



Issues with Pharmacogenetic Testing to Optimize Antipsychotic Therapy

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For over a decade commercial companies have offered pharmacogenetic testing to psychiatric providers with the promise that the results will assist medication choice or dosing. While the concept of personalized medicine has great appeal and represents the forefront of research in many areas, the applicability and value in psychiatric practice remains a subject of intense debate. As will be discussed below, the problems with testing lie not only in what is reported, but also the difficulties encountered by clinicians when interpreting the significance of assay findings and implementing them to benefit patient care.

Fundamental to this debate rests on the fact that there is large variation in what various guidelines and commercial reports recommend to clinicians, even for basic information such as the significance of interactions between prescribed drugs and genetic variants that influence pharmacokinetics (i.e. drug clearance). A 2022 commentary entitled *Clinical Use of Pharmacogenomics in Psychiatry: The Future Has Not Yet Arrived* in the prestigious journal *European Neuropsychopharmacology* lamented: "The challenges of the translation of candidate genes with relevance to pharmacokinetic mechanisms (e.g., CYP2C19, CYP2D6, CYP2C9) into clinical practice is also demonstrated by the fact that various guidelines on the use of pharmacogenomic information for specific drug-gene pairs (including 33 relevant for Psychiatry) show large variation, demonstrate in part contradictions in

recommendations even on the same drugs and lack wide adoption by clinical services."¹ This lack of agreement among commercial tests has been noted for over half a decade,² with reviews and expert consensus papers in 2018 concluding that the data did not establish the value of such testing.^{3,4}

Recently published papers do recognize the possible benefits in identifying genetic variations associated with slower drug clearance (leading to higher rates of adverse effects for a given dose) or more rapid drug clearance (leading to lack of effective drug levels), but clinicians may not fully appreciate the caveats in using this information. Commercial tests report information on 6 or more cytochrome P450 enzymes (CYP 450), yet a comprehensive 2021 review focusing on commonly used antipsychotics and antidepressants noted that evidence, guidelines, and product labels supported testing for only 2 of these genes (CYP2D6, CYP2C19).⁵ Moreover, a 2019 study of patients with major depression found genetic testing did not significantly improve the average extent of symptom reduction, but did increase the proportion rated as responders.⁶ The conclusion from this literature is that testing can alert clinicians to situations where drug levels might be lower than expected for a given dose and thereby pursue higher dosages in those patients who clear medications more quickly, assuming that the medication is metabolized by one of those two CYP genes;

however, this will not influence the maximal ability of the drug to be effective once therapeutic drug levels are reached.

While one would correctly conclude that a similar principle applies to antipsychotics, namely that certain genetic variations present a risk for drug levels that are too high or too low, the situation may be a bit more complex for several reasons:

- 1) Clinicians may focus so heavily on the genetic testing results that they overlook potential interactions from other co-prescribed medications that can slow or accelerate antipsychotic clearance. Patients living with schizophrenia are often on complex medication regimens;
- 2) Individuals may have variations in more than one CYP enzyme making it difficult to determine the net effect on drug clearance;
- 3) Inherent to many chronic disorders, especially serious mental illnesses such as schizophrenia, is poor adherence with oral medication therapy. Genetic testing will not help a clinician decide why a patient might be an inadequate responder to seemingly effective antipsychotic dosages – only plasma drug levels will provide that answer;⁷
- 4) Certain nutritional supplements and cigarette smoking (e.g. actual burning of the leaf, not vaping) may expose a patient to chemicals that alter antipsychotic clearance; and
- 5) There is no genetic test or imaging study available that predicts response to antipsychotics in general, or to specific agents.

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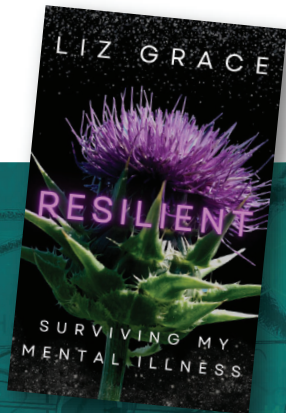
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SCHIZOPHRENIA

SURVIVORS



Liz Grace (Pen Name) *Conquering Deafness and Schizophrenia*



Liz's book, *Resilient: Surviving My Mental Illness* (2023), is available on Amazon. She is actively pursuing speaking engagements in order to share her book, her message, and her story.



Liz Grace is a first-time author and occupational therapist in recovery from Schizoaffective Disorder who lives with the daily challenges of profound hearing loss. Starting at the age of sixteen, she gradually lost her hearing, learned American Sign Language in university and at age twenty-six, was implanted with bilateral cochlear implants.



Liz Grace describes her childhood as happy, up until she was 10 years old, when her mother died from breast cancer. Afterwards, she remembers life as lonely and difficult. Following her mother's diagnosis, her maternal grandparents moved closer to Liz's family and were always loving, supportive, and emotionally close to Liz throughout her whole life. However, she was not close to her three siblings after her mother's death.

Liz remembers doing satisfactory work in elementary and high school, but it was not her best. She was smart, and though she often didn't do her homework, she sometimes corrected her teachers' academic mistakes in math classes.

Liz decided to add another year of high school, often called a "victory lap," because she had failed three of her classes during her fourth year due to lack of motivation, which was caused by her declining mental health.

Staying in high school for an extra year was difficult because all her friends had graduated and moved on to college. During that year, Liz sank into a deep depression. She hated herself and was unhappy. Her memory was failing her, and she struggled with basic memorization in classes.

At times, while in high school, she experienced voices in her head, laughing at her like a laugh track on a TV show. Fortunately, these voices disappeared for many years and would not bother her again until adulthood.

In October 2005, during her fifth year of high school at age 17, Liz experienced her first suicidal thoughts. Her grades dropped, and she chose to see a counselor without telling anyone.

From age 16, Liz also struggled with rapid hearing loss due to a genetic condition. Looking back, Liz believes that her hearing loss exacerbated her struggle to blend in socially.

Liz would be in and out of hospitals five times during her last year of high school. At times, she was incorrectly diagnosed with borderline personality disorder and post-traumatic stress disorder. And though she was struggling with psychosis, her treatment team failed to recognize it, thinking that she was simply seeking attention. During her third and fifth hospital stays, she was forcefully restrained during a meltdown, which is still traumatic to her today. She also was put on an antipsychotic medication which did work well for her, but it had bad side effects such as weight gain.

Liz was excited to graduate from high school and finally move on to enjoy the independence of being an adult. After high school, she enrolled in college in Toronto where she lived in a dormitory on campus. Finally, she realized she needed the antidepressant, and in treatment, she lived in nearly full remission. She excelled in college without any hospitalizations for the next eight years.

After two years, in 2008, she graduated from

college with an occupational therapy assistant diploma and enrolled in undergraduate studies. Unfortunately, while doing her best in school and scoring high grades, Liz's hearing loss progressed, and she developed profound hearing loss by her third year at the university. Over several years, she learned American Sign Language and benefited from a large deaf community in the town where her university was located. In 2012, Liz began studying for a two-year master's degree in occupational therapy.

During Liz's last year of her master's program, in 2014, she had surgery for cochlear implants, enabling her to eventually regain some of her hearing. Though hearing again was a breakthrough and radically changed her life for the better, the stress and excitement of getting the implants led to her first clinical manic episode, though Liz had not had a psychiatric break since her fifth year of high school.

When Liz finished her master's degree, she again became psychotic, and mania and then depression struck. She started medications again, including Lithium and an antipsychotic. She was in and out of the hospital 3 times before eventually moving back in with her grandparents and attending two different day hospital programs, one following the other.

In summer of 2015, Liz determined that she was well enough to work again. She landed a new job in occupational therapy with flexible hours located an hour and a half away in a small town.

But by the beginning of 2016, while working, Liz began to believe that she was collaborating on a physics project with Steven Hawking. She heard someone shouting her name, and there was noise in her head, like a quiet radio where she could not make out the words. Her hygiene suffered and she did not frequently bathe or brush her teeth. At this time, she had no mood symptoms. Her diagnosis was changed from bipolar disorder to schizoaffective disorder.

Finally, thanks to effective antipsychotic medication, in 2016, Liz had achieved recovery. From 2016 until 2022 she worked about 30 to 40 hours a week in her field, living independently. In 2017, she bought a house in a rural community about an hour and a half outside of Toronto.

Liz began another new job at a pain clinic in January 2022. Initially, the stress of changing jobs landed her in the hospital again for four weeks, but that hospitalization was to be her last, to date.

Today, Liz has achieved recovery on the antipsychotic cariprazine, bupropion, and the mood stabilizer lithium. She is surviving and thriving, working full-time while being the primary caregiver for her grandmother. She also has her own small business and participates in various community activities.



TEAM DANIEL

Running for Recovery from Mental Illness



Dr. Laitman with Catherine Ndareba and Bill Rodgers (both 4 times Boston marathon winners) in the 2022 Boston marathon.

When the Laitmans' son Daniel presented with symptoms of psychosis in 2006, they never dreamed that he would achieve a meaningful recovery, let alone that so much good would come out of his struggle with treatment-resistant schizophrenia.

Dr. Laitman remembers his first rotation on a psychiatric ward in the late 70's, where he described the care as "terrible." The older antipsychotic medications (first generation) were in use, and patients often had unbearable side effects, while getting little benefit. Upon his graduation from medical school at Washington University in Saint Louis in 1983, Dr. Laitman decided to become an internist, and then eventually, to specialize in nephrology.

Dr. Laitman married Dr. Ann Mandel in 1986. Over the next decade, they had a daughter, a son and identical twin girls.

In early elementary school, Dr. Laitman's son Daniel seemed to be struggling. He suffered from anxiety, and occasionally had a "meltdown." He was sensitive to loud noises. At age eight, following an allergic reaction, he took steroids, which made him psychotic. Although the medication induced psychosis disappeared quickly, Dr. Laitman looks back on it as a warning sign.

From second grade onward, Daniel was diagnosed with ADD, began therapy, and took medication. But Dr. Laitman remembers Daniel as a happy kid. He had friends and looked forward to summer camp.

Unfortunately, Daniel's struggles soon took a turn for the worse at age 15, during summer camp, when he began to hear voices. Command hallucinations took over his thinking, threatening to steal his soul. He was commanded to hold his arm in uncomfortable positions and not put his head down on a pillow.

As Daniel grew worse, the Laitmans began to read widely about schizophrenia and treatment, and look for advocacy organizations. Dr. Laitman remembers being told that he needed to simply "lower his expectations," and that Daniel would have a "different life." He remembers crying over his son's impossible situation, although he almost never cried.

Despite the hopelessness he encountered, the Laitmans resolved to never give up on Daniel. After several months, it became clear that Daniel was resistant to schizophrenia medications. Looking for help, Dr. Laitman contacted Dr. Deborah Levy, who was the head of Harvard's McClean Psychology Research Lab. At that time, an effective treatment for Daniel was becoming more urgent, as he was becoming suicidal.

Following extensive research and many conversations with experts, Dr. Laitman discovered the underutilized medication clozapine, which is the only medication for treatment-resistant schizophrenia. He was also warned that the medication should only be used for the most severe cases.

With careful monitoring, Daniel began clozapine in March of 2008 at age 17. Within weeks, it was apparent that clozapine was radically different than any other medication Daniel had tried. After a few months, his symptoms were soon in remission.

However, shortly after Daniel started clozapine, he developed aspiration pneumonia and severe constipation. These side effects were treated while he continued to take clozapine. In order to remain on clozapine, Daniel also needed weekly bloodwork, which was a challenge to coordinate with their pharmacy.

As the side effects of clozapine abated, Daniel was able to resume a normal life. Because of this, the Laitmans realized the great need to make clozapine more widely available to treatment-resistant adolescents, enabling many of them to achieve full symptoms remission. They also knew that the side effects needed to be managed carefully.

Dr. Laitman was still practicing nephrology, but he realized that becoming certified to prescribe clozapine (with the Risk Evaluation and Management Strategies, or REMS system) was within his reach. He began collecting Daniel's blood by himself at home and managing Daniel's medications.

Today, Dr. Laitman does not consider himself a psychiatrist but a "psychiatric internist." The COVID pandemic led to a movement of doctors using telehealth. Today, thanks to telehealth, Dr. Laitman sees over two hundred patients in thirty states whom he monitors on clozapine. Many travel to New York to see him in person once a year.

Thanks to Dr. Laitman and like-minded psychiatrists that work for the office of mental health, the use of clozapine has increased in their facilities from 2.8% to 20%. Today, he also travels around the country giving presentations about the use of clozapine and dispelling myths that clozapine should not be used or is dangerous.

For decades, clozapine has been used as a medication of last resort. Sometimes, even today, patients who fail several antipsychotic trials suffer for years before clozapine is even considered. Dr. Laitman's mission is to introduce clozapine earlier on the patient's journey to recovery, to offer the best outcome. Over the years, he has seen many success stories. He hopes that through his professional work, and also through the advocacy work of Team Daniel, more lives will be radically changed as Daniel's has been.

TEAM DANIEL Running for Recovery from Mental Illness

is a charity founded in 2013 to raise funds for schizophrenia research and advocacy, founded by Dr. Robert Laitman, his wife Dr. Ann Mandel Laitman, and their family.



In 2017, Dr. Laitman published a book together with his wife and Daniel titled "Meaningful Recovery from Schizophrenia with Clozapine." In his book, he describes how to minimize and treat clozapine side effects in great detail, including how to treat rare side effects. During this time, Dr. Laitman contacted the organization which had told him to lower his expectations with a message: "Don't grieve your children. Make them better!"

Over the last fifteen years, Dr. Laitman has proposed a change in the position of clozapine from the drug of last resort to a drug that should be considered early in the first episode of psychosis in those not showing an optimal response with the first antipsychotic used. Clozapine can take the care of psychosis from good enough to optimal. Dr. Laitman believes that everyone who is fully engaged and has not shown an optimal response should be given this opportunity.

Issues with Pharmacogenetic Testing to Optimize Antipsychotic Therapy

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This confluence of issues may explain why no study has found that the use of commercial genetic testing significantly improves outcomes in patients living with schizophrenia, but it does explain why there has been a resurgence of interest in directly measuring antipsychotic levels to accurately quantify how the independent effects of nonadherence, genetic variants, other medications, supplements and smoking sum to influence how a given medication is cleared and whether it is being taken as prescribed.^{8,9}

Clozapine is an important example of the limitations imposed by use of genetic testing. Clozapine is the only medication effective for individuals with treatment resistant schizophrenia, but it has complex metabolism, with one study showing the average contributions of CYPs 1A2, 2C19, 3A4, 2C9, and 2D6 were 30%, 24%, 22%, 12%, and 6%, respectively.¹⁰ CYP1A2 is very sensitive to the effects of cigarette smoking, and those who smoke typically require dosages 50% higher than nonsmokers to achieve the same clozapine level.¹¹ The magnitude of this effect will only be seen if the clinician orders a clozapine level. Importantly, given that population variations exist for many of these CYPs, and that a significant proportion of patients living with schizophrenia do smoke, recent recommendations focus on tailoring early clozapine dosing to the patient's ancestry and smoking behavior to avoid unnecessarily high drug levels during the early phase of treatment, and then checking levels to determine the net effects of all of these factors for that patient. To add another layer of complexity to this situation, clozapine has an active metabolite, norclozapine, and 83% of its clearance does not rely on a CYP but instead on a renal (kidney) drug transporter called P-glycoprotein (PGP).^{12,13} Not surprisingly, both the expression of and the function of PGP exhibit population variations in the same manner as do CYPs,¹⁴ and this variability represents an aspect of norclozapine clearance that is not captured by many commercial genetic assays.¹⁵⁻¹⁷

The problems with pharmacogenetic testing (PGx) in psychiatry can be summed up nicely by a 2023 review which concluded: *"Clinicians varied greatly in their application of test results for clinical decision making regarding medications, many were uncertain how much to rely on the results, and differed in perceptions about which patients would benefit from PGx."*¹⁸ There is hope that, in the future, genetic testing will significantly improve the accuracy of antipsychotic treatment and patient outcomes. That future, lamentably, has not yet arrived.

Conflicts of Interest:

Dr. Meyer reports having received speaking or advising fees in the past 24 months from: AbbVie, Alkermes, BioXcel, ITCI, Karuna, Neurocrine, Noven, Otsuka-USA, Sumitomo Pharma (formerly Sunovion) and Teva.

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