Aggressive outbursts and emotional lability in a 16-year-old boy

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Mr. X, age 16, is having increasingly frequent aggressive outbursts that are almost always preceded by inappropriate laughing or crying. How would you help him?

CASE Worsening outbursts and emotional lability

Mr. X, age 16, has cerebral palsy (CP), idiopathic normal pressure hydrocephalus (iNPH), and a history of impulse control disorder and behavioral instability, including episodes of aggression or combativeness. Mr. X's mother reports that these episodes are almost always preceded by inappropriate laughing or crying. His outbursts and emotional lability have gotten worse during the last 6 months. Due to his disruptive behaviors, Mr. X has been unable to attend school, and his parents are considering group home placement. Although they were previously able to control their son's aggressive behaviors, they fear for his safety, and after one such episode, they call 911. Mr. X is transported by police in handcuffs to the comprehensive psychiatric emergency room (CPEP) for evaluation.

While in CPEP, Mr. X remains uncooperative and disruptive; subsequently, he is placed in 4-point restraints and given haloperidol, 10 mg IM, and lorazepam, 2 mg IM, to prevent harm to himself or others. After 2 hours, he is unable to maintain a reality-based conversation but has become semi-cooperative. Mr. X's mother decides to take him home and immediately makes an appointment with his outpatient psychiatrist.

What is the most likely cause of Mr. X's emotional lability and aggressive outbursts?

a) impulse control disorder
b) bipolar disorder
c) a secondary neurologic disorder resulting in inappropriate and exaggerated affect
d) pseudobulbar affect

The authors' observations

Pseudobulbar affect (PBA) is a disorder characterized by sporadic episodes of inappropriate laughing and/or crying that are incongruent with situational context and are frequently exaggerated in comparison with the actual feelings of the patient. The duration of PBA episodes can last seconds to minutes and arise unpredictably.

PBA typically develops secondary to a neurologic disorder, most commonly Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Parkinson's disease (PD), stroke, or traumatic brain injury (TBI).[1] PBA symptoms are present in an estimated 29.3% of patients

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Disclosures

Dr. Capote is a speaker for Acadia Pharmaceuticals, Merck, Otsuka Pharmaceuticals, Sunovion Pharmaceuticals Inc., and Teva Pharmaceutical Industries Ltd. Mr. Asbach is a speaker for Neurocrine Biosciences.

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Clinical Point

PBA is frequently misdiagnosed as depression, although the 2 disorders can occur simultaneously

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with AD, 44.8% of patients with ALS, 45.8% of patients with MS, 26% of patients with PD, 37.8% of patients with stroke, and 52.4% of patients with TBI.[2] Although PBA appears far more frequently in patients with MS or ALS compared with those with PD, PD represents an under-recognized and larger patient population. A small fraction of patients also develops PBA secondary to hyperthyroidism, hypothyroidism, Graves' disease, Wilson's disease, brain tumors, and a multitude of encephalopathies.[3] These neurologic disorders cause dysregulation of the corticopontine-cerebellar circuitry, resulting in functional impediment to the normal affect modulator action of the cerebellum.[4]

The neurologic insults that can result in PBA may include CP or iNPH. Cerebellar injury is a frequent pathological finding in CP.[5] In patients with iNPH, in addition to altered CSF flow, enlarged ventricles compress the corticospinal tracts in the lateral ventricles,[6] which is theorized to induce PBA symptoms.

PBA is diagnosed by subjective clinical evaluation and by using the Center for Neurologic Study–Lability Scale (CNS-LS). The CNS-LS is a 7-question survey that addresses the severity of affect lability (***Table 1,***[7] ***page 50***). It may be completed by the patient or caregiver. Each question ranges in score from 1 to 5, with the total score ranging from 7 to 35. The minimum score required for the diagnosis of PBA is 13.[7]

PBA is frequently misdiagnosed as depression, although the 2 disorders can occur simultaneously (***Table 2,***[1,8] ***page 52***). A crucial distinguishing factor between depression and PBA is the extent of symptoms. Depression presents as feelings of sadness associated with crying and disinterest that occur for weeks to months. In contrast, PBA presents as brief, uncontrollable episodes of laughing and/or crying that last seconds to minutes. Unlike depression, the behaviors associated with PBA are exaggerated or do not match the patient's feelings. Furthermore, a neurologic disease or brain injury is always present in a patient with PBA, but is not imperative for the diagnosis of depression.

Compared with individuals without PBA, patients with PBA also experience more distress, embarrassment, and social disability, and are consequently more likely to suffer from other psychiatric conditions, including depression, anxiety/panic attacks, bipolar disorder, posttraumatic stress disorder, psychotic disorder, and schizophrenia.[1] The Patient Health Questionnaire (PHQ-9), a tool for measuring depression severity, can be used in addition to the CNS-LS to determine if the patient has both depression and PBA.

HISTORY Poor response to anxiolytics and antipsychotics

Mr. X previously received a ventriculoperitoneal shunt for treating iNPH. He was not taking any medications for CP. To address his impulse control disorder, he was prescribed olanzapine, 20 mg/d, risperidone, 2 mg/d, and diazepam, 5 mg three times a day. Mr. X is uncontrolled on these medications, experiencing frequent behavioral outbursts at home. His mother completes a CNS-LS for him. He receives a score of 20, which suggests a diagnosis of PBA. His PHQ-9 score is 8, indicating mild depression.

What is the next best step in treating Mr. X?

a) start dextromethorphan/quinidine
b) increase diazepam
c) decrease risperidone
d) all of the above

TREATMENT Introducing a new medication

Mr. X is started on dextromethorphan/quinidine, 20/10 mg twice a day. His diazepam is reduced from 5 mg three times a day to 5 mg twice a day, his risperidone is continued at 2 mg/d, olanzapine is maintained at 20 mg/d,

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Table 1

Center for Neurologic Study–Lability Scale (CNS-LS)

Patient assessment	Applies never	Applies rarely	Applies occasionally	Applies frequently	Applies most of the time
There are times when I feel fine 1 minute, and then I'll become tearful the next over something small or for no reason at all	1	2	3	4	5
Others have told me that I seem to become amused very easily or that I seem to become amused about things that really aren't funny	1	2	3	4	5
I find myself crying very easily	1	2	3	4	5
I find that even when I try to control my laughter, I am often unable to do so	1	2	3	4	5
There are times when I won't be thinking of anything happy or funny at all, but then I'll suddenly be overcome by funny or happy thoughts	1	2	3	4	5
I find that even when I try to control my crying, I am often unable to do so	1	2	3	4	5
I find that I am easily overcome by laughter	1	2	3	4	5

Source: Reference 7

Clinical Point

Dextromethorphan/quinidine is the only FDA-approved medication for PBA, but its use in patients younger than age 18 is investigational

and he is scheduled for a 1-month follow-up visit. At the 1-month follow-up visit, Mr. X's parents report a drastic reduction in their son's aggressive outbursts and mood swings within the first week of starting dextromethorphan/quinidine. His PHQ-9 scale score is reduced to 0, CNS-LS scale score is reduced to 5, and Mr. X reports "100% improvement." Due to the robust response to dextromethorphan/quinidine, he is weaned off risperidone.

The authors' observations

Decreasing the severity and frequency of episodes constitutes the mainstay of treating PBA. In the past, off-label treatments, including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, were prescribed to reduce PBA symptoms.[5] Currently, dextromethorphan/quinidine is the only FDA-approved medication for treating PBA; however, its use in patients younger than age 18 is considered investigational.

Dextromethorphan/quinidine contains 20 mg of dextromethorphan hydrobromide, the pharmacologically active component of the medication via cytochrome P450 (CYP) 2D6, and 10 mg of quinidine sulfate, which increases the systemic bioavailability of dextromethorphan via CYP2D6 inhibition. The most common adverse effects associated with dextromethorphan/quinidine are dizziness, nausea, and diarrhea.[9]

Atypical antipsychotics, such as olanzapine and risperidone, have more warnings and precautions than dextromethorphan/quinidine. Risperidone has a "black-box" warning for QT prolongation, in addition to death and stroke in elderly

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Table 2

Differences between PBA and depression

Clinical component	PBA	Depression
Spectrum of emotional lability	Crying, laughing, or both	Crying, loss of interest, thoughts of worthlessness or suicide
Episode duration	Seconds to minutes, sporadic	Weeks to months
Stimulus	No evident stimuli	Specific mood-related scenarios
Episode control	None	Coping mechanisms may shorten episodes
Underlying neurologic condition	Neurologic disease of brain injury always present	May or may not possess underlying neurologic condition
Affect	Exaggerated or incongruent with situational context	Flattened, saddened, or apprehensive. Rarely demonstrates elation

PBA: pseudobulbar affect

Source: References 1 and 8

Clinical Point

Dextromethorphan/quinidine used simultaneously with an SSRI that also inhibits CYP2D6 may increase the risk of adverse effects

patients.[10] Although dextromethorphan/quinidine does not have a black-box warning, it does increase the risk of QT prolongation, and patients with cardiac risk factors should undergo an electrocardiogram before starting this medication. Additionally, risperidone and olanzapine are known to cause significant weight gain, which can increase the risk of developing hyperlipidemia, metabolic syndrome, and type 2 diabetes mellitus.[10,11] Neuroleptic malignant syndrome (NMS) is a potentially life-threatening adverse effect of all antipsychotics. NMS is characterized by fever, rigidity, altered consciousness, and increased heart and respiratory rates.[12]

Quinidine increases the bioavailability of dextromethorphan by inhibiting CYP2D6. When dextromethorphan/quinidine is simultaneously used with an SSRI that also inhibits CYP2D6, such as paroxetine or fluoxetine, the patient may be at increased risk for developing adverse effects such as respiratory depression and serotonin syndrome.[13]

What is the purpose of adding dextromethorphan/quinidine to Mr. X's treatment regimen?

a) to induce a low-level sedative state
b) to decrease the frequency and severity of PBA episodes
c) to decrease serotonin levels
d) to create a synergistic effect with diazepam
e) b and c

The authors' observations

Although the exact pathophysiology of PBA is unknown, multiple theories may explain the principle elements of the condition. In the absence of a neurologic insult, the cerebellum acts as an affect regulator, inhibiting laughter and crying at times in which they are considered inappropriate. Parvizi et al[4] have theorized that the lesions involved in PBA disrupt the corticopontine-cerebellar circuitry, which impedes the ability of the cerebellum to function as an affect modulator.[3] In addition to the dysregulation of cerebellar circuitry, altered serotonin and glutamate levels are believed to contribute to the deficient affect regulation observed in PBA; therefore, adding dextromethorphan/quinidine potentiates serotonin and glutamate levels in the synaptic cleft, resulting in a reduction in PBA episodes.[4]

OUTCOME Affect stability

Seven months after beginning dextromethorphan/quinidine, Mr. X has experienced resolution of his PBA episodes. His PHQ-9 score was reduced to 0 (no clinical signs of depression) within 1 month of starting this medication and his PHQ-9 scores remain below 5, representing minimal depressive severity. The CNS-LS scale is not conducted at further visits because the patient's mother reported no further PBA episodes. Mr. X no longer exhibits episodes of aggression. These episodes seemed to have been a manifestation of his frustration and difficulty in controlling his PBA episodes. Furthermore, his dosage of diazepam was reduced, and he was weaned off risperidone. Mr. X's parents report that he has a drastically improved affect. He continues to tolerate his medication well and no longer demonstrates any exacerbations of his psychiatric symptoms.

Acknowledgements

The authors thank Anthony S. Graziano and Rachel M. Watt, both Physician Assistant students, Daemen College, Amherst, New York.

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Related Resources

- Frock B, Williams A, Caplan JP. Pseudobulbar affect: when patients laugh or cry, but don't know why. Current Psychiatry. 2016;15(9):56-60,63.
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Drug Brand Names

Dextromethorphan/quinidine • Nuedexta
Diazepam • Valium
Fluoxetine • Prozac
Haloperidol • Haldol
Lorazepam • Ativan
Olanzapine • Zyprexa
Paroxetine • Paxil
Risperidone • Risperdal

Clinical Point

Mr. X's aggressive outbursts seemed to have been a manifestation of his frustration and difficulty in controlling his PBA episodes

Bottom Line

Pseudobulbar affect (PBA) may occur secondary to various neurologic insults, including cerebral palsy and idiopathic normal pressure hydrocephalus. The condition is diagnosed by a subjective clinical evaluation and use of the Center for Neurologic Study–Lability Scale. Dextromethorphan/quinidine can significantly reduce PBA symptoms.