Our Path to Pursuing a Differentiated and New Treatment for Schizophrenia

For more than 40 years, I have dedicated my professional life to advancing the science related to the causes and treatment of serious mental illness. Through numerous roles in academia and across the biopharmaceutical industry, my goal has remained the same, and continues now at Karuna: to transform the way serious psychiatric conditions are treated. At Karuna, a clinical stage biopharmaceutical company, we are applying our extensive knowledge of drug discovery and development with the goal of delivering transformative medicines for people living with neuropsychiatric conditions, starting with our lead product candidate, KarXT.

I can attest firsthand that one of the most challenging pursuits of the biopharmaceutical industry to date has been the successful development of highly effective, safe, and tolerable medicines for common psychiatric and neurological conditions. The path to developing treatments that can reduce the disabling symptoms of these conditions without producing burdensome side effects has been a very challenging one.

Antipsychotic medications have historically been the most commonly prescribed treatment for adults with schizophrenia, beginning with first-generation or “typical antipsychotics” introduced in the 1950s. Their discovery and development, at the time, was considered a breakthrough in the treatment of schizophrenia, allowing patients to be treated and managed in an outpatient setting. These first-generation treatments are now known to primarily target postsynaptic dopamine 2 (D2) receptors, which is a type of receptor that also controls normal motor movements. While these drugs clearly improve symptoms of psychosis, such as hallucinations and delusions, many patients taking these drugs experience burdensome side effects that make these medicines difficult for some to tolerate.

Second-generation, or “atypical antipsychotics,” emerged in the late 1980s, beginning with the breakthrough re-development of clozapine. Atypical antipsychotics, which also target D2 dopamine receptors, as well as a number of other neurotransmitter receptors, were found to generally exhibit less severe motor symptom side effects than first-generation antipsychotics, although other adverse effects, such as weight gain and associated metabolic changes, including diabetes, high blood pressure and elevated cholesterol, became more commonly associated with these newer agents.

Moreover, while current antipsychotic therapies can be effective in managing positive symptoms, such as hallucinations, delusions, and difficulty organizing and expressing thoughts, they do not treat the other major symptom domains of schizophrenia, such as persistent negative symptoms (e.g., difficulty enjoying life and social isolation) or cognitive difficulties (e.g., deficits in memory, concentration, and executive functions).

Today at Karuna, we are advancing a novel drug that has the potential to treat schizophrenia and other conditions where symptoms of psychosis are prominent and disabling. Our potential new treatment KarXT (xanomeline + tropism) was born from a collaborative passion to seek transformative medicines to meet patient needs. Over a decade after my team and I at Eli Lilly serendipitously discovered the antipsychotic properties of xanomeline, my colleague Andrew Miller, Karuna’s co-founder and chief operating officer, was determined to find a way to harness the therapeutic benefits of xanomeline. He assessed more than 7,000 possible combinations of other therapeutics to find an optimized combination which has the potential to markedly enhance the tolerability of xanomeline without reducing its antipsychotic properties. From there, the idea for KarXT was created.

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The Story of Michael Brisbin

In my first two years of high school, academics came easily to me, and I was an honors student. As a member of the National Honor Society, National Technical Honor Society and student council, my future looked bright. I made plans to major in computer science in college.

However, during my junior and senior years of high school, I started struggling academically, and losing interest in the hobbies I had always enjoyed. I began experiencing extreme anxiety and alternated between sleeping hours on end and being unable to sleep for days at a time. My teachers, family, and friends began to notice something was different, but they did not know what it was. At the time, no one in my life realized this was the beginning of my journey into the world of mental illness.

I barely managed to graduate from high school. Fortunately, due to my previous academic accomplishments, I had already been accepted at the College of the Ozarks with a full scholarship.

In 2016, during my first semester of college, I experienced my first delusions and feelings of paranoia. I thought my teachers were against me. I believed subliminal messages were being broadcast from the TV and radio. I had trouble falling asleep and couldn’t wake up in time for classes. When I did homework, I found myself reading the same text over and over without comprehension.

Unable to concentrate, I skipped my classes and isolated myself in my room. I couldn’t understand why schoolwork had become so difficult. I failed my classes and returned home that summer confused and discouraged.

Over the course of the next several months, my mental health declined. I wasn’t sleeping and experienced cognitive issues. I began having visual, audio, and tactile hallucinations, hearing voices, and experiencing extreme fear. I was no longer able to study or work. My parents sought treatment for me, and in November 2016, I was diagnosed with schizoaffective disorder.

We tried numerous medications and treatment options for improved cognition and anxiety control: clean eating, gluten and diary free foods, supplements, vitamins, holistic and naturopathic medicine. Nothing worked. Finally, in my desperate and confused state, I believed that more medication might work better to relieve my symptoms, and took a two week supply of medicine all at once. This resulted in being picked up by ambulance and hospitalized with multiple organ failure. This was my fourth and last hospitalization.

After thirteen failed antipsychotics, numerous mood stabilizers, antidepressants, and four hospitalizations, my parents finally found a doctor who was unwilling to give up on me. This doctor started me on a rarely used medication called clozapine, for treatment resistant patients.

On clozapine, my concentration and memory began to improve. I began to experience less anxiety and fear and enjoy old hobbies like reading. Over several months, the delusions, hallucinations and voices faded away. As these schizophrenia symptoms began to fade, my cognitive abilities slowly improved. I enrolled in community college, and each semester proved a little easier than the last.

I have now been in meaningful recovery for three and a half years. I am back at my previous college, which is three and a half hours away from home, and I am living in a dorm on campus again. I work fifteen hours a week in the campus library. I have made friends and am enjoying college life. My grades are excellent.

In 2019, I founded a NAMI peer support group in my hometown for people living with mental illness (NAMI stands for National Alliance on Mental Illness). In 2020, I started a “NAMI on Campus” support group for the Metropolitan Community College of Kansas City. I am a board member of NAMI of Greater Kansas City and the program director for all “NAMI on Campus” groups in Kansas City colleges. I have been arranging zoom meetings, and people from all over the United States attend virtually. I was featured on the PBS Documentary “The Hidden Pandemic.”

I recently changed my major from computer science to social work. After graduation, I want to work in the mental health field. I believe that people living with mental illness need help, hope, and understanding, and I want to work with patients to improve their lives. I want them to know that recovery is possible with the right medication and that they are not alone.

I hope that through sharing my story, more young people will seek appropriate treatment so they can rebuild their lives as I have.
LONG-ACTING INJECTABLE ANTIPSYCHOTICS

Hope in a Needle

When the FDA authorized the first vaccines for COVID-19, they were called miracles of modern medicine and saviors of society. Pictures of people weeping tears of joy while receiving the vaccine flooded the internet. What stood out to me was that these were not people who were already sick with COVID — they were completely healthy. But they saw the vaccine as a symbol of hope and the first step in overcoming the oppression of living in fear of an uncertain future. It made me wonder, why do we have such a hard time believing that people living with schizophrenia could find hope in a needle too?

Long-Acting Injectable antipsychotics (LAIs) offer numerous well-documented potential advantages for the treatment of adults with schizophrenia, but less than 15% receive them.1 Perhaps one reason they are so underutilized is that clinicians have assumed that patients would not be interested in receiving an injection every 2 to 4 weeks, as LAIs historically required. However, I can attest that even if the COVID vaccine needed to be taken every month to stay safe, I would still want to be the first in line!

Furthermore, recent advances have allowed the interval between injections of certain LAIs to increase dramatically over the past decade. For instance, paliperidone palmitate was introduced as a once-a-month LAI in 2009, but a newer preparation given just every 3 months became available in 2015. Even more exciting, a version administered every 6 months is likely to be approved by the FDA later in 2021. If this pace continues, perhaps there could be a once-a-year version in 2027!

There is considerable evidence that schizophrenia is a neurodegenerative brain disorder, similar to Parkinson’s or Alzheimer’s Disease, but that psychotic relapses drive the progressive loss of brain tissue.2 As such, clinicians must think about relapse prevention in schizophrenia with the same urgency that we currently attempt to prevent someone from having a second or third strokes.3 Broader use of LAIs could go a long way towards minimizing the brain loss and the resulting decline in functionality and quality of life that each relapse brings. Research has shown LAIs may reduce relapse rates in schizophrenia by 20% and mortality risk by 33% compared to taking the same antipsychotic in oral form.4

Despite these substantial benefits, most clinicians seem to reserve LAIs solely for patients who are more severely or chronically ill.5 In contrast, clinicians typically prescribe medications that slow the decline of Alzheimer’s Disease early in the illness to protect the person’s mental functioning at a higher level rather than waiting until there’s less quality of life left to preserve. Given the evidence that each relapse accelerates the cognitive and functional decline for people with schizophrenia, LAIs should be considered as an early option, not a last resort intervention. There is no grace period for the destructive effects that schizophrenia has on the brain.

Some clinical practice guidelines have begun to recommend using LAIs in first-episode psychosis, and I have adopted this approach in my practice.6 I explain it to patients with the analogy that if I jumped out of an airplane, I’d prefer to open my parachute at 50,000 feet above the ground, not 50 feet. In the fight to achieve a richer, fuller, and longer life, LAIs are too powerful of a tool to be as underutilized as they are. Earlier aggressive treatment of first-episode psychosis and subsequent relapses with LAIs can dramatically improve long-term outcomes.

I have found that LAIs can be a remarkable source of positivity in the lives of people with schizophrenia. With the confidence that the medication’s consistency is optimal and the improved stability that LAIs often bring, both the clinician and the patient can focus on other issues such as deepening their therapeutic alliance or working on coping skills. The next step could be to foster the engagement needed to successfully pursue even higher goals, like going back to school, getting a job, or finding a relationship. LAIs can be life-saving interventions, but only if clinicians do their part by offering and educating about them.

References:
Xanomeline, the active therapeutic ingredient in KarXT, works by targeting a brain receptor called the “muscarinic receptor.” Subtypes of this muscarinic receptor are expressed in brain regions implicated in the pathophysiology of schizophrenia, suggesting that targeting these receptors mediates the antipsychotic activity of xanomeline. Tropism is a medication approved in the United States and Europe for the treatment of overactive bladder that blocks all five muscarinic receptor subtypes but only in the body, not in the brain. Together, xanomeline and tropism, or KarXT, is designed to maintain the efficacy of xanomeline while reducing its side effects through the use of tropism. KarXT preferentially activates muscarinic receptors in the brain, but unlike all current antipsychotic drugs, does not directly block dopamine and/or serotonin receptors. This novel mechanism of action of KarXT could result in a treatment for psychosis without the side effect burden often associated with the direct blockade of dopamine receptors. If it is approved by the FDA, KarXT, with its novel antipsychotic mechanism of action, has the potential to usher in a new treatment paradigm for schizophrenia.

In a recently completed Phase 2 trial, KarXT demonstrated improvement in both the positive and negative symptoms of schizophrenia, as well as trends towards improvement in cognition in an exploratory analysis. The most common adverse events of KarXT reported in this trial included constipation, nausea, dry mouth, dyspepsia, and vomiting, and all were mild-to-moderate in severity. Preliminary data suggests that KarXT is not associated with common problematic side effects that may result from taking current antipsychotic medications (e.g., weight gain, tremors, muscle contractions, drowsiness, metabolic changes, somnolence). Results from this study were recently published in The New England Journal of Medicine (Muscarinic Cholinergic Receptor Agonist and Peripheral Antagonist for Schizophrenia).

Currently, KarXT is being evaluated in Phase 3 trials for the treatment of schizophrenia. More information on these trials is available on clinicaltrials.gov.

Our work at Karuna began with a mission to create and deliver transformative medicines for people living with psychiatric and neurological conditions, and this continues to be why we are inspired each day to push forward. Our belief is that exploring new therapeutic options with differentiated ways of working, or mechanisms of action, could enable more people living with schizophrenia and other psychiatric and neurological conditions to find an effective and safe treatment that addresses not just the positive symptoms, but potentially also the negative and cognitive symptoms, of schizophrenia. While the development process will take some time, our investigational therapy, KarXT, is one potential treatment option on the horizon.

Please consider making a donation to the CURESZ Foundation online at CURESZ.org

Your contribution will help provide education and referrals to persons with schizophrenia, their families, and those who work with the seriously mentally ill. CURESZ informs the general public to better understand this serious brain disorder, and to provide scientific advances showing that there is hope for recovery, and a return to a fulfilling and normal life. The CURESZ Foundation is a 501(c)(3) nonprofit organization. All contributions are tax deductible.

“\textbf{We are committed to helping individuals to cope with and recover from schizophrenia.}”