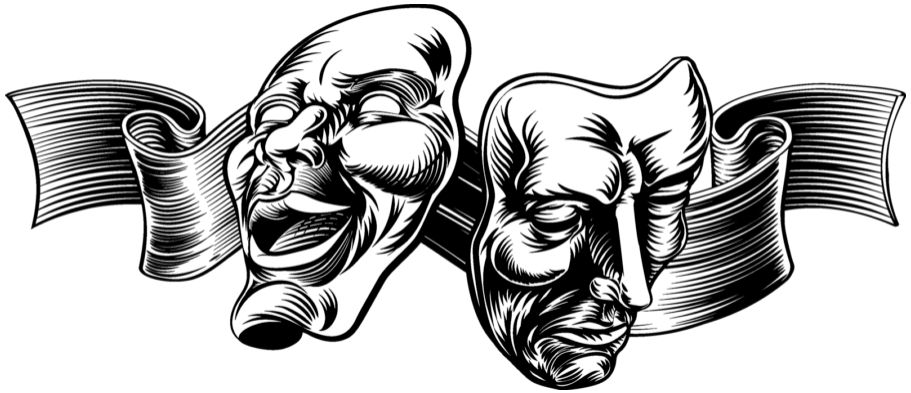
ADDING INSULT TO INJURY: THE CHALLENGE OF PSEUDOBULBAR AFFECT

Learning Objectives

- Recognize the neuropathology hypothesized to underlie PBA
- Implement evidence-based treatment strategies for patients with PBA

Pseudobulbar Affect Disorder (PBA)



- PBA is characterized by uncontrollable, inappropriate laughing and/or crying
- Patients with PBA often have:
  - Increased risk of depression and anxiety
  - Decreased quality of life
  - Impaired social interaction (due to embarrassment)

Occurs in the context of brain injury, including TBI, stroke, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS)

Cummings JL et al. CNS Spectrums 2006;11(6):1-7; Garnock-Jones KP. CNS Drugs 2011;25(5):435-45; Miller A et al. Expert Rev Neurother 2011;11(7):1077-88; Pioro EP. Drugs 2011;71(9):1193-207; Work SS et al. Adv Ther 2011;28(7):586-601.

A Rose By Any Other Name Is…Distracting

- Affective lability
- Emotional dyscontrol
- Emotional dysregulation
- Emotional incontinence
- Emotional lability
- Emotionalism
- Excessive emotionality
- Forced laughter or crying
- Inappropriate hilarity
- Involuntary emotional expression disorder
- Labile affect
- Pathological affect
- Pathological laughter and crying
- Pathological weeping
- Pseudobulbar crying

Stahl SM. CNS Spectr 2016;21:419-23.

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Need for PBA Guidelines

- Inconsistent use of terminology results in debate and confusion
- Involuntary Emotional Expression Disorder (IEED) is a medically accurate and unifying term
- For differential diagnosis of IEED, most important step is distinguishing crying as part of IEED versus crying in the context of a depressed mood
- In the literature on IEED, a distinction has been made between mood (defined as internal state) and affect (defined as external physical manifestations of emotion)
- This is confounded by labeling some mood disorders (e.g., bipolar, MDD) as affective disorders

Cummings JL et al. CNS Spectrums 2006;11(6):1-7.

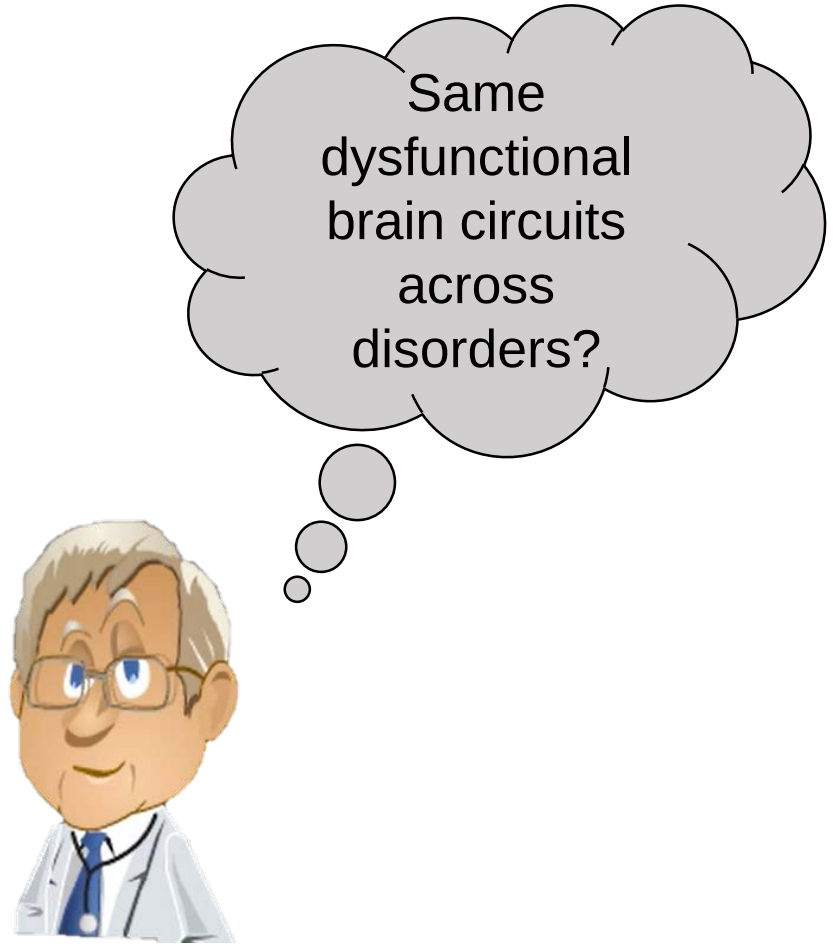
Involuntary Emotional Expression Disorder (IEED)

- Core clinical feature of IEED is involuntary outbursts of crying/laughing
- Emotional outbursts have shared common features:
  - -Outbursts are stereotyped
  - -Mood incongruent, with an intensity out of proportion to the stimulus
  - -Episodic, with a return to baseline upon conclusion
- Episodes of IEED may be accompanied by signs of pseudobulbar palsy (PBP): hyperactive jaw, facial reflexes, dysarthia
- Autonomic, respiratory, and vocal changes may occur in IEED
- Bulbar involvement in any disorder is followed by deterioration of the voice, difficulties in phonation, mastication, articulation, and respiration
- Affect changes, especially episodic anger

Cummings JL et al. CNS Spectrums 2006;11(6):1-7.

Symptoms of Disordered Emotional Expression

- Pathological laughing
- Pathological crying
- Labile affect
- Irritability
- Temper
- Disinhibition
- Aggression
- Impulsivity
- Unpredictable and rapidly changing emotions



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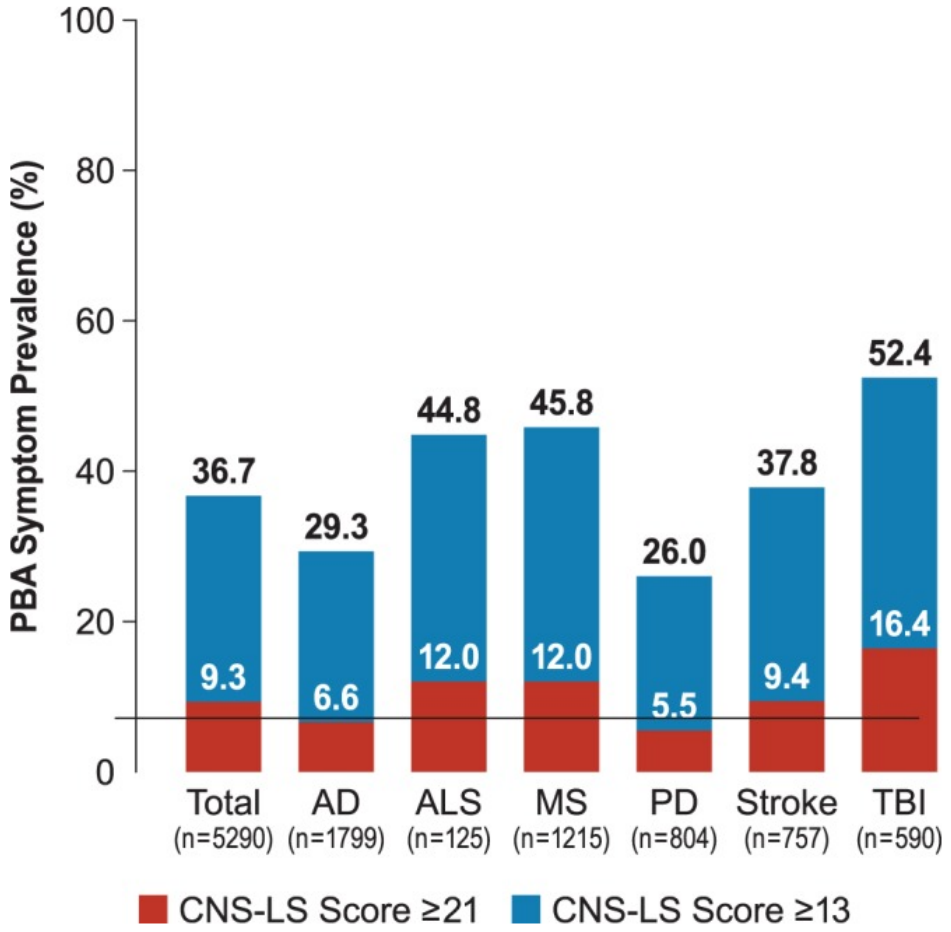
Potential psychiatric conditions with disordered emotional expression due to dysfunction of the same brain circuits underlying pseudobulbar affect: loss of top-down control of bottom-up emotional drives
-Traumatic brain injury (symptoms of emotional dyscontrol beyond pathological laughing and crying)
-Dementia (neuropsychiatric and behavioral symptoms of dementia, especially agitation, and not just pathological laughing and crying)
-PTSD (symptoms of impulsivity and self-harm)
-Borderline personality disorder (symptoms of impulsivity and self-harm)
-Major depression, depression with mixed features, and bipolar depression, especially treatment-resistant; suicidality
-Miscellaneous impulsive compulsive disorders: • Impulsive violence • Intermittent explosive disorder • Impulsive gambling, binge eating, Internet use • Impulsive/compulsive substance abuse • Impulsive attention deficit hyperactivity disorder (ADHD) • Oppositional defiant disorder (ODD) • Disruptive mood dysregulation/ temper tantrums

Stahl SM. CNS Spectr 2016;21:419-23.

PBA Registry Series (PRISM) Data



PBA symptom prevalence by CNS-LS threshold.

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CNS-LS, Center for Neurologic Study–Lability Scale; MS, multiple sclerosis; PBA, pseudobulbar affect; PD, Parkinson's disease; PRISM, PBA Registry Series; TBI, traumatic brain injury.

Brooks BR et al. PLOS One 2013;8(8):e72232.

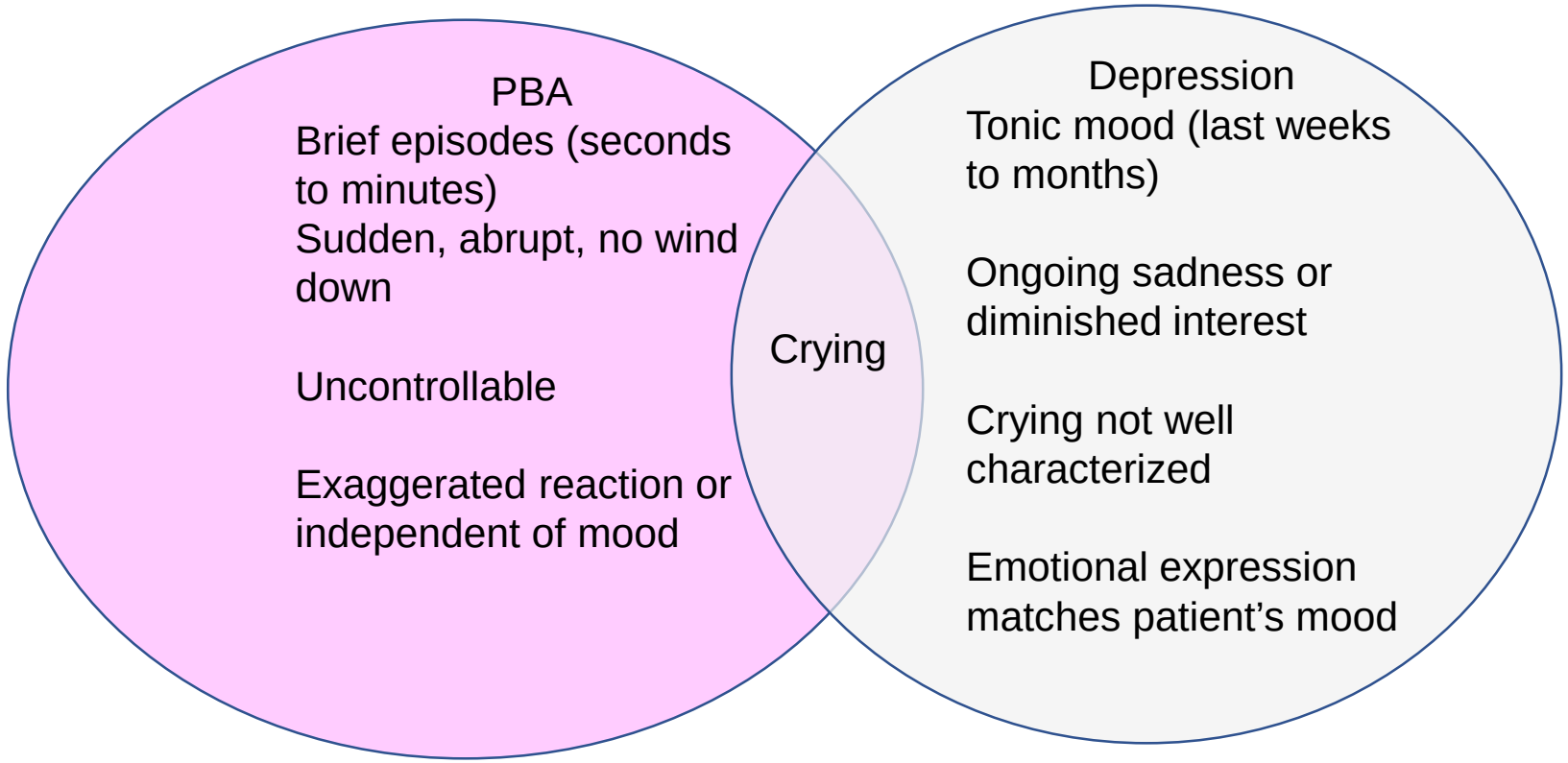
Table 2 Diagnostic criteria for pseudobulbar affect
Poeck (1969)
The emotional response is situationally inappropriate
The patient's feelings and the affective response are not closely related
The duration and severity of the episodes cannot be controlled by the patient
Expression of the emotion does not lead to a feeling of relief
Cummings (2006): necessary elements of the episodes
A change from previous emotional responses
Inconsistent with or disproportionate to mood
Not dependent on a stimulus, or excessive relative to that stimulus
Cause significant distress or social/occupational impairment
Not accounted for by another psychiatric or neurologic disorder
Not due to a drug

Distinguishing Between PBA and Depression

- PBA is often underrecognized, misdiagnosed, and undertreated
  - Only 40% of individuals who discuss PBA symptoms with a clinician are diagnosed
- PBA is a disorder of affect (the expression of mood), not mood itself
- Often mistaken for depression
  - Duration of PBA episode is shorter (seconds vs. weeks)
  - Crying is not congruent with subjective mood
  - Other symptoms of depression (e.g., fatigue, anhedonia, hopelessness, guilt) are not associated with PBA
  - PBA generally responds faster to pharmacotherapy
- Can be comorbid with major depressive disorder (MDD), making it difficult to diagnose
- Ictal laughing and crying can also be signs of complex partial epilepsy
  - Usually accompanied by alterations in consciousness

Miller A et al. Expert Rev Neurother 2011;11(7):1077-88; Work SS et al. Adv Ther 2011;28(7):586-601; Wortzel HS et al. CNS Drugs 2008;22(7):531-45; Pioro EP. Drugs 2011;71(9):1193-207.

Distinguishing Between PBA and Depression

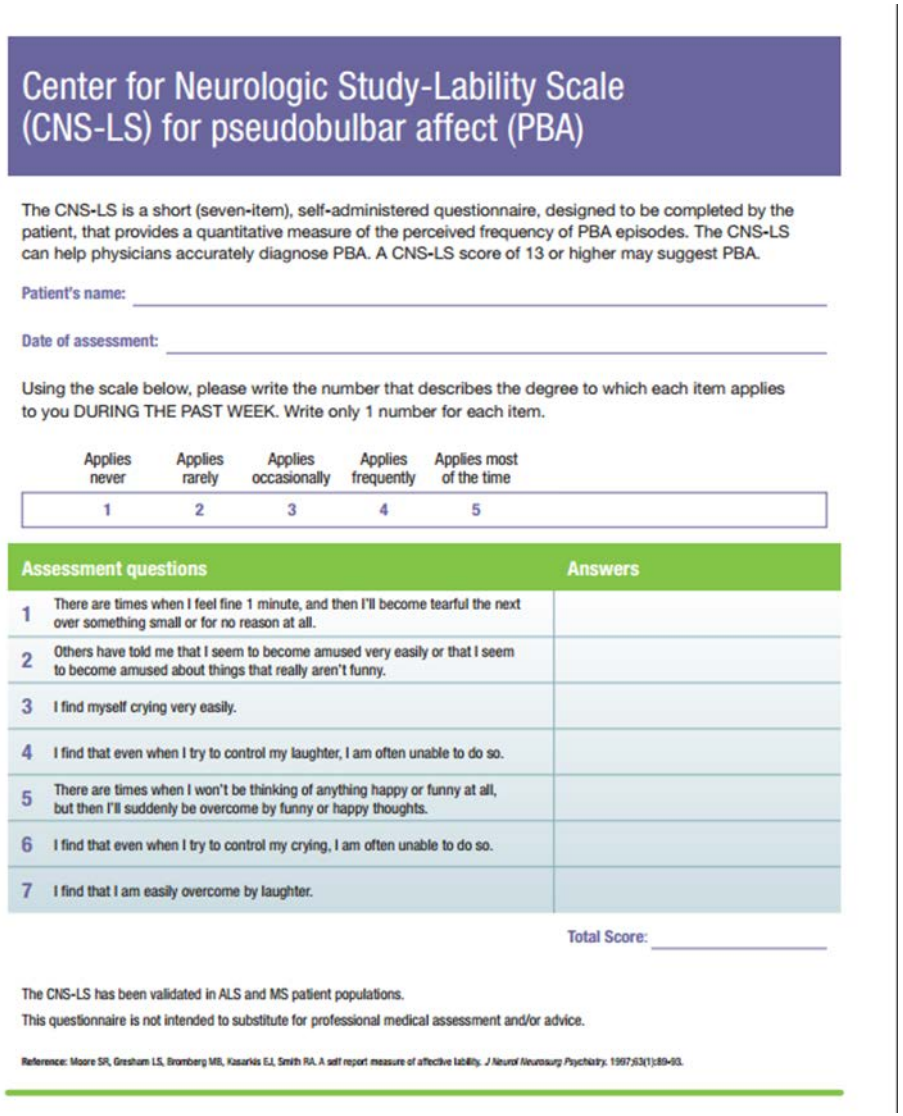


Distinguishing Between Bipolar Disorder and PBA

- PBA may be associated with bipolar disorders, especially with rapid cycling or mixed mood episodes
- Laughing or crying episodes are briefer
- No disturbances between episodes
    - Mood, cognition, and behavior show sustained changes in bipolar disorders

Miller A et al. Expert Rev Neurother 2011;11(7):1077-88.

Screening for PBA: CNS-LS



Center for Neurologic Study-Lability Scale (CNS-LS) for pseudobulbar affect (PBA)

The CNS-LS is a short (seven-item), self-administered questionnaire, designed to be completed by the patient, that provides a quantitative measure of the perceived frequency of PBA episodes. The CNS-LS can help physicians accurately diagnose PBA. A CNS-LS score of 13 or higher may suggest PBA.

Patient's name: _____

Date of assessment: _____

Using the scale below, please write the number that describes the degree to which each item applies to you DURING THE PAST WEEK. Write only 1 number for each item.

Applies never	Applies rarely	Applies occasionally	Applies frequently	Applies most of the time
1	2	3	4	5

	Assessment questions	Answers
1	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.	
2	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.	
3	I find myself crying very easily.	
4	I find that even when I try to control my laughter, I am often unable to do so.	
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.	
6	I find that even when I try to control my crying, I am often unable to do so.	
7	I find that I am easily overcome by laughter.	

Total Score: _____

The CNS-LS has been validated in ALS and MS patient populations.

This questionnaire is not intended to substitute for professional medical assessment and/or advice.

Reference: Moore SR, Gresham LS, Bromberg MB, Kasarskis EJ, Smith RA. A self report measure of affective lability. *J Neurol Neurosurg Psychiatry*. 1997;63(1):89-93.

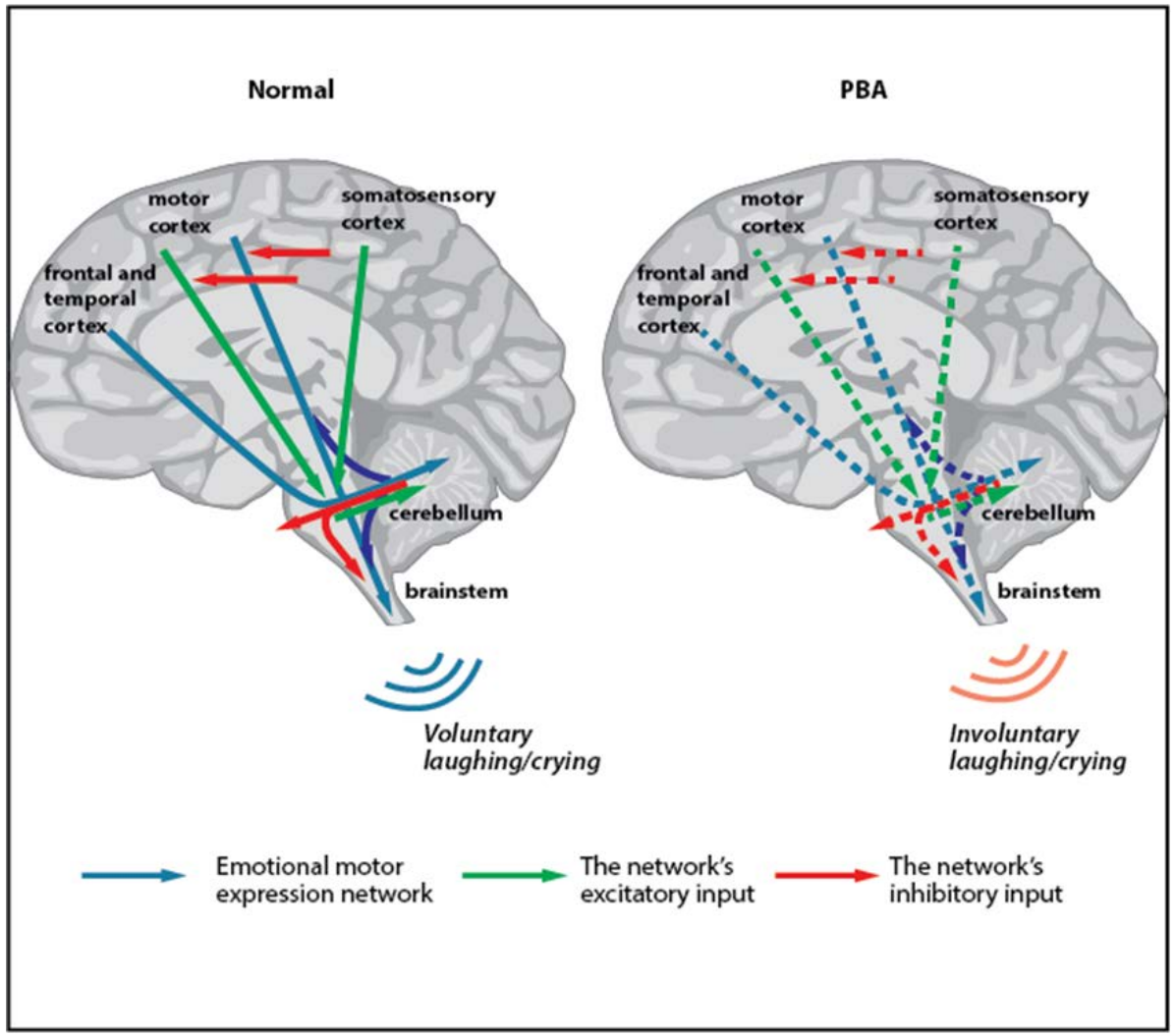
Neurobiology of PBA

- Involves the cortico-pontine-cerebellar circuit
  - Includes motor, limbic, and association cortices
  - Descending pathways to brainstem, basis pontis, and cerebellum
    - The basis pontis is a convergence point for descending input to the cerebellum
- Pseudobulbar affect:
  - Inhibition from sensory cortices to motor and limbic cortices is reduced
  - Results in disinhibition of the cerebellar gate-control

Miller A et al. Expert Rev Neurother 2011;11(7):1077-88.

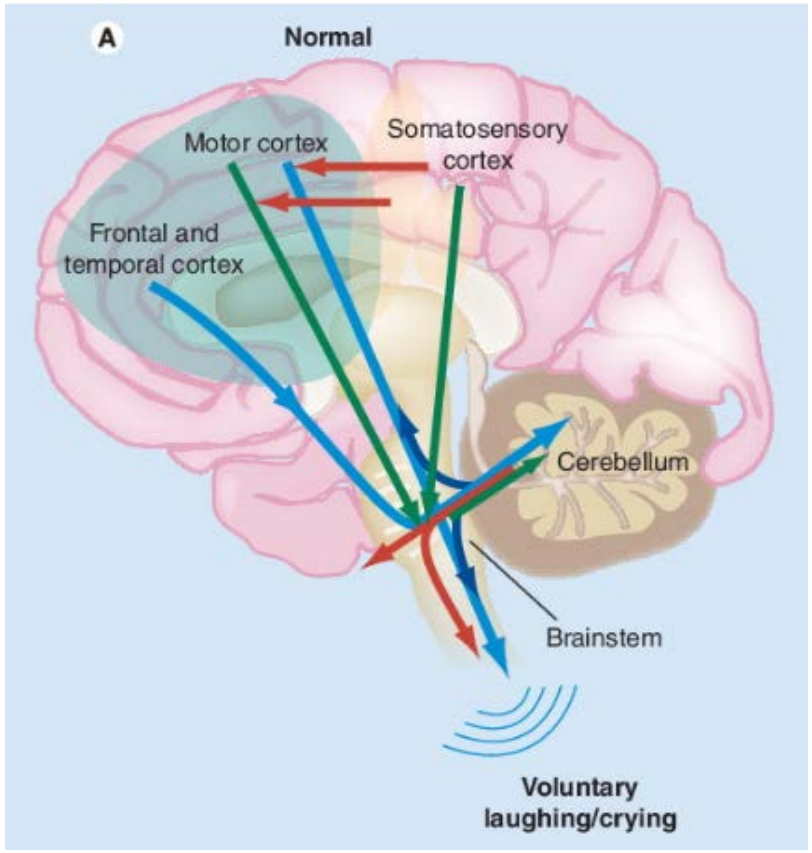
PBA Pathophysiology

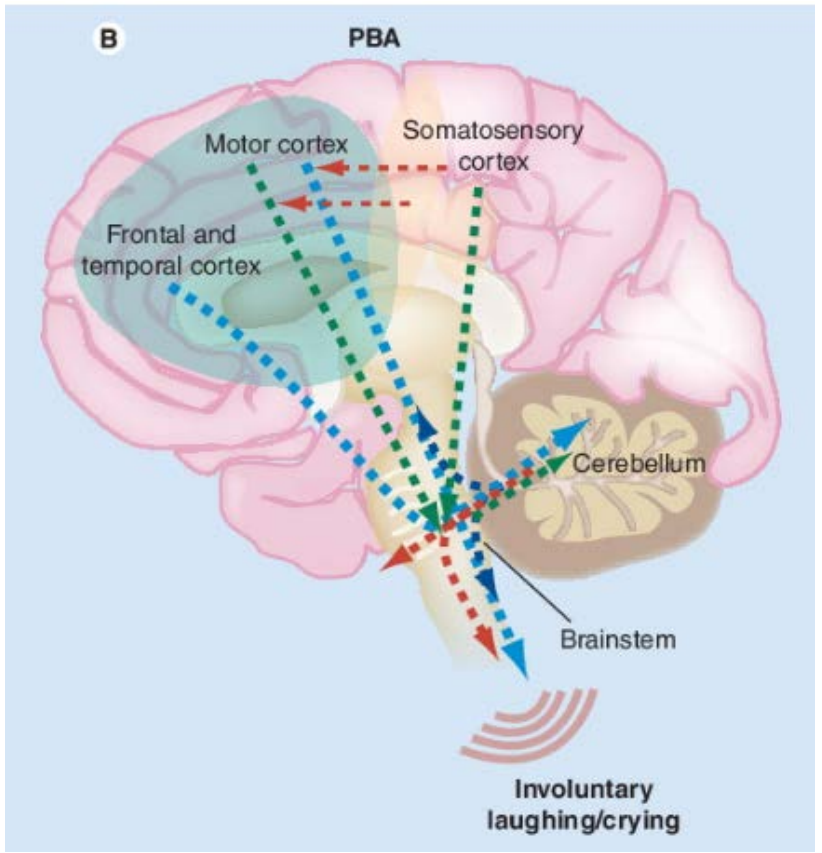
- Involves neural network of frontal lobes, limbic system, brainstem, cerebellum, or interconnecting white matter tracts of this network
- Cerebellum appears to play a much greater role than was previously hypothesized
- Cerebellum- key role in modulating emotional responses, based on input from cerebral cortex
- Disruption of the corticopontine–cerebellar circuits results in impairment of this cerebellar modulation
- Variety of neurotransmitters are involved: NE, DA, 5-HT, glutamate, and acetylcholine



Gate-Control Theory of Emotional Expression

Contextual information sent from cortex



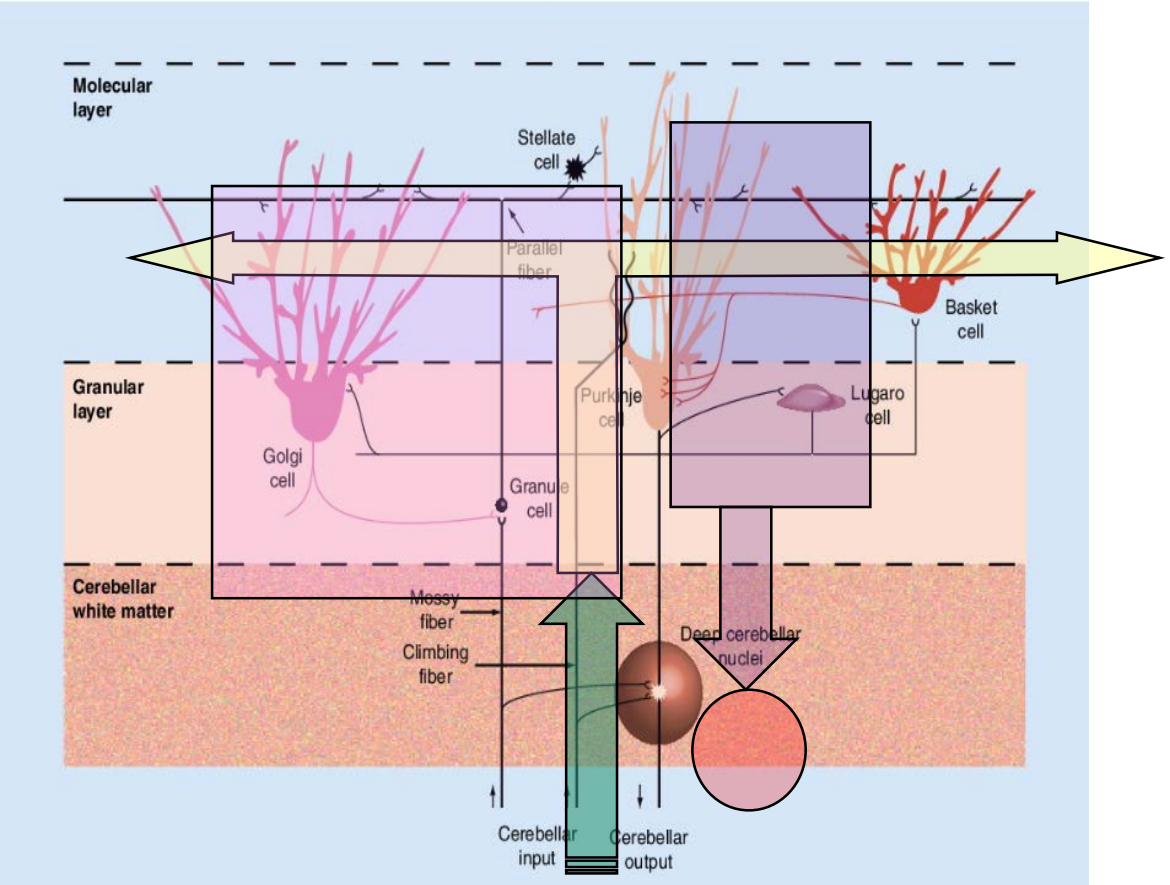


Emotionally congruent response scaled and produced by cerebellum

Emotional motor expression network → The network's excitatory input → The network's inhibitory input

Miller A et al. Expert Rev Neurother 2011;11(7):1077-88.

Cerebellar Circuitry



- Granule cells receive input from pontine nuclei (via mossy fibers)
- Parallel fibers transmit info from granule cells to Purkinje cells
- Axons from Purkinje cells project to deep cerebellar nuclei
- Golgi cells are thought to perform gating function on cerebellar output

Miller A et al. Expert Rev Neurother 2011;11(7):1077-88.

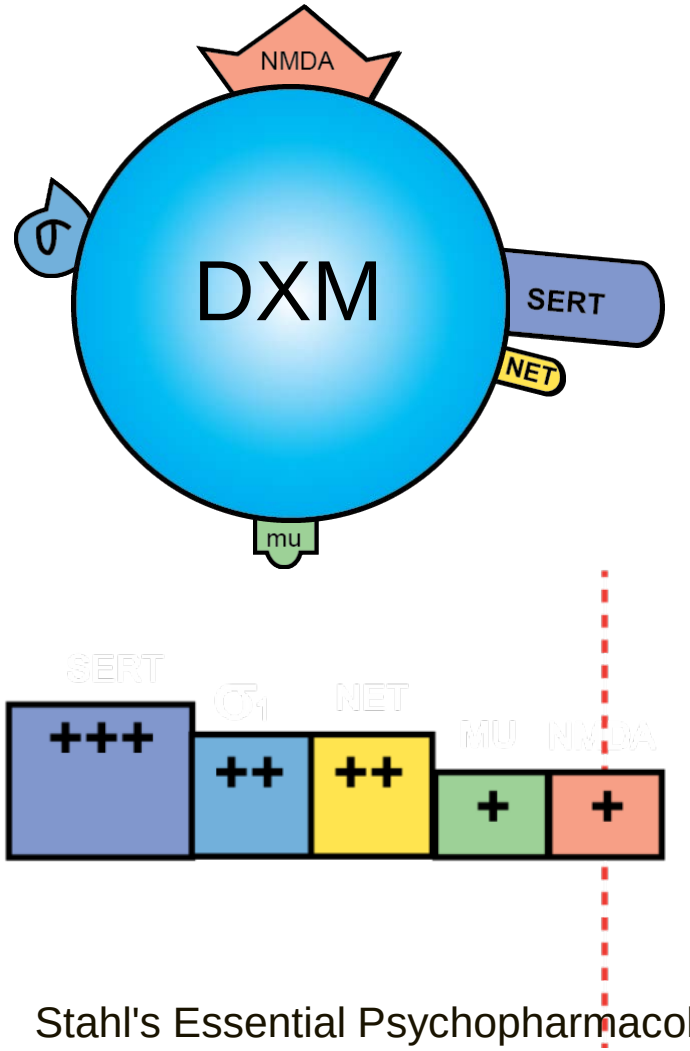
Neurobiology of PBA

- Neurotransmitters/neuromodulators involved may include:
  - 5HT
  - Glutamate
  - Norepinephrine
  - Dopamine
  - Acetylcholine
  - GABA
  - Adenosine
  - Corticotropin-releasing hormone
  - Corticosteroids

Chahine LM, Chemali Z. Epilepsy Behav 2006;8:610-15; Garnock-Jones KP. CNS Drugs 2011;25(5):435-45; Miller A et al. Expert Rev Neurother 2011;11(7):1077-88; Moore SR et al. J Neurol Neurosurg Psychiatry 1997;63:89-93.

Hypothesized Mechanisms of Dextromethorphan Action

- These receptors/systems are all implicated in the function of the brainstem and descending pathways relevant to PBA

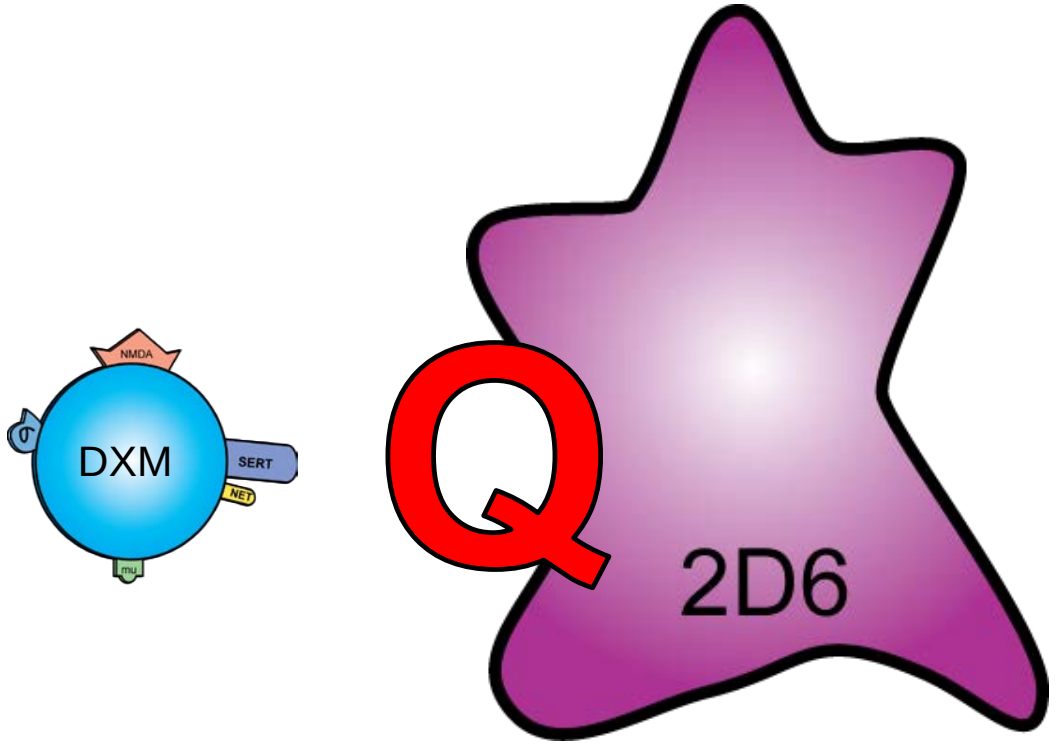


- Agonist at sigma-1 receptors
- Blocks NMDA glutamate receptors
- Inhibits serotonin and norepinephrine reuptake

Stahl's Essential Psychopharmacology. 4th ed. 2013; Yang, Deeks. Drugs 2015;75:83-90; Taylor CP et al. Pharmacol Ther 2016;164:170-82.

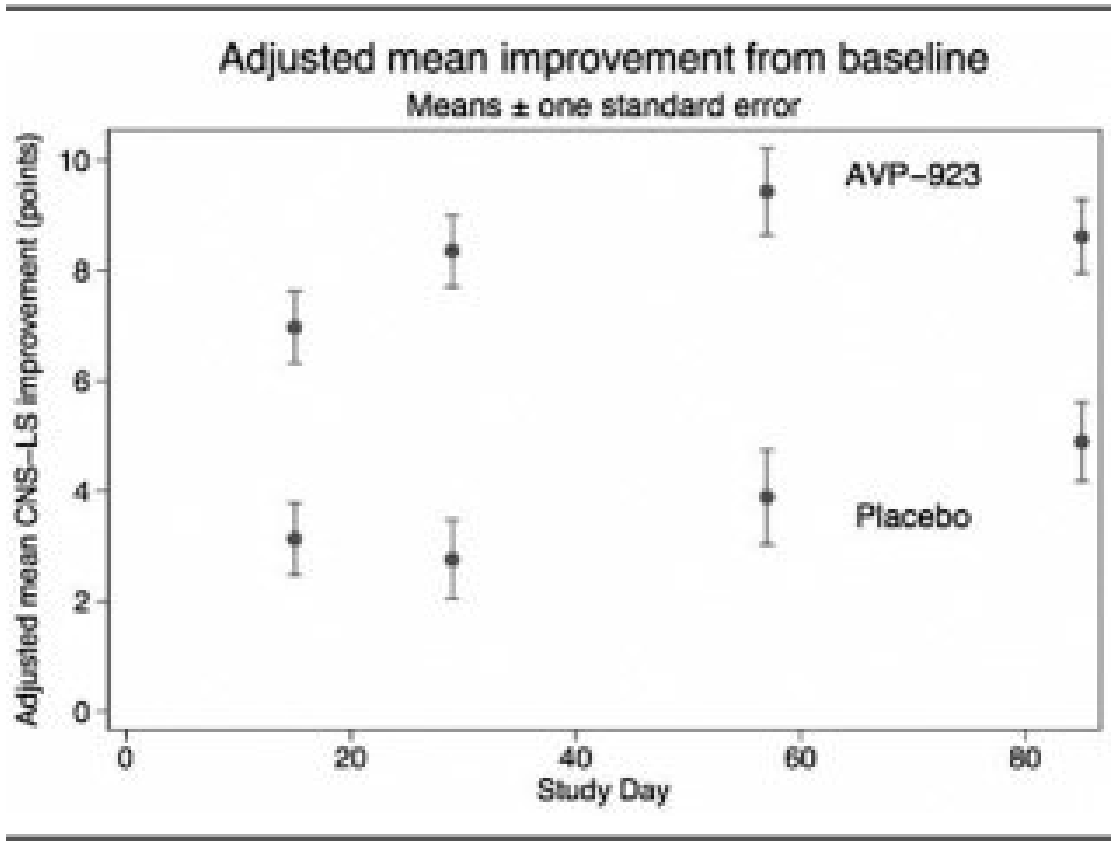
Why Quinidine?

- Quinidine inhibits the cytochrome P450 2D6 enzyme that metabolizes dextromethorphan, increasing the bioavailability of dextromethorphan 20-fold



Stahl's Essential Psychopharmacology. 4th ed. 2013; Taylor CP et al. Pharmacol Ther 2016;164:170-82.

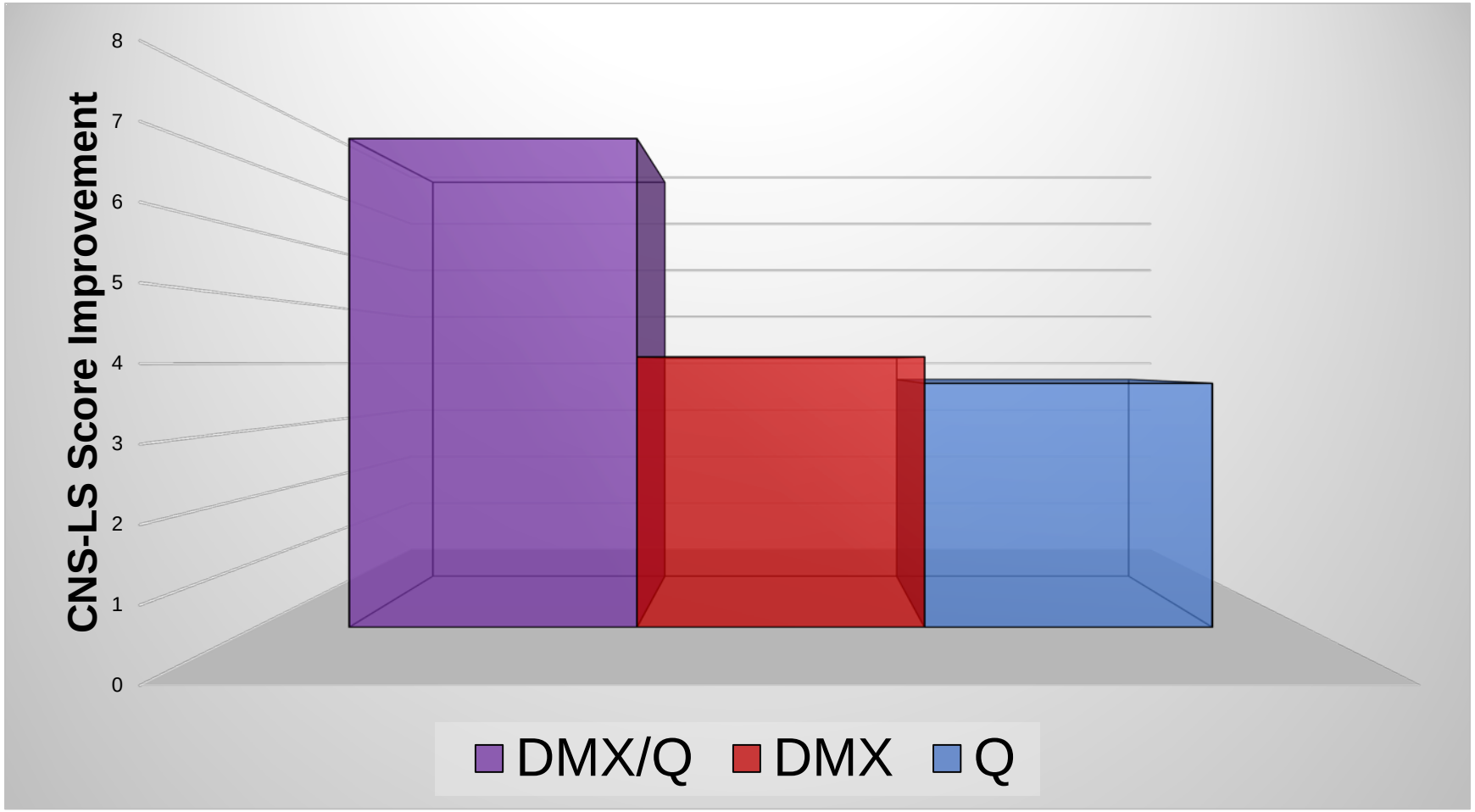
Dextromethorphan-Quinidine in PBA Associated with Multiple Sclerosis



CNS-LS: Center for Neurologic Study–Lability Scale
AVP-923: Code name for dextromethorphan-quinidine

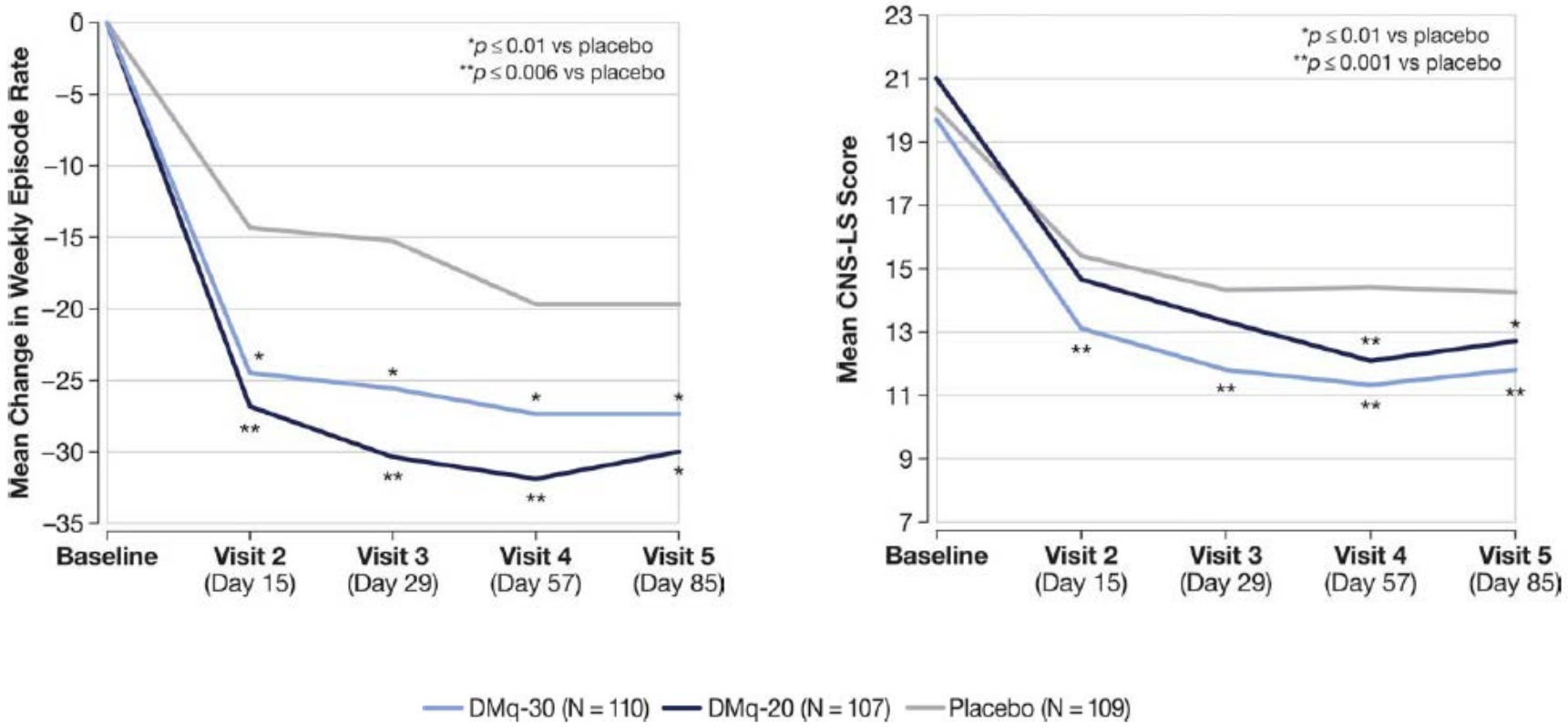
Panitch et al. Ann Neurol 2006;59(5):780-7.

Dextromethorphan-Quinidine in PBA Associated with Amyotrophic Lateral Sclerosis



Brooks BR et al. Neurology 2004;63:1364-70.

Low-Dose Dextromethorphan-Quinidine in PBA Associated with MS or ALS



Pioro EP et al. Ann Neurol 2010;68:693-702.

Treatment Options for PBA

- Antidepressants:
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Tricyclic Antidepressants (TCAs)
- Can help reduce the frequency and severity of PBA episodes
- Typically prescribed at lower doses than for depression
- Evidence supporting the efficacy of these agents is limited and further research is needed
- Dextromethorphan hydrobromide/ quinidine sulfate (Neudexta) is the only FDA-approved medication designed specifically to treat PBA

Ahmed et al.Ther Clin Risk Manag. 2013, 9:483-489.

Summary

- Pseudobulbar affect may result from damage to brain circuitry that includes motor, limbic, and association cortices as well as descending pathways to the brainstem, basis pontis, and cerebellum
- Effective differential diagnosis should result in improved treatment for PBA
- Numerous neurotransmitter/neuromodulator systems may be disrupted in pseudobulbar affect
- Dextromethorphan-quinidine is the only agent FDA-approved for the treatment of pseudobulbar affect
- The efficacy of dextromethorphan in the treatment of pseudobulbar affect is hypothetically related to its actions on sigma-1 and NMDA receptors as well as serotonin and norepinephrine reuptake transporters