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Dextromethorphan/quinidine sulfate (Zenvia) for Pseudobulbar Affect

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SUMMARY

A new agent containing a combination of Dextromethorphan and Quinidine is currently under development for the treatment of pseudobulbar affect (PBA). PBA is a disorder of emotional regulation, characterized by uncontrollable outbursts of laughing and/or crying that are disproportionate to the emotions being experienced. The pathophysiology of PBA is currently unknown, although the disorder is thought to occur exclusively in the setting of neurological disease. The most influential theory on PBA posits that emotional outbursts are being generated in the brainstem autonomously due to loss of regulatory control by the frontal lobes. Although rarely life-threatening, PBA can have significant impact on patients' quality of life and thus merits treatment.

There are currently no approved treatments for PBA. Several agents have been found to be effective in small placebo-controlled trials and case series, with the most commonly used agents being tricyclic antidepressants and selective serotonin reuptake inhibitors. Both these treatments are inexpensive and relatively low-risk, although the quality and quantity of the available data on their efficacy are not optimal.

DM has several pharmacological mechanisms of action relevant to the brain. It is an NMDA-receptor antagonist, which prompted investigators to study its potential for slowing progression in ALS, where glutamate toxicity is thought to be a factor. The combination agent DM/Q was developed to slow the metabolism of DM by P450 2D6 enzymes in the liver. DM/Q was not effective in slowing ALS progression, but patients noted that it helped to control their emotional outbursts, suggesting it might be useful as a treatment for PBA. DM is also a sigma1 receptor agonist. These receptors are widely distributed in the brain, but probably most heavily in the limbic system, suggesting that DM may exert its emotion-controlling effects via these receptors. The endogenous ligands for sigma1 receptors are not altogether known, although they appear to include gonadal steroids.

DM/Q was recently shown to be effective in reducing the severity of PBA in two large studies of Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS), which are probably the most common neurological settings. These are the largest treatment studies of PBA ever done. The agent was safe and relatively well tolerated. Further studies are being conducted to see if efficacy can be maintained with lower doses of quinidine. If DM/Q is approved by the FDA for treatment of PBA, this would be the first agent approved for this purpose. Currently, the antidepressants are probably the most attractive pharmacologic options for treatment of PBA. The choice of whether to use DM/Q in this setting will likely depend on individual patient factors, as well as cost.

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INTRODUCTION

What is pseudobulbar affect?

Clinical features—Pseudobulbar affect is a dramatic disorder of emotional expression, characterized by uncontrollable outbursts of laughing and/or crying. The episodes are differentiated from normal emotion by the fact that they are not consistent with how the patient is feeling, and they often disrupt normal social interaction, sometimes appearing to come with no provocation whatsoever. Although patients can experience laughing, crying, or both, crying episodes appear to be more common. In some cases, episodes of laughter may evolve into episodes of crying, or visa-versa. Episodes can range in frequency from less than once a week to many times a day, and they may occur when patients are alone or with other people. As far as this author is aware, the episodes do not occur during sleep. The duration of episodes varies from a few seconds to volleys of emotion lasting one or two minutes, and individual patients may experience episodes of varying duration and severity. The onset of episodes is quite rapid, and patients have little warning that they are about to occur, although some patients can learn to predict types of stimuli or specific thoughts or events that are likely to provoke them. Once an episode has begun, most patients say that there is little they can do to stop them, but rather they must “wait them out”.

PBA can be evoked by a wide variety of stimuli, including an individual beginning to move their face, or seeing someone approach. Sometimes, it can be difficult to be sure about what has elicited the event, particularly in patients who have impaired cognition or expression (such as a patient with aphasia). However, episodes of PBA can be provoked by stimuli that are consistent with the emotion expressed (1–3). For instance, crying episodes may be induced by genuinely sad events, or by events that are poignant in nature (such as touching scenes involving children or families), while laughing episodes may be induced by stimuli that patients find amusing. PBA episodes appear to outsiders to be identical to normal laughing and crying, and there do not appear to be any qualitative features that make these episodes feel different than normal emotional expression. What makes the episodes pathological is the fact that patients have clearly developed a new threshold for crying and/or laughing, so that they are reacting with large displays of emotion that they cannot control to stimuli that would have evoked only mild and controllable displays, if they invoked any emotional display at all, in the past.

The dramatic and uncontrollable nature of the episodes can have significant effects on patients’ lifestyles. PBA can disrupt communication by preventing patients from speaking until an episode has resolved. They are misleading to onlookers because they believe the patient to be profoundly emotionally disturbed unless the patient has the opportunity to explain his or her predicament. Episodes can also be embarrassing, such as laughing at a funeral, and many patients curtail their social activities to avoid getting into these situations (4). Episodes of laughing can lead to respiratory compromise, especially in patients with a neurological disorder that already compromises respiratory function, such as ALS. For these reasons, treatment should be strongly considered in any patient with PBA.

History and pathophysiology

PBA is a fascinating window into the organization of emotions in the brain. One of the earliest recorded references to what was probably PBA was made by Darwin who observed in his writings on emotions that “certain brain diseases, as hemiplegia, brain-wasting, and senile decay, have a special tendency to induce weeping” (5). However, the landmark medical description of the disorder was made by S.A. Kinnear Wilson in 1924, who described a series of cases of PBA, most secondary to strokes, and enumerated the core clinical features discussed above (6). In that paper, he also proposed what is still the most influential theory on the mechanism by which brain disease causes PBA. Wilson observed that laughing and crying

involve the synchronized efforts of facial and vocal musculature, along with respiratory and secretory functions, thus involving the coordinated action of cranial nerves VII, IX, and X in the pons and medulla. He proposed the existence of a center for control of these nerves somewhere in the brainstem, possibly in the pons, which he referred to as the fasciorespiratory control center. Wilson further pointed out the well-known fact that brain injury affecting descending motor pathways from the cortex to the brainstem can impair voluntary activation of facial musculature but leave involuntary facial expression, as occurs in emotion, intact. Thus, patients with lesions affecting the pyramidal tracts may only be able to smile weakly on command, but may be able to generate a full smile when genuinely amused or happy. Thus, Wilson proposed the existence of two types of pathways running from the cerebral cortex to the brainstem for control of emotion: 1) involuntary pathways that allow stimuli with emotional content to activate the brainstem faciorespiratory control center and to produce emotion, and 2) voluntary centers that allow regulation of brainstem faciorespiratory center activation. While he was unsure of the exact location of the involuntary pathways, Wilson firmly postulated that the voluntary pathways ran along with the corticobulbar pathways controlling other voluntary motor activity, particularly those emanating from the lower end of the precentral gyrus. He observed that, indeed, many of the patients he had seen with PBA had difficulty with voluntary control of facial musculature, and that many of the lesions described as causing PBA could conceivably affect these pathways.

Unfortunately, we have made relatively little progress in verifying Wilson's theory on the origins of PBA over the last 80 years. Few, if any empiric studies designed to study the mechanisms responsible for PBA have been conducted. However, the clinical contexts in which PBA arises provide some support for the motor control theory. PBA occurs exclusively in the setting of neurological disease, probably most often in amyotrophic lateral sclerosis (ALS), a degenerative disease affecting the descending motor fibers from the cortex, as well as the anterior horn cells in the spinal cord. The frequency in ALS has been estimated as high as 50% (7). Other common neurological contexts include multiple sclerosis, atypical parkinsonian disorders, in particular progressive supranuclear palsy, and focal brain injuries from trauma, tumors and strokes (3,8,9). The prevalence of PBA within and across these disorders is difficult to assess, because the difficulty in recognizing the disorder has led to differences in diagnostic approaches, with some authors accepting behaviors that are congruent with mood (2), or not differentiating mood-congruent from mood-incongruent laughing and crying (10). Estimates of the prevalence of PBA among stroke patients ranges from 11 to 52%. While these disorders all affect motor function, they do so in different ways, for instance ALS affects pyramidal motor pathways while parkinsonian disorders affect basal ganglia function.

Wilson's theory would also suggest that a careful analysis of the locations of focal lesions causing PBA would converge on the motor pathways running from the precentral gyrus to the brainstem. However a perusal of the literature does not clearly confirm this. Focal lesions causing PBA have been observed in many parts of the brain including frontal cortical and subcortical structures, brainstem regions and anterior temporal regions (2,10–18). PBA has been observed in both unilateral and bilateral injuries. Very few cases have been reported with isolated parietal and occipital injury. While the lesion evidence does not allow any firm conclusion about the precise lesion location responsible for PBA, the bulk of the studies suggest anterior more that posterior brain lesions, most of which could conceivably affect the descending motor pathways highlighted by Wilson either in the cerebral cortex, basal ganglia/internal capsule region, or the brainstem.

Diagnosis

A key to the diagnosis of PBA is recognizing that the episodes are incongruent with or are greatly exaggerated compared to what the patient is feeling. In 1969, Poeck characterized PBA with four main features, which are sometimes used as diagnostic criteria (11):

1. The episodes are inappropriate to the situation and can be precipitated by nonspecific stimuli.
2. There is not a close relationship between the emotional expression and how the patient is feeling.
3. The episodes are relatively stereotyped, and it is very difficult for patients to control the extent and duration of the episodes.
4. There are no episodic mood changes corresponding to the episodes, and there is no sense of relief as the emotions are expressed. This last criterion tries to capture the fact that the episodes appear to come from nowhere, and are out of context.

However, it should be remembered that, while PBA is, by definition, a dissociation between emotional feeling and expression, Poeck's criteria may exaggerate this dissociation and give the impression that the evoking stimulus is never appropriate, when this is often not the case, as discussed above. Diagnosis of PBA relies on taking a careful history to determine the context in which the events occur so that these criteria can be assessed. Thus, PBA is more difficult to diagnose in patients with aphasia or other forms of cognitive impairment. In addition, it is very useful to observe the episodes if possible, to see the whether they have the typical nearly-paroxysmal quality. Often, episodes can be evoked by asking patients to describe them and to recall the types of situations where they arise. Differentiation of PBA with crying episodes from crying due to depression can be difficult. Again, the key distinction is that the crying in depression is congruent with the expressed mood, whereas this is not the case in PBA (19). The distinction is sometimes made more difficult by the fact that many of the neurological disorders that cause PBA can also be associated with depression.

Two formal scales are commonly used to measure the severity and frequency PBA. The Pathological Laughing and Crying Scale (PLACS) is based on a patient interview (20) and the Center for Neurologic Study Lability Scale (CNS-LS) is based on self report (21). They are mostly used in clinical trials. The PLACS may be useful as a screen, but should not be considered a substitute for a clinical history and direct observation of the episodes, as it may be sensitive to emotional lability due to mood disorders.

Nomenclature

There are many terms that have been used to describe this phenomenon. The term pseudobulbar affect is probably the most commonly used because PBA episodes frequently occur in the context of loss of voluntary control of brainstem (or bulbar) musculature due to injury in the descending corticobulbar tracts, a phenomenon referred to as pseudobulbar palsy. PBA has been referred to as pathological laughing and crying (3,6), affective lability (21), emotional incontinence (22), emotionalism (23) and involuntary emotional expression disorder (IEED) (24). The advantage of using these terms is that they do not specify a pathophysiological mechanism or specific clinical context, but they may also be overly general. For example, emotionalism and affective lability can be applied to crying from depression. The term emotional incontinence describes the clinical presentation because it evokes the nearly paroxysmal and uncontrollable nature of the episodes but does not imply a cause. However, it has probably been avoided because it is distasteful to patients. Pathological laughing and crying is also used to describe inappropriate laughter due to gelastic epilepsy, where seizures take the form of laughing fits. The term involuntary emotional expression disorder is somewhat

misleading, since most true emotions are involuntary. However, the term has merit because it does not imply a specific clinical context, and invokes the most influential theory on PBA, which posits loss of voluntary control. The best term will likely emerge as the pathophysiology becomes better understood.

TREATMENT

No agents are approved by the Food and Drug Administration (FDA) for treatment of PBA. The only available information on treatment comes from a few small trials (some placebo controlled), case series, and anecdotal reports indicating that pharmacologic treatment can be effective for PBA. The goal of therapy is to reduce the frequency of attacks. There is no data comparing the efficacy of various agents, nor is there any consensus on the optimal approach to treatment. The two classes of agents that have seen the most use are the tricyclic antidepressants and selective serotonin reuptake inhibitors. Case reports and case series have used other antidepressants (25), dopaminergic agents (26,27) and antiepileptics (28) as well, with some success.

Tricyclic antidepressants

Several small placebo controlled trials of tricyclic antidepressants (TCAs) have shown efficacy in PBA using low to moderate dosages of these agents (1,20,29). While generally safe and inexpensive, these agents have several potential adverse effects which must be considered, particularly in the elderly.

TCAs may be started in very low doses for PBA (usually lower than the typical doses used to treat depression) and the dose can be raised slowly until a satisfactory effect is achieved. Amitriptyline may be effective in doses as low as 10 mg daily, and has been used for PBA in doses up to 75 mg (29). Imipramine has been used in doses of 10 to 20 mg daily (1) and nortriptyline has been used in doses up to 100 mg, with a reasonable starting dose being 10 to 25 mg daily (20).

TCAs are contraindicated in patients status-post a recent myocardial infarction or patients who have recently been on an MAO inhibitor or cisapride. They should be used with caution in patients with cardiovascular disease, urinary retention or prostatic hypertrophy, asthma, diabetes, liver dysfunction, or seizures because of their anticholinergic effects. A baseline EKG is advisable prior to starting TCAs because they can slow the P-R interval. Other side effects include urinary retention, sedation, and orthostatic hypotension, gait instability, constipation, dry mouth, blurry vision and sexual dysfunction. All these effects are less likely at lower doses.

TCAs should be used with particular caution in elderly patients, particularly those with dementia or neurodegenerative disease such as Parkinson’s disease or Alzheimer’s disease. These patients are exceptionally sensitive to the anticholinergic properties of TCAs, so that they may induce a confusional or delirious state, in addition to the other symptoms noted above.

Selective serotonin reuptake inhibitors

Support for the role of serotonin in PBA comes from studies showing reduced brainstem serotonin transporter activity in patients with PBA from cortical lesions (30). A case series (31) and two placebo controlled trials (32,33) have demonstrated efficacy of selective serotonin reuptake inhibitors (SSRIs) in PBA. SSRIs should also be started at a low dose and increased very slowly every few days until they are effective. Fluoxetine has been used at a dose 20 mg daily (31), citalopram has been used in doses ranging from 10 to 30 mg daily (32), and sertraline has been used at a dose of 50 mg daily (33).

Like TCAs, SSRIs are considered safe, but they are not without potential adverse effects. SSRIs are contraindicated in patients taking MAO inhibitors, which increase the risk of developing serotonin syndrome, a life-threatening syndrome of altered mental status, fever, tachycardia, hypertension, agitation, tremor, myoclonus, hyperreflexia, ataxia, incoordination, diaphoresis, shivering and gastrointestinal symptoms. Phenothiazines and pimozide may produce cardiac arrythmias in combination with SSRIs. SSRIs can also increase the risk of bleeding in patients taking anticoagulants. Other side effects of these agents include nausea, decreased libido and sexual dysfunction, and exacerbation of anxiety or panic disorder.

In general, SSRIs are generally considered safer in the elderly than TCAs. However, as with most agents, side effects are more likely in the elderly than in younger individuals. Hyponatremia is a particularly dangerous adverse effect that should be kept in mind.

Dextromethorphan/Quinidine

Two recent trials have indicated that a new agent consisting of a combination of dextromethorphan and quinidine (DM/Q) is effective in treating PBA due to ALS and MS (34,35), which are probably the most common neurological settings. These two trials included nearly 300 patients between them so that DM/Q has been evaluated in a larger number of patients than any other drug used to treat PBA. However, it has not been compared to other agents traditionally used to treat PBA, such as TCAs and SSRIs.

Pharmacology—The dose used for DM/Q in the two published studies was 30mg of DM and 30mg of Q twice daily. The mechanism of action for DM/Q's efficacy in PBA is unknown. DM is the active ingredient and Q is used to slow down the metabolism of DM by P450 2D6 enzymes in the liver (36). DM is an N-methyl-D-aspartate (NMDA) receptor antagonist (37). DM/Q's potential efficacy for PBA was discovered coincidentally while it was being evaluated for slowing progression in ALS. Patients reported that it helped them control their involuntary emotional outbursts. An NMDA receptor mediated effect on PBA seems unlikely, because other NMDA antagosists such as riluzole have not been reported to affect PBA. DM is also a sigma-1 receptor agonist. The functions of sigma-1 receptors and their endogenous ligands are not completely known but may include gonadal steroids (38). In non-human primates sigma-1 receptors are expressed throughout the brain, but particularly in limbic and motor regions in the central nervous system and therefore they may play a role in emotional functions (39). DM and other sigma-1 receptor agonists have been shown to reduce stress responses in rats (40).

Efficacy—Brooks et al. (34) conducted a multicenter, randomized double blind, placebo controlled trial of DM/Q in 125 patients with ALS and PBA. The patients were divided into three groups: 1) Those who would receive DM 30 mg and Q 30 mg in a combination pill, 2) Those who would receive DM 30 mg alone, and 3) Those who would receive Q 30 mg alone, with twice as many patients receiving DM/Q as those receiving either of the components. Patients were evaluated 3 times over 30 days, with the primary outcome being the score on the CNS-LS. Patients also recorded laughing and crying episodes in diaries and filled out quality of life measures. Patients treated with the DM/Q showed a significantly larger decrease in their CNS-LS scores compared with the DM and Q alone groups. In addition, the reduction in the number of episodes with DM/Q was twice that seen in the other groups, with 52% being symptom free over the last two weeks of the study, vs. 23% for DM and 12% for Q. Quality of life improvement was also greater in the DM/Q group.

Panitch et al.(35) evaluated DM/Q in 150 patients with MS, with half receiving DM/Q and half receiving placebo, again using the CNS-LS as the primary outcome, and the same secondary outcomes as in Brooks et al. Patients were seen 5 times over 85 days. Over the course of the study, the DM/Q group showed a reduction in CNS-LS score more than twice that in the placebo

group, a magnitude difference similar to the ALS study. The DM/Q group also showed significantly greater improvements in quality of life and in the number of episodes, with 21% of the DM/Q group having no episodes over the entire 12 weeks of the study, vs. 6% of the placebo group. Overall, the DM/Q was calculated to cause a 46% reduction in the number of episodes, which is similar to the 50% reduction calculated in the Brooks et al. study. Interestingly, the Panitch et al. study also noted a significant decrease in pain ratings in the DM/Q group compared with placebo.

Safety and tolerability—DM/Q is relatively well-tolerated. In the study of ALS patients, nausea (33% of DM/Q patients), dizziness (20%), and somnolence (13%) were more common in DM/Q than in other groups. In most cases, these effects were mild or moderate, with 24% of patients discontinuing treatment. There were significant increases in the QT interval and decreases in heart rate between DM/Q and Q alone, which were not judged to be clinically meaningful. Studies are currently being conducted to see if lower doses of quinidine may be used, because of concerns over possible cardiotoxicity.

In the study of MS patients, about 15% of patients discontinued DM/Q because of adverse effects, vs. 11% of placebo treated patients. In this study, only dizziness (26%) was more common with DM/Q than placebo (10%). A small, but significant increase in the QT_C developed over the course of the study in DM/Q treated vs. placebo treated patients.

Conclusion—Because DM/Q will not be available as a generic formulation for some time, it will likely be more expensive than traditional agents such as TCAs and SSRIs. However, if it is ultimately approved by the FDA it will be the only agent approved for this purpose, which is enough to make it a strong consideration for treatment. In addition to cost, clinical factors should be considered in the decision of which agent to try. For example, if the patient also suffers from depression, antidepressants could first be considered. On the other hand, if there is no evidence of depression or if TCAs and SSRIs are contraindicated or have not been effective, DM/Q will likely be a valuable alternative.

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