

# It's Not You, It's Me (Your Genes)

by Gillian Heckler



*“Just as cancer invades the body, depression invades the psyche. Just as we keep working to find cures for deadly cancers, we need to find ways to help people overcome the depression that cuts short too many lives”*

*-Jill Harper, MD*

## Outcome Disparities of Medications

### Patient 1:

There was no denying that something more than circumstances was playing a role in my depression. I went to my doctor, explained my symptoms and walked out with a prescription for an antidepressant that day. I stopped thinking about the medicine and the fact that I was taking it. As time went on, I noticed subtle changes like having more energy, and thinking more stably. When I watched movies I actually laughed aloud and my interactions with people were less anxiety-filled. I surrounded myself with my family, found a new job that I really liked and started a new life. I also found a psychiatrist who I was very honest with and came to genuinely trust. Together we decided I should switch to a different medicine, Prozac. The first antidepressant worked, but there were some effects that never quite went away. The new medicine worked perfectly. The year since I started medication for my depression has brought me a new life. I have a job I love, and I am closer than ever to my family. Every once in a while, I flirt with stopping my medicine. Then I think of my life prior to Prozac, and I walk to my medicine cabinet to make sure I am fully stocked. For now, medication helps me to live the life I want, a life that I am proud of, and I have no doubt starting medication was the best decision for my family and I.<sup>1</sup>

### Patient 2:

I started going back to therapy and seeing a psychiatrist. I was prescribed one antidepressant, but I felt far from ‘normal,’ so I decided to try Prozac. The first few weeks were fine, and then I started to get really bad fatigue. I’d try to spend as much time in bed to rest before work, but then I’d still feel like a spacey zombie once I got there. It felt like being day-drunk without the alcohol. My head felt thick and cloudy and my memory was super off and I had to set a million reminders out of fear of messing up at work and in life. It was exhausting. My doctor had me try taking the Prozac at night before bed, but that only slightly minimized the fatigue. I had to sleep 12 to 16 hours a day, and it made my behavior more erratic. Last week, I felt like I was going to pass out at work and ended up going to the ER because it was so bad. I stopped taking it since, and though I can definitely feel my major depression coming back, it’s almost comforting because the brain fog and fatigue had gotten so extreme. There’s a lot of trial and error and ‘shopping around’ when it comes to mental health, so hopefully, I will eventually find something that works for me.<sup>2</sup>

Both of these patients struggle from the same disorder. Both of these individuals took the same antidepressant, Prozac. Yet their experiences in response to this medication resulted in dramatically different outcomes. Why do medications have such varying effects for the same disorder?

### Does One Size Really Fit All?

When a ten-year-old boy who is four foot six and a 50-year-old man

who is six foot three try on the same “one size fits all” suit, the suit will be ill-fitting on at least one of them. Creating and finding that perfect fit is not so simple. Even if people have the same goal, of appearing clean cut or formal, the clothing item needed will vary person to person. People have drastically different body compositions. So, confining all people who want to dress up into the same sized suit will create a haphazard effect. A tailored approach is a more efficient way to create the perfect fit that

caters to an individual’s needs, both for clothing and pharmaceutical treatments.

### The Future is Here

Fortunately, a groundbreaking method now exists that can use our genetic information to help formulate precise treatments. Next Generation Sequencing (NGS) is an exciting technological advancement of the 21st century that will transform our understanding of cells and our approach to treating diseases.

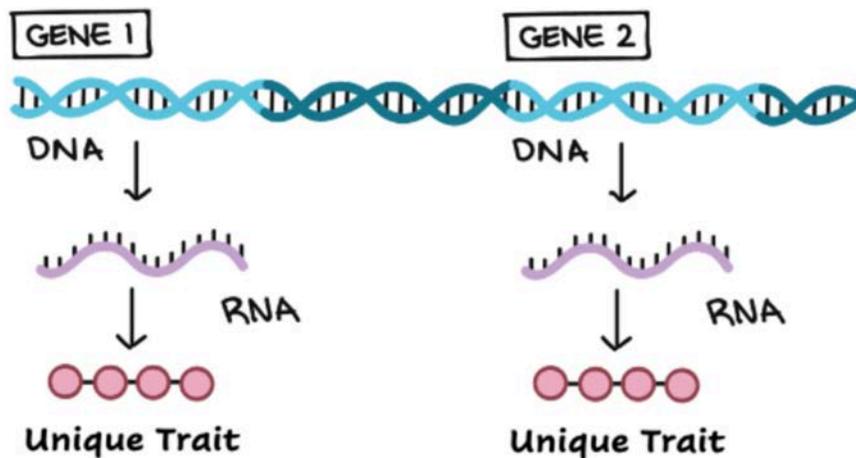


Figure 1. Genes are sections of DNA that code for RNA, which will determine an individual's unique traits.<sup>15</sup>

These innovative machines allow researchers to sequence strands of RNA. DNA is a material that contains the information to build and maintain our cells. DNA is read, or transcribed, into this RNA material. Genes are sequences of DNA that code for functions which determine our unique traits (Figure 1). Through sequencing we can study individual cells and precisely identify which genes contribute to diseases, like Major Depressive Disorder (MDD).

We can compare DNA to all of the possible services that the tailor can perform, from hemming the length of jackets to taking in the waist of pants. Then, we can think of RNA as the messenger to communicate which particular service is selected. The uniquely tailored suit that results as the final product can represent our unique traits. So even if all individuals have the same services to order from, their end product can be drastically different. We all practically have the same DNA, but the unique traits made from this DNA differ from person to person. The NGS technology considerably advances our understanding of genes, the segments of DNA, that contribute to many disorders in need of superior treatments, including MDD.

## An Invisible Pain

Articulating mental pain presents a challenge because the phenomena is intangible. Therefore, it sometimes does not seem as legitimate compared to other physical disorders. Everyone may not fit into the same sample size suit, and everyone may not have the same gene activity or concentration of chemicals. Neurotransmitters—dopamine, serotonin, and norepinephrine—are chemicals that send signals and communicate with your brain. These chemicals in particular regulate mood and help make you feel good. Low levels of these chemicals are considered hallmarks of MDD. This chemical imbalance could be an aftermath of gene dysregulation that sequencing can help us pinpoint. Recognizing the legitimate biochemical alteration occurring in MDD can help validate an individual's experience and encourage people to seek help for management of the disorder.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) describes MDD as being characterized by distinct changes in affect and cognition with episodes lasting for at least two weeks.<sup>3</sup> MDD can arise at different time points for different people. A breadth of factors may contribute to the

onset of MDD, including economic pressures, social environments, trauma, neurobiology, and genetics. Not only can MDD affect an individual's mental health, but it can also alter physical health, inducing headaches, appetite changes, and disruptive sleep patterns.<sup>3</sup> Individuals with MDD can experience varying symptoms, but often feelings of hopelessness and internal criticism pervade.

The specific reasoning for the development of MDD remains ambiguous due to the complex interactions between an individual's genetic makeup and their environment. Understanding the causal mechanisms for MDD can allow for more concrete diagnostics, and therefore implement more effective therapeutic offerings. While the disorder can involve behavioral, psychological, and cultural factors, there is substantial evidence that the disorder relates to DNA with a 40% chance of heritability.<sup>4</sup> Additionally, if an antidepressant has been effective for a family member, there is a higher likelihood that it will be more effective in comparison to an antidepressant prescribed by the general trial and error method.<sup>5</sup> A more intentional practice of assigning patients to medication based on their unique genetic composition can offer necessary transformation to the treatment process of MDD.

## Do You Have to Do Drugs?

Medications are a major relief for many individuals who experience this disorder. While pharmaceuticals are a fundamental option, there are also alternative routes for treatments such as psychotherapy, and dietary changes. According to the most decorated Olympian, Michael Phelps, who struggles with depression, speaking to a therapist

offers him stability, growth, and support in his darkest of days.<sup>6</sup> We do not expect individuals to manage their diabetes or coronary artery disease on their own. Why would we expect individuals to manage MDD on their own? Psychotherapy is an invaluable approach to manage MDD, particularly in conjunction with medication. With a trained psychologist, individuals can confide in a professional to understand their feelings and behaviors, while also gaining coping skills. A popular type of psychotherapy is cognitive behavioral therapy, where the therapist and patient work together on constructive ways to modify and improve behaviors and beliefs.<sup>7</sup> Acquiring help through therapy exemplifies strength by prioritizing health and seeking personal growth.

Incorporating nutritional elements, like omega 3-fatty acids found in foods such as cold-water fish and flax seed, has the potential to alleviate symptoms of MDD. In nations where the population consumes large quantities of fish, depression rates are lower.<sup>8</sup> Furthermore, saffron extract has shown to inhibit a decrease in serotonin levels, improving MDD symptoms in adult patients.<sup>9</sup> Another promising option, vitamin D supplementation, provides therapeutic relief by promoting extracellular levels of serotonin.<sup>10</sup>

Consistent physical exercise can also increase chemicals in the brain, like dopamine and serotonin. A misconception persists that only vigorous exercise serves as an effective treatment.

In reality, individuals who engage in moderate physical activity, such as taking 30-minute strolls three times a week, reduce the risk of experiencing major depressive episodes.<sup>11</sup> Integrative styles of yoga that incorporate meditation and breathwork have

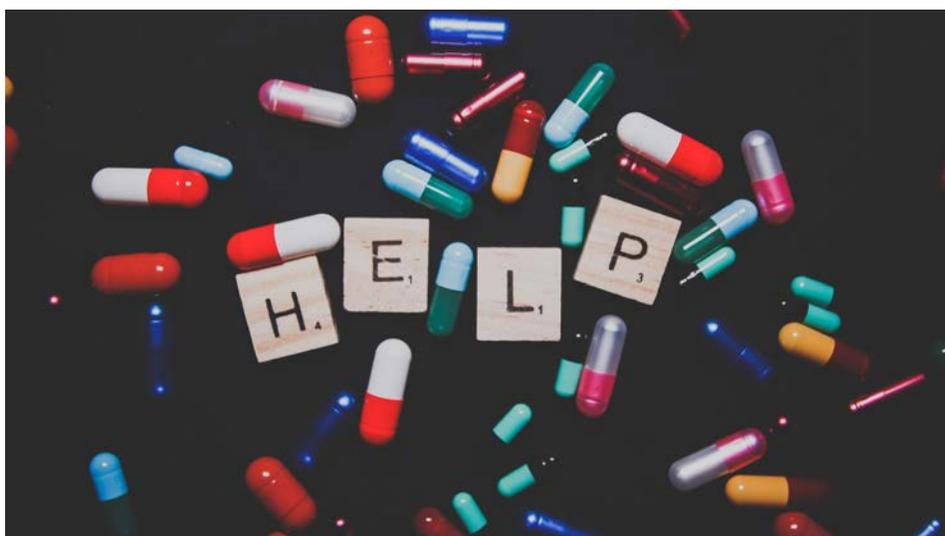
also been shown to be quite valuable. Mindfulness based interventions show effective results of reducing depression, anxiety, and stress.<sup>12</sup> However, holistic approaches take ample amounts of time to take effect and may not initially be realistic for individuals with severe cases of MDD who already reside in a very fragile mental state. Many of these approaches could offer maximum efficacy as an adjunct to more traditional pharmacological approaches.

## Shortcomings of Pharmacological Options

If you have a chronic headache, why would you not take an ibuprofen? If someone experiences chronic depression, similar logic follows with taking antidepressants. Finding medication can often be associated with a "quick fix". In reality, quite an extensive amount of time is expended to properly allocate the most efficacious medication for each patient. The process of doctors distributing prescriptions occurs by a trial-and-error method. This method is like going shopping and not looking at the size on the tag beforehand. Then you go to the dressing room and go through the hassle of

trying on multiple poorly fitting outfits. Unfortunately, you leave feeling displeased because none of them fit, as none of them were intentionally chosen for you.

Currently, a symptom-based approach is often utilized to treat people with MDD.<sup>5</sup> Physicians will try to take into account a patient's symptoms to speculate if one medication may be more suitable than another to minimize undesirable side effects. Unfortunately, this method does not suffice for people who require more immediate relief, as not every patient has the luxury of time to try three different medications. Altering medications can also pose challenges since weaning off the prescriptions can sometimes emulate flu-like symptoms. People alter their medications due to the unbearable side effects. Some of the side effects make it difficult to adequately function with overwhelming feelings of fatigue and a sense of overall numbness. In the one size fits all scenario, you have an item that allows you to pass the requirements of a formal dress code, but you are far from feeling comfortable. From constantly having to pull up your pants to having your sleeves drag throughout your food, these side effects are far from desirable. In addition to adverse side effects, the medication can also take



several weeks and even months for patients to feel an effect. If you take your suit to get tailored for an upcoming event, but the suit isn't ready until a month after your event, was it even worth it?

Another shortcoming with current medication involves individuals initially experiencing or developing resistance to the treatment medications offered. To counter this issue, individuals have to either wait even longer for an effect, increase dosages, or take multiple antidepressants. These approaches can often feel confusing and tumultuous for patients as months pass without experiencing any improvement. Current antidepressants can provide critical relief to subside internal pain but desperately require further innovation.

## The Power of Sequencing

Different expression levels of genes are often responsible for cells' behaviors in diseases.<sup>13</sup> Gene expression can be considered to

have an on/off switch. Variances in gene expression are due to the instructional code of DNA producing different quantities of functional products. By comparing gene expression activity of patients with MDD to people that are considered healthy, we can observe the discrepancies of gene activities between the two groups. Using the novel technology of NGS, we can perform single cell RNA sequencing (scRNAseq), which clusters or groups cells with similar characteristics. Established in 2009, this scRNAseq method is still in its infancy stages in the science world and offers great transformative promise. An analogy for scRNAseq is the classification process of desserts. Dessert is an overarching category that comprises many subcategories. Characteristics of the desserts, whether they have chocolate or fruit, or whether they are baked or frozen, can help us classify each dessert. For instance, ice cream, gelato, and frozen yogurt may comprise one cluster, while cobbler, crumble, and crisp may comprise another. The

same process happens in order to distinguish cell subtypes based on gene expression characteristics.

The first ever scRNAseq study of MDD published in 2020 reveals that 16 unique subtypes have distinct gene activities in patients with MDD (Figure 2).<sup>14</sup> Instead of a uniform disorder, MDD may be an umbrella construct with multiple biologically distinct disorders that each require unique treatments. Neurons, which are the primary cells that transmit information throughout the brain, make up six of the cell subtypes. Non-neuronal cells, which are cells that help support and maintain the nervous system, make up four of the cell subtypes. Each cluster is considered a cell subtype and has similar gene expressions to other cells in that subtype. Deconvoluting the complexities of different cell subtypes in the nervous system with scRNAseq offers great potential to develop novel medicine. This method can help us discover and then target specific genes in cell subtypes with greater precision. If we discover that only a particular subtype has discrepancies in MDD patients compared to control patients, we can target that particular subtype. Rather than distributing medication to all cells throughout the entire brain and potentially harming healthy cells, targeting one cell subtype will increase effectiveness. We have the power to develop superior treatments aiming to minimize the treatment resistance, late onset period, and side effects of current medications.

## The Science Behind Happiness

The majority of dysregulated genes in MDD patients are downregulated.<sup>14</sup> When genes are downregulated in a cell, production of that gene product

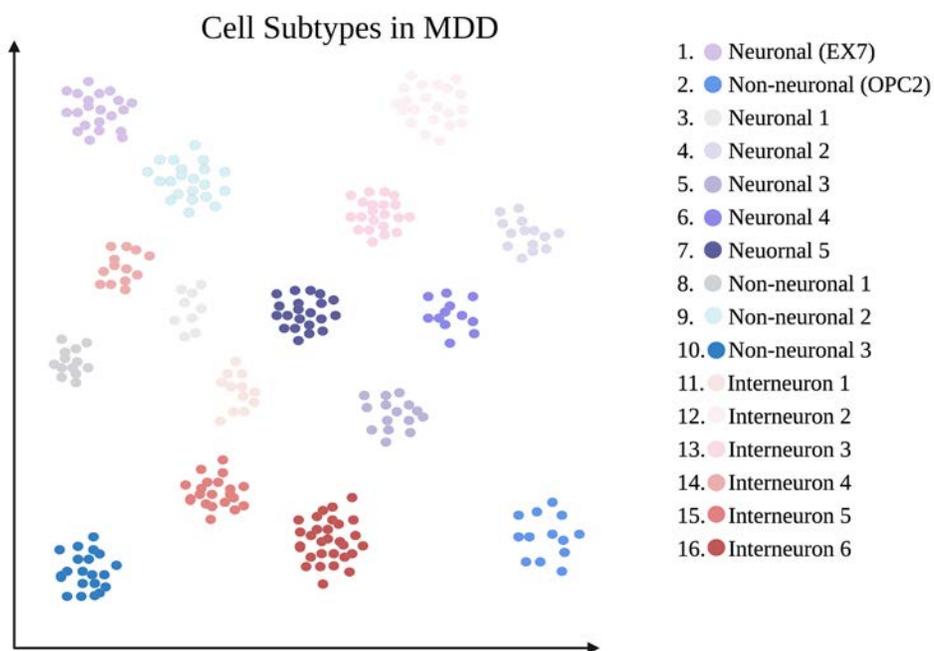


Figure 2: In MDD, scRNAseq reveals 16 different subtypes that are represented in distinct clusters. Each point indicates a single cell that has similar characteristics to other cells in that cluster. The characteristics of each cell are determined by gene activity levels. Original image by Gillian Heckler. Created in BioRender.

decreases. Sometimes the effect of downregulation does not have a negative implication. For example, we often do not see adults with naturally occurring blonde hair. If an individual is born with blonde hair, those genes are often downregulated by the time that individual reaches adulthood. While this example of downregulation does not have any dire consequences, downregulation of genes that regulate nerve cells can result in harmful ramifications on the psyche.

Out of the 16 subtypes discovered, two cell subtype clusters had the most prominent changes in patients with MDD in comparison to the control.<sup>14</sup> The first subtype, composed of excitatory neurons, was termed Excitatory 7 (EX7). The cluster EX7 involves a gene that regulates neuronal excitability. Excitatory cells fire and send messages to other areas of the brain. In MDD, downregulation of excitatory neurons is quite common. In order for our neurotransmitters like serotonin to bind to its receptors, we need to have excitation. The other prominent group is a non-neuronal cell type labeled OPC2. This subtype, OPC2, is suspected to be involved in brain plasticity. Brain plasticity signifies the brain's ability to change and adapt to the environment and new experiences. In MDD brains, genes that regulate plasticity are turned off. One of the defining characteristics of this OPC2 cluster is the downregulation of the PRNP gene (Figure 3). The absence of the PRNP gene is implicated in a lack of cell division and brain plasticity.

If you only want the waist taken in, rather than shrinking your entire suit in the dryer, you can only alter that one section and prevent the disruption of functional components. This approach holds for targeting genes in subtypes

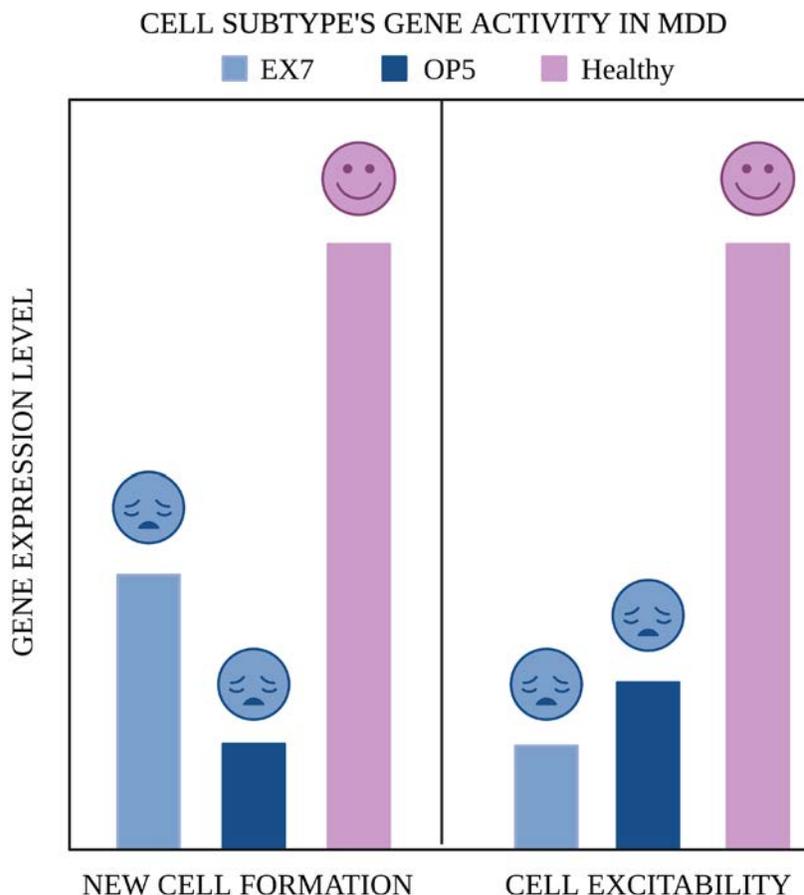


Figure 3: The happy face cells are found in the control patients, and the sad face cells are found in MDD patients. The cell subtypes, OPC2 and EX7 have lower gene expressions in comparison to the healthy controls. The gene PRNP is expressed at very low levels in the OPC2 subtype. Genes involved in excitation are expressed at very low levels in the EX7 subtype of MDD patients. Original image by Gillian Heckler. Created in BioRender.

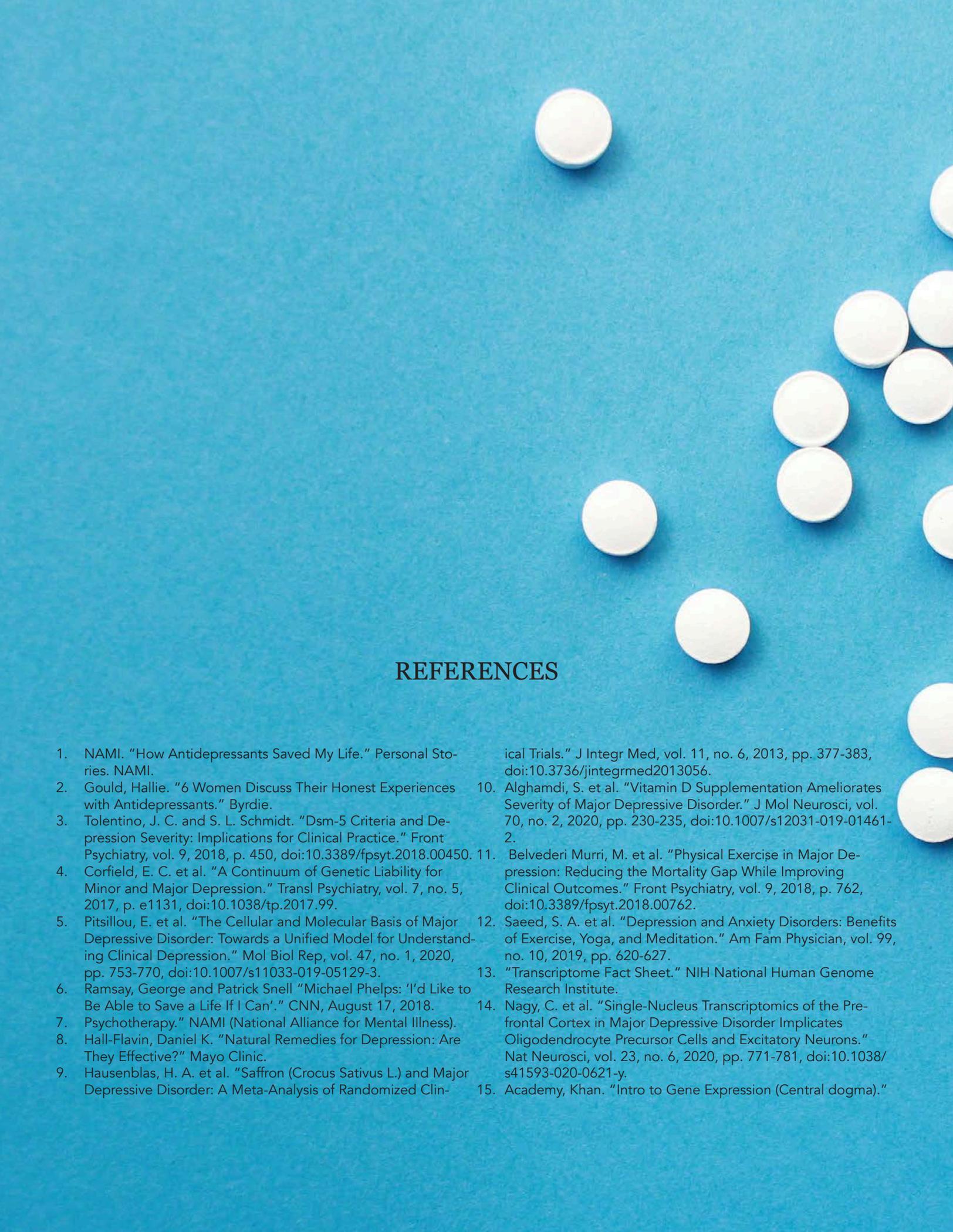
rather than your entire system. Potentially increasing the levels of the PRNP gene in only the particular OPC2 subtype could serve as an effective treatment for MDD.

## Hope is Here

A suit precisely designed for an individual will help ensure a good fit. The same logic applies for designing precise treatments for MDD patients. ScRNAseq can shed light on the ambiguous complexities of MDD. Instead of continuing on the prescription method of trial and error, we can take a more methodical

approach to target downregulated genes with greater precision. With societal acknowledgments of MDD and advancements in genetic research, we have so much potential to improve the quality of life for those struggling with MDD. By raising awareness on topics, we can foster empathy, rather than fear unfamiliarity. The disorder may not be something that you "defeat", but people can be empowered with tools to support their health. Implementing novel therapeutics and destigmatizing MDD can allow for the vast majority of people to live fulfilling and vibrant lives. ■

***"There is hope, even when your brain tells you there isn't"***  
-John Green



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