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# Dextromethorphan-quinidine is helpful for pseudobulbar affect disorder in stroke patients

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## INFORMED CONSENT:

# Dextromethorphan-quinidine is helpful for pseudobulbar affect disorder in stroke patients

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**ABSTRACT** An informed consent article using

Hammond FM, Alexander DN, Cutler AJ, et al. PRISM II: an open-label study to assess effectiveness of dextromethorphan/quinidine for pseudobulbar affect in patients with dementia, stroke or traumatic brain injury. *BMC Neurology*. 2016;16:89. https://doi.org/10.1186/s12883-016-0609-0

for a patient with pseudobulbar affect following stroke.

***Keywords***: *pseudobulbar affect, cerebral vascular accident, theory of the mind, mirror neurons, scales and measures*

## Clinical-Social Context

Matthew Webb [pseudonym] is a 57-year-old man who presented with an acute stroke. The patient could make decisions when asked questions, give answers, and communicate through verbal utterances and body language. He consented to disclosing personal health information with his sister at the bedside and allowed us to interview her. His youngest sister, Lucile Harris [pseudonym], tells us her brother is incredibly strong-willed and communicative. That's why she told us she was shocked when interacting with him for the first time after this most recent stroke. Mr. Webb had two prior strokes, but through support from his wife, and mother, together with his sister, Ms. Harris said he was able to regain almost full function without neurological deficit. But now, he was nearly nonverbal, limited to 1-2 word phrases and head gestures, with weakness in all four limbs. Despite these profound changes, Ms. Harris said it was Mr. Webb's unprompted mood swings that unnerved her. She had never seen him lose control of his emotions, and certainly never imagined a scenario where she couldn't accurately discern even his basic feelings. This disruption of human cognition of understanding the intentionality of others is known as the theory of the mind.[1-3]

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This history was presented to the attending physician, and a discussion developed about the topic of Pseudobulbar Affect (PBA). Pseudobulbar Affect (PBA) is associated with neurological disorders or injury affecting the brain, and characterized by frequent, uncontrollable episodes of crying and/or laughing that are exaggerated or unrelated to the patient's emotional state. While the clinical team (other than the attending) had never personally seen the condition itself, a brief search of the clinical research showed there was a potential medical treatment for this condition. These clinical research trials used the Center for Neurologic Study-Lability Scale (CNS-LS)[4,5] as the outcome measure for studies treating PBA. We downloaded and printed the scale so we could evaluate our patient within the context of the available clinical research.

When interviewing Mr. Webb, he was able to communicate his feelings and preferences, but not without three episodes of unprompted laughter. This unexpected social interaction was scary for the medical student. Each episode would last 3-4 seconds despite Mr. Webb's attempt to stifle them. When resolved, a grimace of pain would cross his face, followed by tears. He would have additional outbursts of intense crying, lasting only seconds, followed by the same grimace. Despite this, a wave of relief passed over his face as he completed the CNS-LS scale; the questions seemed to "read his mind." He fervently pointed at his scores in response to the questions, at one point grabbing the paper from the clinician to emphasize his symptoms were occurring "Most of the time." It seemed as if he was finally being heard. His CNS-LS scale score was 35 (scale range 7-35), indicating maximal symptomatology.

Ms. Harris arrived at the hospital and watched helplessly as her brother burst into laughter from a period of silence. She began telling us she had always been the one to take care of him but realizing now she could not. There wasn't any hesitation in her voice when she told us "Whatever needs to be done, I'm gonna do it," but at the same time said, "I don't know what to do—I need help." She described him as strong willed, family oriented, and previously in complete control over his emotions, which is why his current situation was such a shock for her.

Ms. Harris informed us that Mr. Webb's highest level of education was 12th grade, but that his emotional intelligence, especially regarding interpersonal relationships, flourished beyond that. He had not worked in some time due to arthritis in his back, but he was a former cook. During this conversation, Mr. Webb beamed, and though the sounds were incoherent, he spoke up at this point, clearly touting this skill. His desire to communicate remained intact.

The clinical care team had a discussion regarding his new diagnosis of PBA and future directions. Mr. Webb was trapped under a mask of false emotions. He has a strong support network with such a dedicated sibling, but she has her own life and difficulties as well. Ms. Harris tells us she also cares for her ill mother and her own four children, meaning any assistance we could provide Mr. Webb would be an enormous relief for caregiver stress. Treating Mr. Webb's neurological condition would make him feel more like himself, but it also has widespread implications on the network of lives around him.

During our initial purview of the clinical research literature, dextromethorphan-quinidine was suggested as a treatment for PBA. During this acute hospitalization, we needed to decide if this therapy was appropriate for our patient with a condition most of us had never seen.

## Clinical Question

Is dextromethorphan-quinidine helpful in the treatment of Pseudobulbar Affect Disorder secondary to cerebrovascular accident (CVA)?

## Description of Related Literature

Using PubMed, we used "Pseudobulbar Affect AND Therapy" as search terms and filtered with Clinical Trials, which resulted in nine articles returned. We reviewed titles and abstracts to screen for articles that could answer the clinical question. We found only one



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article by Hammond, et. al. that pertained to treatment of PBA that included stroke patients.[6] A second trial by the same authors was a sub-group analysis of patients with traumatic brain injury. The Brooks trial was a randomized controlled trial that evaluated dextromethorphan/quinidine for the treatment of PBA in Amyotrophic Lateral Sclerosis patients, but did not include a placebo control.[7] The Panitch trial was a randomized controlled trial that evaluated dextromethorphan/quinidine for the treatment of PBA in Multiple Sclerosis patients.[8] One study described the safety of dextromethorphan/quinidine, but included only 51 patients with stroke and 502 patients with over 30 neurologic diseases.[9] Treatment related adverse events averaged about 10% and included dizziness, headache, nausea, and other non-specific symptoms.[9] Two articles reported open-label, three-week studies of healthy adults administered dextromethorphan-quinidine and paroxetine or memantine which measured pharmacokinetic outcomes.[10,11] One article was completely off topic and not reviewed further.

Using PubMed, we performed a broader search with only “Dextromethorphan-Quinidine” but this only returned the previously reviewed studies and articles about other unrelated neurologic disorders. We limited the relevant literature to PBA in stroke patients. Using PubMed, we performed another broad search with only “Involuntary emotional expression disorder” (IEED) but that search returned only two articles that were unrelated to PBA.

We next used the PRISM II trial, which was the relevant study on PBA in stroke patients, and located it in Google Scholar, and used the “Related Articles” function. This provided another 101 articles for review. We reviewed the first two pages of results and found only papers previously screened and opinion pieces or summaries, which were not reviewed.

With our initial PubMed search, we found an observational trial that included the treatment of interest for patients with stroke[6] but the stronger methodological study using a randomized double blind placebo controlled trial used a population of patients with a different neurological disorder.[8]

## Critical Appraisals

The PRISM II trial was an open-label phase III observational study that examined the effectiveness of Dextromethorphan-Quinidine in treatment of PBA in patients with a history of dementia, stroke, and/or traumatic brain injury (TBI).[6] The primary outcome measured was mean change from baseline in the Center for Neurologic Study - Lability Scale (CNS-LS)[4] at 90 days of treatment. Patients who received Dextromethorphan HBr and Quinidine Sulfate 20mg/10mg had a statistically significant decrease in mean CNS-LS at 90 days of treatment. At 90 days of treatment over 70% of participants in the study answered that they generally felt “Much Improved” or “Very Much Improved,” consistent with the mean decrease in CNS-LS at 90 days. The outcome measure was a mean score change from baseline. Baseline CNS-LS scores had a mean of 20. Stroke patients have expected neurological improvement within the first three months and because there was no control group and no comparison with placebo, it is difficult to ascertain how much improvement was naturally occurring and how much was a result of the study drug. The authors tried to account for this lack of comparison by reporting the mean score change to other studies that used the same CNS-LS scale to treat multiple sclerosis and amyotrophic lateral sclerosis (ALS). Multiple sclerosis may have waxing and waning symptoms without treatment, creating a problematic comparator, but ALS has a consistently progressive worsening symptom trajectory, making a more compelling argument for drug efficacy. The magnitude of improvement was similar in all disease states. The PRISM II study has other significant bias. “This study and medical writing and editing services were funded by Avanir Pharmaceuticals, Inc”[6] and the authors had conflict of interest disclosures with the funding agency. The PRISM II trial has a Strength of Recommendation Taxonomy Level of Evidence[12] (SORT-LOE)=2.

The Brooks, et. al. trial was a multi-center, randomized, double-blind controlled trial that compared dextromethorphan-quinidine to dextromethorphan alone and quinidine alone in 140 ALS patients. The improvement with the combination drug was a mean of 7.4 points on the CNS-LS scale compared to 5.1 and 4.9 in the other two groups. There was a fairly large measure of dispersion for each group. Yet, the authors concluded this was validation for the mechanism of action—quinidine inhibits cytochrome P450 2D6 enzyme (CYP2D6), yielding higher levels of dextromethorphan, which is thought to provide the benefit in PBA. The authors noted that cases with higher baseline CNS-LS scores showed greater effect size. This trial also evaluated safety and adverse events. The treatment drug showed increased incidence of nausea, dizziness, somnolence and loose stools, ranging from 13-33%. QTc intervals were not different between groups. This trial was also sponsored by the drug manufacturer. SORT-LOE=1.



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Panitch, et. al. conducted a multi-center randomized, double-blind, placebo-controlled trial in 150 patients with multiple sclerosis. Baseline CNS-LS scores were 20, similar to all other reported trials. Again, the study drug showed a mean score change of approximately 7.7 compared to 3.3 for placebo. This is similar to the PRISM II and Brooks trials. Adverse events were similar between the study drug and placebo. This trial was also sponsored by the drug manufacturer. SORT-LOE=2.

Pioro et. al. randomized 326 patients with ALS or multiple sclerosis (MS) suffering with PBA and 283 completed the trial. Average baseline CNS-LS scale score was 20, slightly higher than the PRISM II trial. Mean score reduction after 12 weeks was 8 for the treatment groups compared to 5.7 compared to the placebo group, which is considered clinically marginal benefit. Similar side effects of dizziness, headache, nausea, diarrhea, and somnolence ranged from 10-20%, but only dizziness seemed to differ between placebo and study drug. QTc did not exceed 500 milliseconds for any group. SORT-LOE=1

Patee, et. al. performed a pharmaceutical company sponsored observational study for 553 patients with PBA and over 30 different neurological diseases. Treatment related Adverse Events (AE) ranged from 5-12% and included the same symptoms described above. Twenty seven percent of patients withdrew because of adverse events over 52 weeks of treatment. SORT-LOE=2.

The Grade of Recommendation for using dextromethorphan/quinidine to treat Pseudobulbar Affect disorder in stroke patients is B, because no single study provided high quality evidence in stroke patients to answer the clinical question.[12]

## Informed Consent

*Flesch Reading Ease = 76.9; Flesch-Kincaid Grade Level 5.1*

"Good morning Mr. Webb. Thank you for being here also, Ms. Harris. We reviewed the answers that you gave us yesterday on the questionnaire. We compared your results to other patients who also had a stroke and have the same symptoms as you. Your score shows worse problems than most. The research studies show a drug might help. The drug is a combination of a common cough syrup and a medicine used to treat irregular heartbeat. So, doctors have experience with these medicines. This drug was also used in people with the same symptoms but have different types of brain damage. It helps a wide range of brain damage that causes these symptoms. We are suggesting that you try this drug. We can monitor your symptoms with the same questionnaire. We are hoping you get better control over the abrupt laughter and crying episodes.

"Just like any other drug, this drug might have some side effects. You might experience diarrhea, headache, sleepiness, or nausea. We don't think these symptoms would be dangerous. We checked your heart and don't think that would be a problem either."

## Clinical Application

Discussion with the patient and his sister at bedside was straightforward. After education on the possibility of treatment with a medication to decrease the frequency of episodes of laughing/crying, the patient began nodding fervently. Both Mr. Webb and Ms. Harris recognized that any improvement would help ease some of the stress and discomfort entering rehabilitation for his CVA. To battle back from this third CVA would be difficult enough; they believed it to be an easy decision to try a medication that may lessen the load of this new mask stuck to his face. Before trying this medication however, they made clear they would not be able to pay out of pocket if the cost was too high. As mentioned, Mr. Webb has been unable to work since 2010, and while he can collect disability, his income is limited in that regard. Ms. Harris told us she was also now collecting disability, following a back injury on the job resulting in multiple surgeries. We tried to incorporate the clinical research evidence into the medical record in anticipation of health insurance pre-authorization and appeal. Because the drug is FDA approved and the only available treatment for PBA and because we were convinced of its efficacy, advocacy for the patient was pro-active, using what we had learned from Clinical Decision Science.



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## Relevance to Clinical Decision Science

Lau reported, "I realize I am part of the social environment for my patients. We can never forget that our own experiences and actions change the way our patients experience life, and death as they make decisions. That means that Clinical Decision Science requires doctors to explore their own inner world; our thoughts and emotions are part of the therapeutic relationship."[13] Friedli reported, "…I mirrored my patient's fear."[14] Given this patient's presentation, the patient's sister was unnerved and the medical student was scared. These emotions are social communications and in the social sciences are known as "The Theory of the Mind" and in neuroscience is understood as a neurocognitive phenomenon.[2,3,15] There is irony that the (un)-ease being treated was a disordered regulation of emotions. The joke about "physicians treating their own anxiety…" is a cultural artifact of an important social dynamic that deserves study within the context of Clinical Decision Science.[16]

Richardson commented on "point of care evidence"[17] and Meza compared information science to the "bench science" training of physicians at the time of the Flexner Report.[18] This report demonstrates how immediate access to clinical research became part of the process of the clinical care of the patient. Indeed, the Center for Neurologic Study - Lability Scale (CNS-LS) became diagnostic for a clinical condition that was previously not experienced or recognized upon presentation for admission to the hospital. This report also builds on the recognition that outcome measures used in clinical research can be usefully integrated into the care of an individual patient.[19]

Another concept of incorporating clinical research evidence into clinical practice comes in the form of incorporating the clinicians' use of clinical research evidence and its interpretation and introducing it into the medical record of an individual patient. This demonstrates how patient advocacy is a by-product of Clinical Decision Science. Because insurance pre-authorizations or appeals always require copies of medical records, by incorporating research evidence into the medical record for a specific patient and explicating decision making, Clinical Decision Science has the potential to change the social constraints experienced in patient care.

## Conflict of Interest Statement

None of the authors declare any conflict of interest for this manuscript.

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