenges to note in the diagnosis of PBA are the criteria themselves, of which there are several, and they are somewhat divergent. Some of the earliest proposed criteria were published by Poeck in 1969, who stated that PBA included the presence of inappropriate laughing and crying that "... may arise in cerebral diseases of the most diverse etiology and location ..."¹⁶ and the following 4 associated features:

- Episodes are inappropriate to the situation and can be precipitated by nonspecific stimuli, such as contraction of facial muscles, removal of bedcovers, or the approach of someone toward the patient.

- There is no close correlation between the patient's emotional expression and how he or she is feeling.
- Episodes are relatively stereotyped, in that each episode follows a similar pattern of building up paroxysmally or stepwise to a maximum peak, then decreasing slowly, and it is difficult for patients or others to control their extent or duration.
- There are no episodic mood changes corresponding to the episodes and no sense of relief as the affects are expressed.¹³

Another set of criteria for "involuntary emotional expression disorder" (IEED), published by Cummings *et al.*,¹⁴ included the following:

- Episodes of involuntary or exaggerated emotional expression that result from a brain disorder, including episodes of laughing, crying, or related emotional displays, with the associated features of episodes representing a change from the person's usual emotional reactivity; episodes may be inconsistent with the person's mood or in excess of the corresponding mood state; and episodes are independent or in excess of any provoking stimulus (ie, crying regardless of whether the person is currently sad, happy, or other).
- Repetitive episodic disturbances cause clinically significant distress or impairment in social or occupational functioning.
- Symptoms are not better accounted for by another neurological or psychiatric disorder (eg, gelastic or dacrystic epilepsy, facial dystonia, facial or vocal tics, facial dyskinesias, mania, depression, panic disorder, psychosis).
- The symptoms are not the direct physiological effect of a substance (eg, drug of abuse or medication).¹⁴

Most recently, criteria for the diagnosis of PBA were proposed by Miller *et al.*,⁵ which consist of essential criteria as well as supportive criteria for the diagnosis:

1. Essential criteria

- Patient experiences episodes of involuntary or exaggerated emotional expression that result from a brain disorder, including episodes of laughing, crying, or related emotional displays.
- Episodes represent a change in the patient's usual emotional reactivity, are exaggerated or incongruent with the patient's subjective emotional state, and are independent or in excess of the eliciting stimulus.
- Episodes cause clinically significant distress or impairment in social or occupational functioning.
- The symptoms cannot be attributed to another neurologic or psychiatric disorder or to the effects of a substance.

2. Supportive criteria

- Patient may experience accompanying autonomic changes (eg, flushing of face) and pseudobulbar signs (eg, increased jaw jerk, exaggerated gag reflex, tongue weakness, dysarthria, and dysphagia).
- Patients may exhibit a proneness to anger.⁵

All 3 sets of criteria have their merits. Poeck's criteria very clearly delineated the episodic nature of affective outbursts in PBA, but do not necessarily acknowledge the notion that episodes can be minimally provoked or out of proportion to internal emotion, rather than being completely unprovoked and contrary to emotional state. Cummings *et al*'s criteria, and the proposed name IEED, did acknowledge out-of-proportion affective display in addition to completely unprovoked displays, and also has the advantage of greater inclusivity, allowing for the possibility of other affects in addition to just laughing and crying. The most recent criteria, proposed by Miller *et al*, possibly encompass all these advantages, acknowledging out-of-proportion affective display in addition to completely unprovoked episodes, while also including the possibility of anger proneness in the supportive criteria. At this time, it is likely to be most ideal to use these most recent proposed criteria when making the diagnosis, not only because of the most recent publication, but also because they most closely resemble the U.S. Food and Drug Administration (FDA) definition of PBA for the approved on-label treatment of such.

Another common challenge in diagnosis of PBA is likely comorbidity, with other disorders being overrepresented in many of the populations PBA is likely to affect. PBA may co-occur with depression as much as 50% of the time,¹⁵ and depression is particularly common in many neurological conditions, such as multiple sclerosis, post-stroke, amyotrophic lateral sclerosis, dementia, etc. It has also been noted that between 40% and 62% of those hospitalized for traumatic brain injury experience depression in the years following injury.¹⁶ Thus, not only are PBA and various psychiatric disorders not mutually exclusive, they could in fact be more likely to appear together, increasing the risk that the symptoms of PBA may be misattributed to other psychiatric illness.

In multiple sclerosis, diagnosis of PBA can be complicated by both depression and bipolar spectrum disorders, which appear to be more common with multiple sclerosis, possibly being as much as 2 or even 3 times more likely than in the general population.¹⁷ Another phenomenon associated with multiple sclerosis is euphoria, which is also distinct from PBA, in that it entails elevated mood, reduced insight into the severity of multiple sclerosis and heightened optimism, distinct from mania for lack of pressured speech, or decreased need for sleep. Pseudobulbar affect can often be mistaken for bipolar disorder, but can be distinguished

by noting absence of other symptoms of bipolar disorder such as pressured speech, grandiosity, flight of ideas, impulsive behavior (manic phase), or consistently depressed mood along with other neurovegetative symptoms (depressed phase).

In traumatic brain injury, as noted above, depression may be more common, along with posttraumatic stress disorder, secondary to the mechanism of the injury, such as motor vehicle accidents or assault, etc. PBA seems often to be overlooked in these cases, with crying episodes attributed to either depression or posttraumatic stress disorder. While affective lability and irritability are part of the diagnostic criteria of posttraumatic stress disorder,¹⁸ it has actually been suggested that crying is not particularly associated with depression, with published findings showing little difference between depressed and non-depressed people when it came to frequency of crying. If anything, it may be that crying is somewhat reduced in depressive disorders, with depressed patients sometimes complaining that they cannot cry even when they feel it appropriate.^{19,20} One confusing and rare condition also associated with traumatic brain injury is known as Witzelsucht, which presents with the patient making inappropriate jokes (most commonly puns) and laughing at things others do not find funny. This is distinct from PBA, however, in that the patient experiences mirth, and the affective displays of laughing are congruent with mood.¹⁶

When faced with multifactorial, confusing clinical presentations, particularly when 2 or more conditions are co-occurring, it can be extremely useful to use standardized scales to assist with diagnosis and the distinction of various symptoms. Many such scales are being more commonly used in psychiatry, including the Patient Health Questionnaire (PHQ-) and the Beck Depression Inventory (BDI) in depression, the Young Mania Rating Scale (YMRS) in bipolar disorders, and even the recently proposed simple screening questions for suspected traumatic brain injury (Brief Traumatic Brain Injury Screen.).²¹ For PBA, a recent and validated screening scale is the Center for Neurologic Study Lability Scale (CNS-LS).²² This scale is self-administered, brief, and simple to understand, and has great potential to identify significant PBA symptoms. Thus, it may be useful to administer this scale to any patient with a history of any condition that could possibly be an underlying cause for PBA.

In summary, the most efficient way to distinguish PBA from other mood- and affect-related disorders is to identify all the other criteria that are part of those disorders but not of PBA, as well as recognizing that in every other psychiatric illness, with the exception of some psychotic disorders, affect is typically mood congruent. For example, laughing in mania, however inappropriate it may be to the circumstance, is associated

with elevated mood, or tearfulness in depression or posttraumatic stress disorder is associated with internal sadness and/or distress.

Burden of Pseudobulbar Affect

In 2012, the first study assessing burden of illness across multiple measures and areas of function was published. In patients suffering from PBA, all measures demonstrated that quality of life suffered in terms of social, occupational, and relationship problems. Furthermore, a substantial number of subjects reported that laughing and crying episodes had contributed to loss of a relationship, divorce, becoming housebound, or having to be placed in a supervised living facility.²³

In a 2016 study of depression in amyotrophic lateral sclerosis, while it was found that higher Patient Health Questionnaire (PHQ-9) scores were associated with lower initial scores on the ALS Functional Rating Scale (ALSFRS-R), they were also associated with higher scores on the CNS-LS, suggesting that patients with symptoms of PBA were more likely to be depressed.²⁴

In a study of veterans suffering from PBA, it was suggested that these symptoms alone led to significantly reduced quality of life reported via standardized scale, as well as substantially increased cost associated with care, whether or not those veterans were also diagnosed with posttraumatic stress disorder.²⁵

In addition to the burden of distress brought on by the symptoms themselves, it is important to consider the potential consequences of undiagnosed and therefore untreated PBA regarding the patient's mental health and treatment over time. As has been noted in many publications, symptoms of PBA are often misattributed to depression, bipolar disorders, and posttraumatic stress disorder, along with others, and could therefore lead to unnecessary treatments that may not be completely benign over time. Increasing polypharmacy in an attempt to augment antidepressant medications, or adding agents intended for mood stabilization (either anti-epileptics or first- or second-generation anti-psychotics) expose these patients to side effects that are distressing to say the least, and in some cases compromise long term health (eg, metabolic syndrome or tardive dyskinesia). It is also possible that while patients may suffer from other disorders in addition to PBA, the affective outbursts may be mistaken for "treatment resistance," again leading to what may be unnecessary escalations in care, creating opportunity for more complications. Furthermore, while there is great stigma associated with mental illness, there is even more stigma associated with treatment-resistant mental illness. Many patients see themselves as untreatable and hopeless, especially after multiple escalations in treatment have

failed to help them. Finally, undiagnosed and untreated PBA may directly interfere with a patient's ability to participate in and benefit from care. Frequent affective outbursts may lead to interrupted and fragmented participation in individual and group psychotherapy, possibly leading patients to give up on psychotherapy entirely out of frustration and embarrassment.

Treatment of Pseudobulbar Affect

If possible, treatment of the underlying condition may be the most elegant way to treat PBA. Sadly, such possibilities are limited, secondary to the nature of most neurological conditions associated with PBA. That said, case reports exist that demonstrate the possibility of effective treatment. One case of "acute pathological laughter" published in 2005 describes a patient with multiple sclerosis who developed acute symptoms of inappropriate, involuntary laughter coincident with a multiple sclerosis flare-up involving lesions in the right frontal and periaxial white matter tract and the bilateral peduncles. The patient was treated successfully with methylprednisone and, as the flare-up resolved, so did the inappropriate laughter.²⁶ In the case noted earlier in which symptoms of PBA were seen to acutely present during chemotherapy, the symptoms resolved within days of completion of the chemotherapy, suggesting that the possible disruption of neural circuitry was transient. These 2 cases illustrate that in some instances, the underlying condition causing PBA symptoms to arise may be a transient one, with the symptoms thus appearing to resolve spontaneously or with treatment. Perhaps PBA symptoms may appear to wax and wane, when it is in fact the underlying condition, such as multiple sclerosis, that is waxing and waning over time.

One case report exists that describes a behavioral approach showing some efficacy in treating symptoms of PBA. Two different interventions were tried in this case, the first being a contingent consequence, in which each tearful episode resulted in attention being withdrawn from the patient. This intervention had no effect whatsoever. The second intervention, however, involving using a breathing technique to forestall tearful episodes was helpful, and the patient's symptoms resolved over the course of 7 months.²⁷ While conclusions cannot be drawn from only 1 case, the underlying condition thought to lead to the affective symptoms was a ruptured middle cerebral artery aneurysm and a right fronto-temporal subdural hematoma, followed by hemicraniectomy and coil embolization. Thus, spontaneous resolution of the underlying pathology, and with it PBA, seems highly unlikely, suggesting that in this case, the behavioral intervention had a role in the patient's recovery.

There is only one medication approved by the FDA for the treatment of PBA: dextromethorphan/quinidine. Dextromethorphan alone is very rapidly metabolized by cytochrome P450 2D6 and its metabolite; dextrorphan is what generally crosses the blood-brain barrier and is thought to be responsible for antitussive effects. When combined with a small dose of quinidine, a potent 2D6 inhibitor, dextromethorphan becomes many times more bioavailable and therefore active in the central nervous system. Dextromethorphan is thought to act at many receptors, including noncompetitive antagonism of the N-methyl-D-aspartate (NMDA) receptor and agonism of the sigma-1 receptor, along with reuptake inhibition of the serotonin and norepinephrine transporters. It is proposed that the mechanism by which dextromethorphan treats PBA is most related to ant glutamatergic properties related to NMDA and sigma-1 binding; it is also noted that dextromethorphan most prominently binds in the brainstem and cerebellum, areas particularly rich in sigma-1 receptors and also neuroanatomically implicated in PBA. Efficacy was shown in 3 large, double-blind, placebo-controlled trials, all of which demonstrated significant reduction in the number of episodes in PBA versus placebo.⁵ Dextromethorphan/quinidine is dosed twice daily, 20 mg/10 mg every 12 hours.

Limited data exist for the use of selective serotonin reuptake inhibitors and tricyclic antidepressants for the treatment of PBA. In most studies, both drugs have shown efficacy in reduction of PBA symptoms, but all published studies to date are limited by small size and in some cases very wide confidence intervals.⁵

Conclusion

We were all taught in school some variation of the phrase “when you hear hoof beats, look for horses, not zebras,” and PBA has traditionally been regarded as a “zebra” for many decades. A growing collection of evidence, however, suggests that PBA is much more common than previously thought, and can be caused by a very wide variety of conditions and disorders, some of which are very common themselves. Furthermore, many people suffering from such conditions are unaware or would never think to report them unless specifically asked. Most people generally associate concussion with loss of consciousness or an emergency room visit, and never think to report a multitude of sports-related head injuries if they were “only” dazed briefly, or a motor vehicle accident in which they “only” suffered whiplash. Those who suffer from substance use disorders may be completely unaware of falling and hitting their heads, or of anoxic injuries after an accidental overdose, yet these are all examples of potentially significant brain trauma that could very easily be the underlying cause of PBA.

Most patients suffering from PBA will not report it as such, because they may not know how to describe it, often reporting they do not know exactly how to describe crying and/or laughing that is not consistent with their mood. Indeed, when asked some version of the single screening question for PBA (“involuntary episodes of crying and/or laughing that were exaggerated or even contrary to how they felt at the time”),²⁸ often patients will experience such intense relief that the look on their faces reveals the answer before they speak. Even without treatment, many newly diagnosed patients have expressed feeling very relieved to have an explanation for symptoms that had simply left them feeling as though they were “difficult” patients who could not be helped. Once treated adequately, as noted above, not only can a very significant source of distress and disability be addressed, but it is also possible that other treatments may prove unnecessary, potentially reducing polypharmacy and side-effect burden.

We can only hope, therefore, that pseudobulbar affect will soon no longer be associated with visions of zebras, but increasingly seen as just another horse in the herd, to be diagnosed and treated in everyday clinical practice.

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1. Research into the pathophysiology of pseudobulbar affect implicates which of the following circuits?
 - A. Cortico-pontine-cerebellar
 - B. Cortico-striatal-thalamic
 - C. Hypothalamic-pituitary-adrenal
2. As part of a diagnostic evaluation, a 26-year-old woman mentions that she has been reprimanded for laughing in company meetings; she states that she's been feeling "really great" lately and that she thought the comments during meetings were funny. Which of the following would you more strongly suspect?
 - A. Bipolar mania
 - B. Pseudobulbar affect
3. Dextromethorphan/quinidine is approved for the treatment of pseudobulbar affect. What is the rationale for the combination of the two medications?
 - A. Each improves symptoms of PBA through unique mechanisms; thus, their effects are synergistic.
 - B. Quinidine enhances the CNS activity of dextromethorphan by inhibiting its metabolism.
 - C. Dextromethorphan enhances the CNS activity of quinidine by inhibiting its metabolism.

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