In order to compensate for the strong CYP2D6 inhibition of DQC, we halved the doses of her comitant CYP2D6-metabolized medications (ampheta mine/dextroamphetamine and venlafaxine). After initiating DQC, she reported significant improvement in crying spells and resolution of laughing episodes. However, lowering the stimulants 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 tapered to pre-DQC clinical effect. Pharmacogenetic testing recommended a different approach for 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 pharmacogenetic-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 interacting CYP2D6 inhibitors. As previously considered non-inducible, which could impact drug metabolism and efficacy, potentially altering therapeutic drug levels in patients.

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/geriatric population, suggesting age is an important factor to consider when utilizing pharmacogenetics.

In a study examining venlafaxine overdoses, the authors concluded that interacting CYP2D6-inhibiting drugs were a larger factor in toxicity than metabolizer status. When CYP2D6-inhibiting drugs were a larger factor in toxicity than metabolizer status.