Pseudobulbar Affect – A Disabling but Under-recognised Consequence of Neurological Disease and Brain Injury

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Abstract

Pseudobulbar affect (PBA) is a condition associated with common neurological diseases or brain injury that manifests as uncontrollable and inappropriate outbursts of laughter or crying. PBA exacts a severe burden on the patient and care-givers in terms of reduced social functioning and often results in the patient's isolation. The pathophysiology of PBA is incompletely understood, but symptoms are thought to result from damage to neural pathways associated with motor functioning and emotional processing. Data suggest that PBA is under-recognised by neurologists and psychiatrists and many cases go unrecognised or misdiagnosed. PBA has been successfully treated with psychoactive drugs, including antidepressants, but these do not have regulatory approval for use in this indication. A combination of dextromethorphan hydrobromide and quinidine sulphate (DM/Q) has demonstrated significant efficacy in reducing PBA symptoms and a favourable safety profile in a series of clinical trials and in regular clinical use. With the availability of an effective treatment for PBA symptoms, it becomes even more pressing to detect the condition so that patients can receive appropriate treatment.

Keywords

Pseudobulbar affect, prevalence, pathophysiology, detection, diagnosis, quality of life, clinical management

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Pseudobulbar affect (PBA), appearing as abrupt episodes of uncontrollable laughter or crying that are incongruent or independent of mood, occurs in many neurological brain diseases or following brain injury. PBA was first described by Lépine in the late-nineteenth century as lower cranial nerve palsy, but was later recognised as a frequent manifestation of acquired brain damage with upper motor neuron dysfunction, especially stroke.[1–5] PBA is prevalent but under-reported because patients tend not to report their symptoms, and doctors frequently fail to ask about them. In addition, there is a general lack of awareness of PBA among the healthcare and lay communities: many healthcare workers and patients do not recognise it as a distinct disease manifestation that can be treated. Furthermore, even when PBA manifestations are recognised, they are sometimes mistaken for a sign of depression or simply a general reaction to the burden of the neurological disease. The term PBA is perhaps misleading because the problem is not so much of affect but of disconnection between affect and emotional expression: to describe it as 'disorders of voluntary emotional expression' may be more accurate. The independence of PBA from mood, disproportion to inciting stimulus, uncontrollable nature, episodic nature and often stereotypical pattern, help differentiate it from depression and other conditions. There have been inconsistent nomenclature to describe PBA, particularly in the EU where it has been called 'emotionalism', 'emotional lability' and 'emotional incontinence' among other terms and these have contributed to difficulties in recognition and diagnosis.[5] The condition can cause or exacerbate social isolation, limit the patient's ability to work and has a detrimental effect on quality of life (QoL).

For many years, most cases of PBA were treated with medications lacking substantive or conclusive clinical evidence of efficacy and safety for this condition. Historically, the most commonly prescribed medicines were antidepressants, which can be effective but clinical trial data supporting such use are limited and none have regulatory approval for this indication.[6] More recently, a combination of dextromethorphan hydrobromide and quinidine sulphate (DM/Q) became the first evidence-based medicine approved in the US and the EU for the symptomatic treatment of PBA, irrespective of underlying neurological aetiology. The indicated use is supported by clinical trial evidence and post-marketing experience.

The purpose of this article is to consider the burden of PBA in neurological disease, its pathophysiology, the challenges of recognition, the available methods for detection and approaches to management of the condition.

The Prevalence of Pseudobulbar Affect in Neurological Disorders

The reported prevalence of PBA in neurological disease varies widely according to the underlying neurological disorder and study

methodology. The varying definitions of the condition, types and location of brain pathology, levels of investigation or types of reporting by neurology practices or health authorities may have contributed to the disparate prevalence estimates.[7] The ranges of reported prevalence are as follows: amyotrophic lateral sclerosis (ALS): 2–60 %;[8,9] multiple sclerosis (MS): 7–29 %;[8,9] Parkinson's disease (PD): 5–17 %;[8,10] Alzheimer's disease (AD): 10–74 %;[8,10–14] stroke: 6–52 %;[8,9,15] and traumatic brain injury (TBI): 5–11 %.[8,9,15,16]

In TBI and stroke, PBA may sometimes be a transient disorder limited to the acute phase of this disorder. The primary diagnosis and reported PBA prevalence are summarised in *Figure 1*. The overall prevalence has been estimated to be approximately 9–10 % among these disorders, but it is accepted that PBA is substantially under-recognised and the frequency may be much greater.[8] PBA has also been reported in: central nervous system (CNS) tumours affecting the brainstem, neurogenetic syndromes, viral cerebellitis, multiple system atrophy, supranuclear palsy, spinocerebellar ataxia, frontotemporal dementia and movement disorders (other than PD).[17,18] In addition, PBA has been reported as a rare side effect of certain other drugs including paroxetine, sumatriptan and ziprasidone.[19–21]

A Harris online survey conducted in the US included 2,318 patients having one of six of the above neurological conditions and other individuals in households of such patients. Among these participants, the prevalence of PBA was found to be 9.4–37.5 %. From this it was estimated that 1.8–7.1 million people in the US were affected. This represents a large patient population.[8] This would predict that 4.2–16.8 million Europeans have PBA.

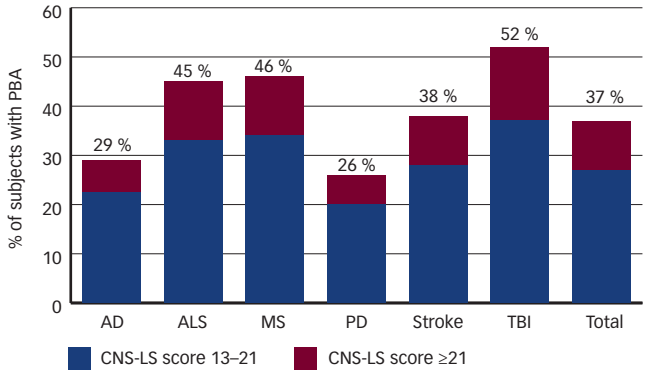
In the US, the PBA Registry Series (PRISM) was established to estimate the prevalence of PBA symptoms in a large representative sample of 5,290 patients at 585 treatment clinics who had one of five common neurological diseases or brain injury.[11] This was the first large-scale focused assessment of the magnitude of the problem caused by PBA. The data show that 36.7 % had a Center for Neurologic Study-Lability Scale (CNS-LS) score ≥13, suggesting the presence of PBA symptoms. The registry also revealed a significant impact of PBA symptoms on QoL scores (6.7 versus 4.7; p<0.0001) and documented a significantly greater use of antidepressants and/or antipsychotics among patients with PBA symptoms compared with those without PBA (53.0 % versus 35.4 %; p<0.0001). The findings indicate that PBA symptoms are common when specifically sought with a structured instrument, it has a potentially detrimental effect on QoL.

Pathophysiology of Pseudobulbar Affect

The mechanisms underlying PBA are not completely understood but are believed to comprise a common pathophysiology across the variety of neurological conditions in which it occurs. Studies have provided insights into the neuroanatomical, neurochemical and cerebellar processes involved in PBA involving several different brain regions. An overall synthesis of how these components collectively produce the condition is needed.

PBA involves a disconnection between mechanisms mediating emotions and the motor responses associated with those emotions. Investigations have shown that lesions and disturbances of the cortico-limbic-subcortico-thalamic-ponto-cerebellar network are likely to cause PBA.[22] The 'release hypothesis' for PBA suggests that lesions or injury causes disruption of cortical inhibition in the upper brainstem

Figure 1: Primary Diagnosis versus Reported Pseudobulbar Affect Prevalence (% Patients at Risk)



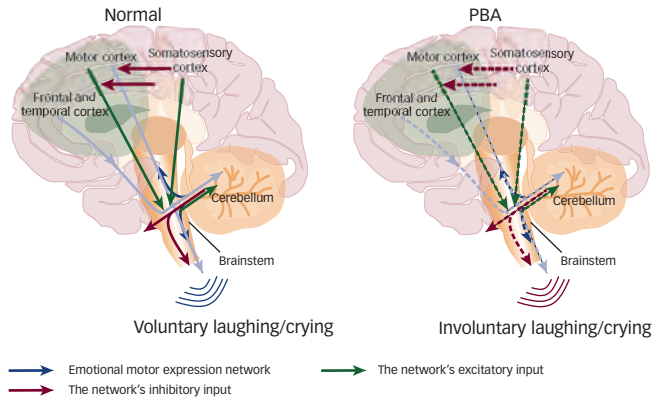
A Center for Neurologic Study-Lability Scale (CNS-LS) score ≥13 may suggest pseudobulbar affect (PBA) symptoms and merits further assessment. The CNS-LS was validated as a PBA tool in amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) populations. AD = Alzheimer's disease; PD = Parkinson's disease; TBI = traumatic brain injury. Source: Adapted from Brooks et al., 2013.[11]

and release of motor programmes of the bulbar nuclei that control motor responses associated with laughter and crying.[22] This hypothesis is supported by post-mortem studies. Further evidence has been provided by a study that measured event-related potentials (ERPs) of 11 patients with PBA and MS compared with 11 MS patients without PBA and 11 control subjects.[23] When given verbal stimuli, the patients with PBA showed much more impulsive responses with overactive motor responses to neutral stimuli than the other two groups and significantly different ERP waveform profiles. These responses involved regions of the cortex associated with sensory-motor and emotional processing. The authors suggested that the results could indicate a disinhibition of a 'gate control' mechanism for emotional expression that would result in a lower emotional expression threshold in patients with PBA.

Neuroimaging studies have shown that PBA involves changes in circuits that are known to involve a variety of neurotransmitter functions.[24] Serotonin and dopamine decreases have been reported, as well as glutamate excess and sigma-type receptor abnormalities.[7,9,13] Single-photon emission computed tomography and positron emission tomography studies have shown significantly lower binding ratios of the presynaptic serotonin transporter (SERT) in the midbrains of individuals with pathological crying compared with those without it.[25] A Danish study in stroke patients reported that pathological crying may be associated with serotonin depletion and greater receptor availability. Administration of selective serotonin reuptake inhibitors (SSRIs) decreased receptor availability and reduced crying.[26] The anatomy of PBA-related circuits involves structures with binding sites not only for monoamines (e.g. serotonin) but also for sigma-1 and glutamate receptors. The importance of these systems in PBA is supported by the observation that DM/Q also binds to these receptors.

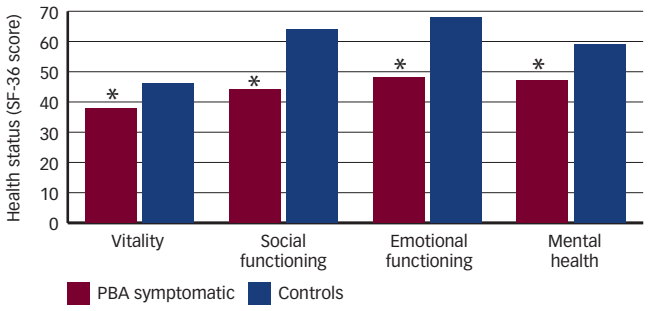
Recently, increasing evidence has suggested that PBA may be associated with damage to the cerebellum.[27] PBA appears more common in patients with cerebellar damage than in patients with disorders sparing the cerebellum although this is not the case in PBA associated with stroke. A chart review conducted at a treatment centre in the US of 27 patients with cerebellar and brainstem atrophy (multiple system atrophy-cerebellar type) revealed that 36 % met PBA criteria.[18]

Figure 2: A Putative Mechanism of Pseudobulbar Affect



Source: Reprinted with permission from Miller et al., 2011.[13]

Figure 3: Short Form-36 Comparison for Patients with Pseudobulbar Affect versus Controls



**p<0.05 independent samples two-tailed t test. Neurological patients and their care-givers were surveyed online using a matched sample design (n=1,052; the exact number of pseudobulbar affect [PBA] patients varied per question). The Short-Form 36 (SF-36) Health Status Questionnaire was administered with a margin of error or 95 % confidence of 4.96 %. Source: Colamonico et al., 2012.*[31]

Golgi cells may have a 'gating function' that sets a threshold preventing low-level stimuli from eliciting a response such as laughter or crying.[28] When the cerebellum is damaged, however, it is proposed that this inhibitory mechanism is disrupted lowering the threshold for emotional expression allowing spontaneous laughter or crying in the absence of adequate stimuli (see *Figure 2*). While this putative mechanism appears plausible, much further evidence from human investigations is required to substantiate it as a pathway in PBA. The anatomical pathways involved in PBA differ from those associated with depression supporting a distinction between these disorders.[29,30]

The Impact of Pseudobulbar Affect on Functioning and Quality of Life

PBA can result in social isolation and an inability to maintain employment. Studies have shown that QoL is seriously decreased in patients with the condition. In a study on 269 adult patients with PD at a treatment centre in the US, 7.1 % showed PBA symptoms.[10] Patients with PBA symptoms had significantly poorer well-being subscores on a 39-point questionnaire (p<0.0001) and higher Beck Depression Inventory scores (p<0.001) than patients without it. A significantly greater proportion of patients with PBA symptoms were taking anti-depressant medications (p=0.0008).

The QoL burden associated with PBA was further demonstrated by a Harris interactive survey of neurological patients conducted in the US involving 399 participants with PBA symptoms and 653 controls. The PBA group showed significantly poorer Short-Form 36 (SF-36) scores (p<0.05), visual analogue scale (VAS) scores for impact of PBA symptoms on QoL and quality of relationships (p<0.05) and work productivity and activity impairment instrument (WPAI) scores (p<0.05). Measures of QoL, work and relationships (using SF-36 and other scores) were also poorer in those with PBA symptoms than controls.[31] In 24 % of respondents PBA symptoms contributed a great deal to or were the main cause of patients becoming housebound and in 9 % PBA symptoms were a primary reason for the patient being moved to supervised living.

More recently, the substantial impact of PBA symptoms on QoL was shown in the PRISM registry (n=5,290). The overall impact of one of six neurological conditions on QoL scores was found to be significantly greater in those with PBA symptoms (Center for Neurologic Study-Lability Scale [CNS-LS] <13 versus ≥13) compared with individuals without PBA (6.7 versus 4.7; p<0.0001).[11] The large population used in the PRISM registry is a reliable guide of the extent of the burden caused by PBA. Another study that included 719 patients with PD or other movement disorders with associated PBA confirmed that PBA also has a marked deleterious effect on an individual's ability to function socially, having an increased likelihood of being housebound and needing to be moved to supervised housing.[32] An online survey of 1,052 neurological patients and their carers conducted in the US showed that individuals with PBA symptoms have significantly poorer vitality, social functioning, emotional roles and mental health compared with matched controls (see *Figure 3*).[31] Confounding these observations is the relationship of PBA symptoms with the severity of the underlying neurological disease that can, in part, account for poorer QoL, impaired social functioning and less independence. In stroke, for example, crying has been shown to be correlated with lesion size.[4] Resolving this confound is an objective for future research.

Detection and Diagnosis of Pseudobulbar Affect

At present, there continues to be confusion around the nomenclature and diagnostic criteria in PBA and a general lack of consensus on definitions.[33,34] Detection and diagnosis of PBA can be challenging. Evaluation and treatment is likely to be focused on the underlying neurological condition and the symptoms of PBA may be unreported or overlooked. PBA is usually detected by exploratory questioning but is sometimes observed directly if the patient has an episode during the course of an examination. PBA can be confused with psychotic disorders such as schizophrenia or mood disorders such as bipolar disorder, depression or even epilepsy. Poor identification of PBA was emphasised by the Harris survey in the US that identified 937 patients who screened positive for PBA. Of these, 637 had discussed their crying or laughter with a doctor and among these 41 % had received a diagnosis.[8] Diagnoses included depression (33 %), 'just part of the condition' (28 %), stress and personality disorders (8 %), bipolar/mood disorder (13 %), 'don't know' (11 %), post-traumatic stress disorder (9 %) and anxiety (7 %).

Depression is the principal differential diagnostic challenge and can be differentiated from PBA by the uncontrollable, stereotypical and excessive nature of the PBA episodes. These discrete events are also less related to provoking stimulus or accompanying thoughts than crying episodes in depression. In addition, the symptoms of other neurological diseases and depression are much more sustained than with PBA (days or weeks rather than minutes) (see *Table 1*).

Table 1: Differentiating Pseudobulbar Affect from Depression*

Clinical Feature	Pseudobulbar Affect	Depression
Emotional expression	Crying, laughing or both	Crying
Emotional duration	Brief, abrupt, episodic (seconds to minutes)	Tonic mood state (weeks to months)
Voluntary control	None to minimal	May be modulated
Emotional experience	Independent or excessive display of expressed emotion	Mood congruent with sadness
Underlying neurological disorder	Always present	Variable presence
Provoking stimulus	May be minimal or non-existent	Crying may be provoked by mood-related situations
Accompanying thoughts	No specific relationships	Worthlessness, helplessness, hopelessness, guilt, thoughts of death

**Note that pseudobulbar affect and depression are not mutually exclusive; both conditions may sometimes be present in the same patient.*

The presence of PBA can usually be detected by simply asking the patient or carer if they have a tendency to laugh or cry for no reason or have an exaggerated response to emotional situations. In addition, various scales have been devised for diagnosing and monitoring treatment in PBA including the Pathological Laughter and Crying Scale (PLACS),[29] which has been adapted as the Emotional Lability Questionnaire[35] for use in ALS. Another main instrument is the CNS-LS, which is a self-report scale that screens for pathological laughing and crying symptoms and has been validated in ALS and MS.[36,37] The Affective Lability Scale[38] assesses lability and intensity of affect, but has been used only in PBA associated with TBI.

Clinical Management of Pseudobulbar Affect and Evidence Supporting Treatments

Various treatment approaches have been attempted in PBA. Cognitive and behavioural therapies have been reported, which are designed to invoke undamaged pathways in the brain and compensate for deficits resulting from structural lesions through muscle movement and other exercises.[39] Patients and care-givers can avoid stimuli that are likely to trigger an episode such as emotional situations but the PBA remains. These approaches are less widely used than drug treatment.

A variety of medications have been prescribed to treat PBA and their use has been supported by a series of small studies (including double-blind randomised controlled trials) and case reports. The drugs most commonly used for PBA are antidepressants of different types – use in this indication is entirely off-label (see *Table 2*).[6,7,13] SSRIs that have shown preliminary efficacy in small trials in PBA include citalopram, sertraline, fluoxetine and paroxetine.[40–44] Tricyclic antidepressants used in PBA include amitriptyline and nortriptyline.[29,30] In addition, several case reports have described the successful use of selective noradrenergic reuptake inhibitors including venlafaxine, duloxetine and reboxetine to treat PBA associated with stroke, ALS and MS.[45–47] A more recent report described the efficacy of treating two elderly patients with vascular dementia and associated emotional incontinence with ifenprodyl.[48] Both patients showed substantial reductions in symptoms over the 2 weeks of treatment but larger randomised trials are needed to substantiate these findings. Although these drugs have shown efficacy in PBA, the evidence supporting their use is limited and none has regulatory approval for use in this indication and so their use for this condition remains off-label.

A fixed combination of dextromethorphan and quinidine sulphate (DM/Q, Nuedexta, Avanir Pharmaceuticals, Inc.) has been approved by the European Medicines Agency and the US Food and Drug Administration (FDA) for use in PBA.[49,50] This drug has been commercially available in the US since February 2011 and will soon be available in the EU for symptomatic treatment of patients with PBA resulting from neurological diseases affecting the brain (e.g. dementia, stroke, MS, etc.) or brain injury. In the US, dextromethorphan hydrobromide (salt) is used with a standard nominal dose of 20 mg, whereas in Europe, the same dose will be labelled as 15 mg dextromethorphan free base. The nominal 30 mg dose of dextromethorphan hydrobromide (not approved in the US) will be available in the EU and labelled as dextromethorphan free base 23 mg. Quinidine sulphate is labelled as 10 mg in the US but as 9 mg quinidine base in the EU.

The exact mode of action of dextromethorphan in PBA is unknown but dextromethorphan is both a sigma-1 receptor agonist and an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist.[51,52] In addition, it shows affinity for the SERT, for the 5-hydroxytryptamine (serotonin) receptor 1D (5-HT1B/D) receptor[53] and the norepinephrine transporter (NET).[54] Through its binding to the NMDA and sigma-1 receptors, SERT and NET, dextromethorphan is thought to have a modulatory effect on neurotransmission involving glutamate and monoamines (including serotonin and noradrenalin).

Dextromethorphan is the pharmacologically active component of DM/Q but is rapidly catabolised in the liver in a major biotransformation pathway involving cytochrome P450 2D6 (CYP2D6) and excreted in the urine.[55] The low dose of quinidine maintains therapeutic plasma levels of dextromethorphan by altering its metabolism. Quinidine competitively inhibits cytochrome P450 2D6 (CYP2D6) but at such a low dose level that it is well tolerated and does not influence the safety profile of the combination treatment. In other applications, quinidine has been associated with increased QTc intervals and ventricular arrhythmias but at daily doses more than 100-fold higher than those used in this DM/Q combination.[56,57]

The efficacy and safety of DM/Q has been shown in a series of clinical trials (see *Table 2*). An initial study including patients with ALS (n=65) showed that DM/Q produced a 3.3-point improvement in CNS-LS over dextromethorphan alone (n=30) and a 3.7-point improvement over quinidine alone (n=34) ($p<0.001$). In this study significant reductions were seen for crying and laughing/crying combined for DM/Q over DM or Q alone ($p<0.001$–0.007). Significant improvements were also reported for QoL and quality of relationships for DM/Q versus DM or Q alone ($p<0.001$ for all). Common adverse events (AEs) included nausea, fatigue, headaches and dizziness.[58] A subsequent study on MS patients (n=150) showed significant reductions in CNS-LS scores compared with placebo ($p<0.0001$), reductions in the incidence of laughter and crying and improvements in QoL and quality of relationships.[49] Both these first two studies utilised higher doses of quinidine (30 mg) than are approved in the EU.

The Safety and Efficacy of AVP-923 (DM/Q) in PBA Patients With ALS or MS (STAR) trial was a larger, randomised, phase III pivotal study

Table 2: Overview of Treatments Used in Pseudobulbar Affect

Drug/ Reference	Study Design	Disease/Patients (Number)	Efficacy Findings
Selective Serotonin Reuptake Inhibitors			
Citalopram[40]	9-week, double-blind RCT crossover	Stroke 16	Citalopram was well tolerated. Crying was decreased by 50 % during treatment versus placebo
Sertraline[42]	8-week, double-blind RCT	Stroke 28	Significant improvements in a global rating of emotionalism and a specific benefit on tearfulness
Fluoxetine[43]	Double-blind	Stroke 152	Significant improvement in emotional incontinence (PSEI), or anger proneness (PSAP) compared with placebo (p<0.01)
Paroxetine[44]	Comparative study versus citalopram	Brain injury 13	Significant (p<0.001) improvements of emotionalism were observed after both paroxetine and citalopram
Tricyclic Antidepressants			
Amitriptyline[30]	Double-blind crossover	MS 12	8/12 patients showed significant improvement with amitriptyline (p=0.02)
Nortriptyline[29]	Double-blind, placebo controlled	Stroke 14	Significantly lower pathological laughing and crying based on PLACS scores than placebo (p=0.008)
NMDA Receptor Antagonist/Sigma-1 Receptor Agonist (Putative)			
DM/Q[58]	Placebo-controlled, randomised parallel-group study	ALS 140	After 29 days, DM/Q (30/30 mg) produced a 3.3-point greater improvement in CNS-LS than DM only (30 mg) (p<0.001) and 3.7-point greater improvement than Q only (30 mg) (p<0.001). CR was achieved in 52 % for DM/Q compared with 23 % for DM and 12 % for Q (p<0.001)
DM/Q[49]	Randomised, double-blind, placebo controlled	MS 150	After 85 days, DM/Q (30/30 mg) resulted in adjusted mean changes in CNS-LS scores of 7.7 DM/Q versus 3.3 for placebo (p<0.0001). CR was achieved in 20.8 % versus 6.9 % of patients (p=0.028)
DM/Q[50]	Randomised, double-blind, placebo-controlled (STAR)	ALS and MS 326	Daily PBA episode rate was 46.9 % lower for DM/Q 30/10 mg and 49 % lower for DM/Q 20/10 mg versus placebo (p<0.0001 for both). Mean change in CNS-LS scores: DM/Q 30/10 mg: –8.2 (p=0.0002), DM/Q20/10 mg: –8.2 (p = 0.0113); placebo: –5.7. The proportions in remission were 47.3 % for DM/Q 30/10 mg, 51.4 % for DM/Q 20/10 mg and 29.4 % for placebo

ALS = amyotrophic lateral sclerosis; CNS-LS = Center for Neurologic Study-Lability Scale; CR = complete remission; DM/Q = dextromethorphan hydrobromide and quinidine sulphate; MS = multiple sclerosis; PLACS = Pathological Laughter and Crying Scale; PSAP = measure of anger proneness; PSEI = pseudobulbar symptoms of emotional incontinence; RCT = randomised controlled trial; STAR = Safety and Efficacy of AVP-923 in PBA Patients With ALS or MS.

Table 3: Most Frequent Adverse Events Occurring during Treatment with Dextromethorphan Hydrobromide and Quinidine Sulphate in the Safety Population of the STAR Pivotal Study

Event	DM/Q 30/10 mg (n=110) (%)	DM/Q 20/10 mg (n=107) (%)	Placebo (n=109) (%)
Adverse Event Frequency (%)			
Fall	20.0	13.1	20.2
Dizziness	18.2	10.3	5.5
Headache	13.6	14.0	15.6
Nausea	12.7	7.5	9.2
Diarrhoea	10.0	13.1	6.4
Somnolence	10.0	8.4	9.2
Fatigue	8.2	10.3	9.2
Nasopharyngitis	8.2	5.6	7.3
Urinary tract infection	7.3	3.7	2.8
Constipation	6.4	6.5	8.3
Muscle spasms	6.4	3.7	9.2
Muscle weakness	5.5	4.7	3.7
Dysphagia	4.5	5.6	3.7
Pain in extremities	4.5	1.9	7.3
Depression	0	0.9	5.5
QTC Changes (Mean ms)			
QTcB/QTcF change from baseline	3.0/4.8	–1.9/1.0	1.6/1.0
Proportion of post-baseline ECGs with QTcB/QTcF >480 ms (%)	0.2/0	0/0	0.9/0

DM/Q = dextromethorphan hydrobromide and quinidine sulphate. QTcB/QTcF = Heart rhythm intervals derived using Bazett's (QTcB) and Fridericia's (QTcF) formulae. Source: Pioro et al., 2010.[50]

including 326 patients with PBA secondary to ALS or MS.[50] The daily PBA episode rate was 46.9 % lower for the DM/Q 30/10 mg dose (equivalent to the 23/9 mg labelled dose of DM/Q free base in the EU) compared with placebo (p<0.0001). This rate was 49.0 % lower for the DM/Q 20/10 mg dose (equivalent to the 15/9 mg labelled dose of DM/Q free base in the EU) compared with placebo (p<0.0001). Both DM/Q doses significantly reduced weekly episode rates and CNS-LS scores over the duration of treatment (see *Figure 4*). These doses also significantly increased the proportion of patients who were episode-free and the proportion of patients with remission of PBA during the final 14 days (see *Figure 5*). In addition, the 30/10 mg dose improved SF-36 scores for social functioning and mental health, suggesting an incremental effect over the lower dose.[50] The 12-week open-label phase of the STAR study (during which all subjects received DM/Q 30 mg/10 mg) showed persistence of the effect observed in the initial blinded study period.[59]

DM/Q is likely to be administered to patients for an extended period of time in chronic and progressive neurological disease such as MS and it is essential that the long-term safety profile is favourable. In the pivotal trial, both levels of DM/Q treatment were well tolerated with a low discontinuation rate. Only the incidence of dizziness and diarrhoea were increased with both doses compared with placebo. The most frequent AEs (see *Table 3*) in the DM/Q 30/10, 20/10 and placebo groups were: fall, dizziness, headache, nausea and diarrhoea. Discontinuation rates were low (lowest with DM/Q 30/10). There was mild prolongation of QTc interval with DM/Q versus placebo (no QTc intervals were >480 milliseconds [with Fridericia correction] or changed from baseline >60 milliseconds) but there were no proarrhythmic events.[50] Serious AEs (SAEs) occurred at similar frequencies in all three groups, (7.3 % for DM/Q 30/10 group, 8.4 %

for DM/Q 20/10 group and 9.2 % for placebo). Two SAEs, both in the DM/Q 20/10 group, were possibly treatment related. One of these was reported as respiratory depression and ALS progression; the other as worsening muscle spasticity. Seven deaths were reported, all occurring in ALS patients: three in patients receiving DM/Q 30/10, three in patients receiving DM/Q 20/10 and one in a patient receiving placebo. All of the deaths had a respiratory cause considered likely to be the result of progression of the underlying neurological disease based on an independent adjudication of the data.

The STAR pivotal trial included patients with ALS in whom respiratory function must be optimally maintained. There were no significant differences between the two DM/Q doses and placebo in changes in nocturnal oxygen saturation levels.[60] This suggests that the DM/Q treatment has little or no detrimental effect on respiratory function in these patients.

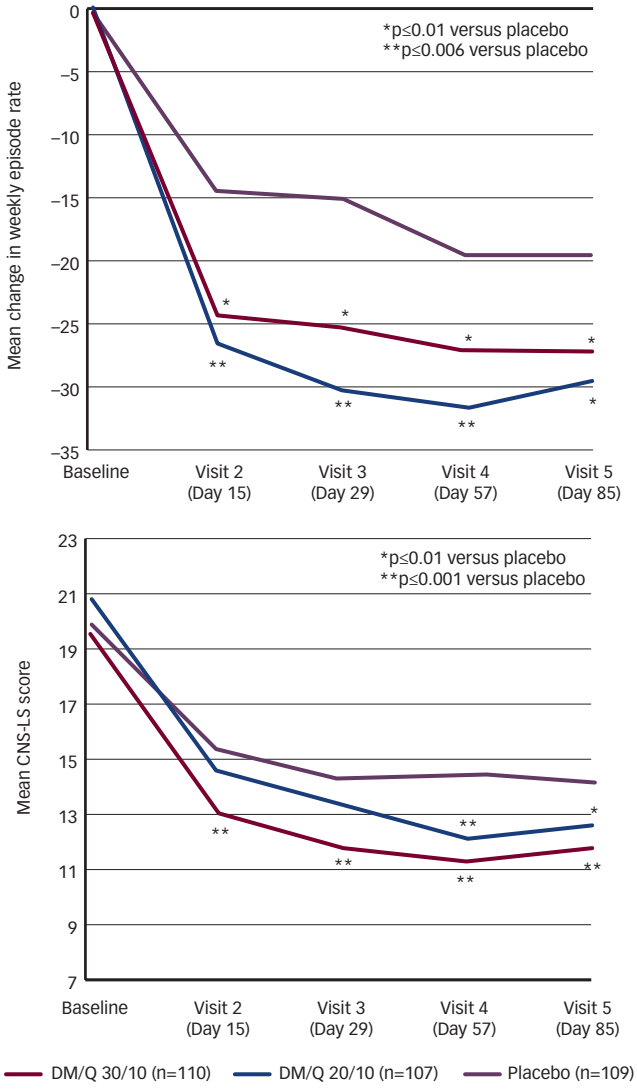
Longer-term safety of DM/Q treatment of PBA has been investigated in an open-label study conducted in the US.[61] A total of 553 patients were recruited (40.3 % MS; 31.8 % ALS; 8.3 % stroke; 3.8 % TBI; 2.9 % primary lateral sclerosis; 2.0 % diagnosed PD; and 2.7 % AD) and were treated with DM/Q 30/30 twice daily in a 52-week trial with an optional extension. Among these patients, 69.1 % completed 6 months and 54.2 % completed 1 year of treatment. AEs were reported by 91.9 % of patients but the type and frequency were generally consistent with a patient population with their underlying neurological diseases. SAEs were reported in 22.8 % in the treatment phase and 29.4 % in extension phase; none were considered treatment related. The most frequent AEs during treatment were: nausea (24.8 %); headache (22.8 %); dizziness (excluding vertigo 19.5 %); fall (16.5 %); diarrhoea (16.3 %); fatigue (14.6 %); and weakness (13.7 %). The most common AEs during the open-label extension phase were: fall (18.7 %); nasopharyngitis (18.3 %); headache (16.4 %); and arthralgia (14.5 %). These results indicated that the safety experience in the pivotal trial was similar when DM/Q is given long term.

Some 'real world' experience in the regular clinical use of DM/Q is emerging. A case series/chart review from a treatment centre in the US recently reported good efficacy in the treatment of PBA secondary to stroke and AD.[62] Another recently reported case series from a US treatment centre included 12 patients with PBA secondary to TBI and highlighted DM/Q as pharmacotherapy for various neuropsychiatric symptoms including PBA.[63] It was suggested that the operational definition of PBA secondary to TBI should be expanded to formally acknowledge the primary impairment of impulse control with which episodes of affective lability frequently occur.

Initiating and Stopping Treatment in Pseudobulbar Affect

Treatment of PBA should be initiated once the condition is diagnosed in patients with an associated neurological disease or injury and PBA is contributory to patient disability.[64] In patients with TBI or stroke, the need for treatment may diminish as recovery occurs and neurological function is restored. In MS, ALS, AD and PD, however, treatment is likely to be needed over extended durations; in progressive disease the PBA symptoms may be long-term. During treatment, the maintenance of the clinical effect as well as the tolerability of DM/Q in the patient should be regularly monitored to ascertain the continued benefit of the drug.[65] Patients with PBA and their care-givers/family need to be educated regarding their expectations of treatment, reporting of PBA symptoms and possible occurrence of AEs.

Figure 4: Twelve-week Time Course of Pseudobulbar Affect Weekly Episode Rate and CNS-LS Score During Dextromethorphan/Quinidine 30/10 mg, 20/10 mg or Placebo Treatment in the STAR Pivotal Study



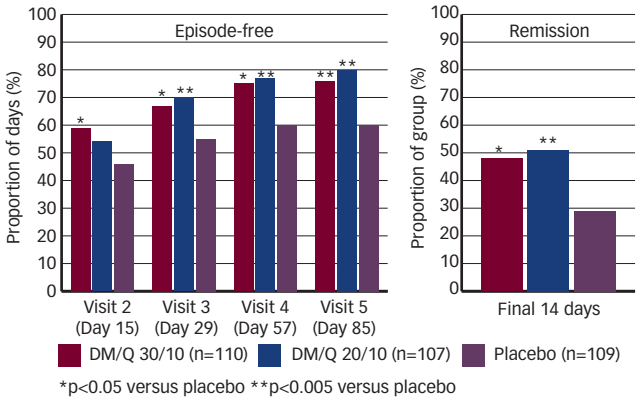
DM/Q 30/10 = dextromethorphan combined with ultra-low-dose quinidine at 30/10 mg; DM/Q 20/10 = dextromethorphan combined with ultra-low-dose quinidine at 20/10 mg. CNS-LS = Center for Neurologic Study-Lability Scale. Source: Pioro et al., 2010.[50]

Conclusion and Future Developments in the Treatment of Pseudobulbar Affect

PBA is a result of damage to specific neurocircuitry, regardless of the inciting illness, and the clinical presentation is similar across different neurological conditions. The pathophysiology of PBA is not clearly understood and further work in this area may elucidate its origins and mechanisms. Clinicians may not look for symptoms or ignore them; failure to recognise the condition may be decreased if screening for the disease can be made standard practice. Routine use of assessment scales may improve detection.

The availability of an effective therapy, DM/Q, for the treatment of PBA in both the US and Europe may motivate increased vigilance for the

Figure 5: Proportions of Patients Free of Episodes of Pseudobulbar Affect Symptoms or in Remission During Dextromethorphan/Quinidine 30/10 mg, 20/10 mg or Placebo Treatment During the Star Pivotal Study



Freedom from episodes (left) was defined as the percentage of episode-free days since the preceding visit. Remission (right) was defined by absence of episodes throughout each patient's final 14 days of treatment. Dextromethorphan hydrobromide and quinidine sulphate (DM/Q) 30/10 = dextromethorphan combined with ultra low-dose quinidine at 30/10mg; DM/Q 20/10 = dextromethorphan combined with ultra low-dose quinidine at 20/10mg. Source: Pioro et al., 2010.[50]

condition and encourage clinicians to look for the condition among their patients. This may help address the current problem of under-recognition and undertreatment.

While various classes of medications, particularly antidepressants, are effective for PBA treatment, DM/Q is the only approved medication for this indication and has shown efficacy in various clinical trials. It is approved for PBA regardless of the underlying neurological disorder affecting the brain, including dementia, stroke, brain injury, MS and ALS. The magnitude and pattern of improvement in changes in PBA symptoms with DM/Q treatment were consistent across three main clinical trials despite differences in underlying aetiology (ALS and/or MS), concomitant medications and comorbidities. The DM/Q combination has been available for a relatively short time and greater clinical experience will improve understanding of how to use the drug, the extent to which it can reduce the burden of PBA in wider populations, and the side-effect profile in 'real world' patients.

With ageing populations worldwide, the prevalence of many neurological diseases is increasing, resulting in a greater frequency of PBA. It is increasingly important therefore that the condition is routinely sought and appropriately treated to reduce a substantial burden on neurological patients and their families. ■

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