References

Tears Without Fears: Psychopharmacologic Considerations When Treating Pseudobulbar Affect

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Background

In 2010, a dextromethorphan (which antagonizes NMDA receptors and agonizes sigma-1 receptors) and quinidine (which inhibits CYP2D6 to increase levels of dextromethorphan) combination drug (DQC) became the first approved treatment of pseudobulbar affect (PBA), characterized by episodes of uncontrollable changes in affect such as laughing or crying out of proportion to the situation. We describe a case of PBA and demonstrate the importance of anticipating drug interactions, notably CYP2D6 inhibition.

Case Summary

The patient is a 31-year-old female with a history of vertebral artery dissection and basilar artery occlusion leading to a cerebrovascular accident. She was diagnosed with Major Depressive Disorder prior to the stroke and failed multiple antidepressant medications while receiving treatment through the resident clinic. Upon transition to a new resident, her symptoms were identified as more consistent with PBA and she was started on DQC.

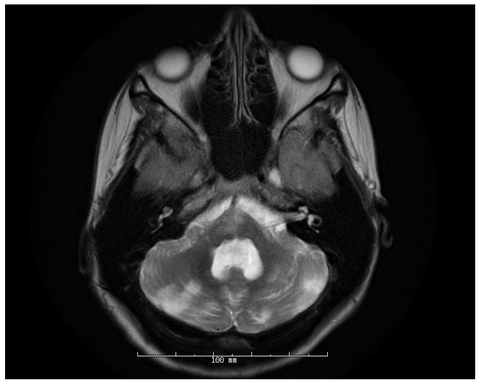


Fig 1: Axial T2 MRI Brain, demonstrating hyperintensities bilaterally in the cerebellum

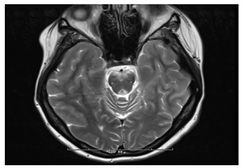


Fig 2: Axial T2 MRI Brain, demonstrating hyperintensities bilaterally in the pons

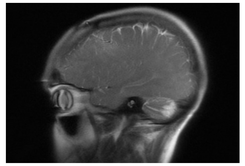


Fig 3: Sagittal T2 MRI Brain, demonstrating hyperintensity of the cerebellum

In order to compensate for the strong CYP2D6 inhibition of DQC, we halved the doses of her concomitant CYP2D6-metabolized medications (amphetamine/dextroamphetamine and venlafaxine). After initiating DQC, she reported significant improvement in crying spells and resolution of laughing episodes. However, lowering the stimulant dose worsened her daytime somnolence, fatigue, and inattention. We found that in our efforts to prioritize patient safety, her treatment initially lost some efficacy. Eventually, both prior psychotropics were increased to pre-DQC clinical effect. Pharmacogenetic testing suggested that our patient has intermediate (below average) activity of CYP2D6, meaning she theoretically may need lower doses of her medications to reach clinical effect. Despite this below average CYP2D6 activity and taking DQC, she required higher than expected doses of venlafaxine and amphetamine/dextroamphetamine.

Discussion

Demographically, her case is unique as she is significantly younger than average for someone with PBA (1), and she is raising a child, making the dysfunction secondary to her emotional incontinence even more distressing. Adequate treatment of PBA is essential to preserve psychosocial functioning, as patients with PBA have been shown to have higher rates of anxiety, depression, and poorer social functioning (2). Younger people with PBA, such as this patient, tend to report higher PBA symptom severity and more apathy than their older counterparts (3). Thus, the prompt, effective treatment of PBA is crucial.

The most challenging aspect of this case was balancing the data surrounding drug-drug interactions with the clinical information our team was receiving from the patient, especially while navigating the ever tenuous balance between patient safety and symptom control. Quinidine is designated as a strong inhibitor of CYP2D6 by the FDA, as it can increase serum levels of 2D6 substrates by more than 500% (4). Other strong inhibitors include medications such as bupropion, fluoxetine, and paroxetine (5). Pharmacologic models suggest that the metabolism of these drugs fluctuates significantly. For example, when co-administered with quinidine, venlafaxine levels increased anywhere from 50% to 1000%, even within patients who were all genotypically normal metabolizers of CYP2D6 (6).

The therapeutic strategy of halving her other prior medications and seeing the patient more frequently upon initiation of DQC incorporated our knowledge of drug interactions to decrease risk of toxicity during the transition onto DQC, however once in the titration, we followed the patient's clinical response to determine the final doses of her amphetamine/dextroamphetamine and venlafaxine. This case is yet another example of how patients do not always read the textbook. Prescribing clinicians need to incorporate both theoretical expectations and real world, patient-specific information when creating and modifying treatment plans, as there can be significant variability between identified genotype and declared phenotype. Despite this ambiguity, there is good evidence that overall, using pharmacogenomic-guided decision support tools to direct treatment does have clinical benefit in some specific populations and clinical situations (7).

One possible explanation for our patient requiring higher than expected doses is that the biotransformation of venlafaxine by CYP2D6 creates an active metabolite, so decreased activity of the enzyme would result in a relatively higher ratio of the less active original compound compared to someone who did not have that allelic variant, however there is currently insufficient evidence demonstrating the significance of this concept clinically. Although we have some guidelines (8) for isolated prescribing recommendations, there are new developments in psychopharmacology that leverage CYP2D6 metabolism for therapeutic effect, complicating the prescribing landscape. Thus, the lack of specific practice guidelines (9) makes dose adjustments of co-prescribed CYP2D6-metabolized medications challenging in the context of initiating and titrating strong CYP2D6 inhibitors such as DQC. In the future, next best steps would be to develop practice guidelines for addressing these drug interactions, balancing both safety and efficacy. Until then, we will continue to prioritize patient safety by utilizing all sources information available to us, valuing both the laboratory and the patient story.

Literature Review

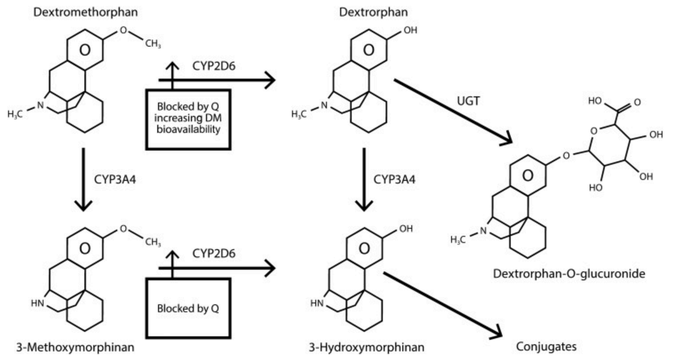
Carvalho Henriques, et al. 2021 (10)
- Genotyping of the CYP2D6 gene has increasingly been used in clinical practice in psychiatric care, as many co-prescribed psychiatric medications are metabolized by CYP2D6 and such drug-drug interactions can have harmful effects.

Konstandi, et al. 2023 (11)
- Repeated physiologic stress has been found to induce CYP2D6, an enzyme previously considered non-inducible, which could impact drug metabolism and efficacy, potentially altering therapeutic drug levels in patients.

Waade, et al. 2014 (12)
- In patients who were identified as poor metabolizers of CYP2D6, venlafaxine levels were found to be significantly higher in geriatric patients compared to the general adult/pediatric population, suggesting age is an important factor to consider when utilizing pharmacogenetics.

Gaedigk, et al. 2017 (13)
- Special consideration can be given to the rate of CYP2D6 metabolism in certain patient populations when prescribing. Diplotype frequencies predicting poor metabolism were highest in Europeans (average, 5.4%) and lowest in East Asians (average, 0.4%). Diplotype frequencies predicting ultrarapid metabolism were highest in Oceanian (21.2%) and Middle Eastern (11.2%) populations.

Launiainen, et al. 2011 (14)
- In a study examining venlafaxine overdoses, the authors concluded that interacting CYP2D6-inhibiting drugs were a larger factor in toxicity than metabolizer status.



Graphic from Taylor, et al. 2016 (15)