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CURESZ FOUNDATION
Newsletter
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Comprehensive Understanding via Research and Education into SchiZophrenia

Secondary Psychosis

Psychotic experiences are common in those who are diagnosed with schizophrenia. In fact, the presence of psychotic symptoms can lead to the diagnosis of this brain disorder if both delusions and hallucinations are present for 6 months, including 1 month of persistent symptoms. In other medical specialties a diagnosis is often made after a physical exam, imaging (X-Rays or CT Scans) and bloodwork that are crucial to determining a diagnosis and appropriate treatment. In psychiatry, however, this same diagnostic process does not often yield much useful information except in the case of secondary psychosis. Secondary psychosis is a term more frequently used in recent decades as there is a growing realization that it is vital to understand when symptoms such as delusions and hallucinations are due to a known medical illness or substance. Previously referred to as *"functional"* when having a psychological origin and *"organic"* when there was an identifiable biological origin, the shift to *"primary"* and *"secondary"* reflects an understanding that every psychiatric condition and symptom has a biological component, first seen in the revised version of the 4th Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) in 2000. Any substance, prescribed drug or medical condition that affects the central nervous system can result in psychiatric symptoms including psychosis and, unfortunately, we continue to see cases where a presumptive diagnosis of schizophrenia is made before a thorough medical evaluation confirms the absence of a secondary psychosis.

In a 2016 article published in The Primary Care Companion to CNS Disorders, Dr João

Stephen Rush, MD
Associate Professor of Clinical Psychiatry & Behavioral Neuroscience

Gama Marques studied how often patients initially diagnosed with schizophrenia had an underlying secondary psychosis that was not recognized. This retrospective analysis of 250 patients in Portugal demonstrated that 25% of patients diagnosed with schizophrenia actually had an underlying medical condition causing psychotic symptoms and, further, that the average delay in correct diagnosis was 12 years. The consequences of such a delay in diagnosis can have devastating consequences to patients and their loved ones.

Through the research of scientists done over decades and centuries we can now say that secondary psychosis can result from 13 main groups of disorders identified in the following graphic.

Causes of Secondary Psychosis

DISORDERS THAT LEAD TO SECONDARY PSYCHOSIS	
Trauma	Traumatic Brain Injury
Autoimmune	SLE, AE (N-methyl-D-Aspartate receptor Encephalitis)
Congenital Disorders	Velocardialfacial syndrome, agenesis of corpus collosum
Toxic/Substance Induced	PCP, cocaine, cannabis, lead, arsenic, mercury
Latrogenic	Steroids, antimalarials, isoniazid
Cerebrovascular	Stroke, subdural hematoma
Space-Occupying Disorders	Tumors
Metabolic Disorders	Wilson's Disease, Pheochromocytoma
Dietary Disorders	Pellagra, B12 deficiency, Vit D deficiency
Infection	HIV, Syphillis, toxoplasmosis
Degenerative Disease	Parkinson's, Huntington's, MS, Lewy Body Dementia
Seizure Disorders	Temporal Lobe Epilepsy
Endocrine Disorders	Thyroid, parathyroid disease

SLE = Systemic Lupus Erythematosus
AE = Auto-immune Encephalitis
HIV = Human Immunodeficiency Virus
PCP = phencyclidine
MS = Multiple Sclerosis

Adapted from Keshavan M and Kaneko Y. Secondary Psychosis: An Update. World Psychiatry. 2013;12:4-15

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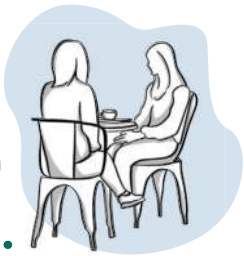
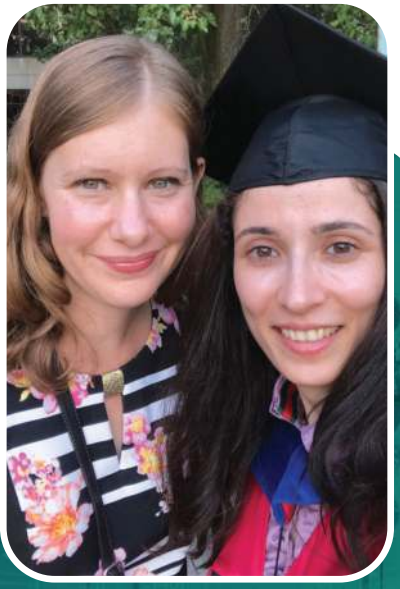
WhatSZ IN THIS EDITION

CureSZ News

THE IMPORTANCE OF FRIENDSHIP





Bethany Yeiser, BS, magna cum laude

CURESZ Foundation President

(Bethany is on the left, shown here with one of her friends.)

Friendships have been vital in my fourteen-year sustained recovery from schizophrenia. Close friendships have especially enriched my life in so many ways.

Prior to developing schizophrenia in college, I had no close friends. I see my former inability to form close friendships as an early symptom that was probably too subtle to be noticed. However, struggling to form close friendships is not unusual in the general public[1].

When I began exhibiting signs of schizophrenia, including delusions and the inability to concentrate, but was not yet diagnosed, I had an affinity for friends from other countries who were unfamiliar with American culture. I enjoyed visiting Southeast Asia three times, despite my worsening psychiatric symptoms. I spent so much time with Chinese friends that they teased me I was actually Chinese myself.

After my delusions and lack of concentration led me to drop out of college, I spent a lot of time in university libraries where I made friends with several international students, including a Turkish graduate student studying math. Today, the Turkish young woman is the only international friend I have kept in touch with from that time. Looking back, I probably chose these friends in part because, due to culture differences, I thought they would be less likely to ask personal questions and notice I had dropped out of college and then eventually become homeless.

As my undiagnosed schizophrenia progressed, I began experiencing hallucinations. One day I went to a library and saw that the name of the library was changed by one letter and spelled incorrectly. In reality, this was not true. As my hallucinations became a daily ordeal, I went for several days at a time without seeing anyone. Excessive isolation can be dangerous, even for people who are mentally healthy[2]. Many people with mental illness tend to isolate themselves when they need friends the most, and lack of companionship was exacerbating my symptoms. As I isolated myself, my hallucinations and delusions became worse.

After my diagnosis, I spent twelve months trying five medications, up to two at a time. Because I was treatment resistant, these medications were only partially effective. They also caused me to have severe exhaustion, and a flat affect. I felt like a shadow of the person I had once been years prior to my schizophrenia. That year was the most difficult time I have ever gone through socially, as I was reluctant to see anyone. In essence, I was hiding away.

But after beginning clozapine in 2008, my severe side effects from other medications dissipated. As true recovery began with steadily diminishing symptoms, I found myself easily making friends and enjoying them. I looked forward to dinners, concerts and long conversations. Most of my new friends were American, but in recovery I retained several international friendships, including a few Southeast Asian roommates and friends.

One of my closest friends today is a psychologist who I met through my church. We have a mutual interest in mental health advocacy. She was also the first person to review my memoir *Mind Estranged* who was not directly involved in the editing process. I appreciate her knowledge and insight.

I also made friends with a physics graduate student at the University of Cincinnati. Over a few years, we have had many adventures together. She is compassionate, dependable and kind. When there was a death in my family, she insisted that I spend a night at her house as a guest. Then, she dropped by to see how I was doing every day for over a week. Looking back, I needed a true friend during that time, and she was important in helping me process my grief in a healthy way. I will always hold a special place in my heart for her.

I enjoy many other friendships. I have kept in touch with University of Cincinnati students who graduated with me and a roommate who shared an apartment with me for four years. On medication and in recovery, I find making friends to be more fulfilling than I ever experienced before in my life.

I am grateful for my circle of friends and cannot imagine my life without them.

In my role as a mental health advocate, when families contact me to discuss their loved one's recovery, I emphasize the vital importance of a social network. It is a key component in a successful treatment plan. Everyone needs people.

It is my earnest wish that I can be a friend to others in their journeys to recovery.

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CureSZ News

A DECADE OF DRUG DISCOVERY FOR SCHIZOPHRENIA

TAAR1 AND MUSCARINIC AGONISTS

Elizabeth Beam, MD, PhD

Jacob Ballon, MD
Stanford University, Department of Psychiatry & Behavioral Sciences

Just over a decade ago, several major pharmaceutical companies decided to abandon research and development in schizophrenia. The move was disheartening to patients and researchers alike who had repeatedly heard promises of controlling more symptoms with fewer side effects. So why did big pharma make its departure? The data had come in from a massive trial comparing *"typical"* antipsychotics, discovered serendipitously in the 1950s to *"atypical"* ones released in the 1990s after years of benchwork and trials. Little to no improvement with the *"atypicals"* could be confirmed. The investment in drugs for schizophrenia had been costly and did not pay off – that is, not yet.

In retrospect, it's not too surprising the first two classes of antipsychotics had similar efficacy. They both worked by blocking dopamine receptors. Pharmaceutical companies seemed to have run with dopamine as their target for schizophrenia the same way they ran with serotonin for depression and acetylcholine for Alzheimer's disease. Each chase for the cure was stalling. Just because a drug reduces symptoms did not mean it treated the underlying pathophysiology of disease. Imagine symptoms were a fire in the brain – a drug acting like water could douse the flames, but it wouldn't cool the hot air or stop the initial spark from reigniting.

However, the past decade has generated several promising directions for treating schizophrenia by turning to a fresh set of drug targets. Two new classes have no direct dopamine activity at all, acting instead on trace amine and muscarinic receptors. In early trials, they have shown potential to address a broader range of symptoms, including the negative and cognitive symptoms that have eluded dopamine receptor-blocking agents for decades.

Trace Amine Receptor 1 (TAAR1) Agonists.

In early 2020, news broke amid the pandemic headlines of a promising new pharmacologic approach to treat schizophrenia. TAAR1 agonists had been singled out in a search for non-dopamine-blocking drugs that reduced schizophrenia symptoms in in animal models. TAAR1 agonists have also shown in mice that they may help better regulate blood glucose levels – possibly avoiding one of the major side effects of the atypical antipsychotics. In a randomized controlled clinical trial in patients, researchers found that a specific TAAR1 agonist known as ulotaront had outperformed placebo in reducing the total PANSS score, a global measure of schizophrenia symptoms. The drug also reduced the difficult-to-treat negative symptoms of schizophrenia (a preliminary result that was not adjusted statistically for the number of tests they ran, limiting our ability draw firm conclusions). While the mechanism of this new drug remains somewhat mysterious, the idea behind it is something like putting out the spark that ignites symptoms. Ulotaront is thought to work by preventing neurons from firing in the ventral tegmental area, which serves as a starting point for dopamine along the pathway implicated in schizophrenia. In addition to ulotaront, another TAAR1 agent, this one a partial-agonist called ralmitaront, is also in development, but at an earlier stage in the process.

Muscarinic (M1/M4) Agonists

If you've ever taken diphenhydramine (Benadryl) and felt foggy afterward, you've discovered for yourself that blocking acetylcholine in the brain can have adverse cognitive effects. On the flip side, could drugs that stimulate acetylcholine receptors improve memory? This is the idea behind using agonists of muscarinic receptors, which mediate cholinergic activity to treat the cognitive symptoms of schizophrenia. Because muscarinic agonists can have unwanted side effects outside the brain (muscarinic receptors are located throughout the body and impact most organ systems), one strategy has been to pair the muscarinic agonist xanomeline which acts throughout the body, including the brain, together with the muscarinic antagonist trospium which acts only in the body but not the brain because it cannot cross the blood-brain barrier. By laying a trospium tarp from the neck down, the combination also helps ensure more xanomeline flows into the brain. The balance between the two remains a work in progress – common side effects include a mix of those related to increased cholinergic activity (nausea, vomiting) and those related to anticholinergic effects (constipation, dry mouth, blurry vision, memory loss). Another drug in the pipeline, emraclidine, acts predominantly at only one of the 5 muscarinic receptors (M4) to help minimize the risk of the full-body side effects while still improving psychotic symptoms.

You can get up-to-date information on ongoing trials for TAAR1 and muscarinic drugs by searching the clinicaltrials.gov site managed by the National Institutes of Health. It will be important to remain cautious in our optimism, remembering how the early excitement for atypical antipsychotics in the 1990s was tempered by a larger trial that compared drugs directly. For now, it is worth celebrating the shift in momentum toward innovative new mechanisms of action and drug discovery advances for schizophrenia.

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Secondary Psychosis

(continued from Page 1)

How do clinicians determine if a psychotic disorder is *"primary"* or *"secondary?"* First, the substance or medical condition must be identified. Then, the relationship between a medical condition or substance used and the psychotic symptoms should be identified. In doing so, clinicians should consider three key aspects of the patient's symptoms: atypicality, temporality and explicability.

An underlying medical cause of psychosis should be suspected if the presentation is atypical as pertains to the age of onset and the type of symptoms seen. For example, the presence of multiple types of hallucinations (auditory, visual, tactile, and olfactory) is not typical in schizophrenia and increases the likelihood of a secondary psychotic disorder such those seen in dementia or some types of epilepsy. The temporality of symptoms, or when they occur, should be considered when the psychotic symptoms follow the start of a medical illness or ingestion of a substance and resolve when the medical condition improves, or the substance is eliminated from the body. Finally, because comorbid medical illnesses are very common in people who have schizophrenia, it is important to ask if the symptoms present are best explained by a primary or a secondary psychotic disorder. For example, in a patient with a strong family history of schizophrenia in their parents and siblings, psychotic symptoms, even in the context of a co-occurring medical illness, may be most accurately explained by schizophrenia given the genetic predisposition present.

In April of 2018 the University of Cincinnati Medical Center instituted the First Episode Evaluation and Services (FEELs) program. This includes a multidisciplinary team of physicians, nurses, social workers, pharmacists, psychologists, occupational and recreational therapists who work together to rule out secondary causes of psychosis in patients within the first 2 years of symptom onset while on a psychiatry inpatient unit. This work-up includes thorough bloodwork, imaging, review of any medications taken and substances and psychological testing. This evaluation helps the treatment team to identify the most likely cause of psychosis in any given patient and guide treatment. If a medical condition is identified, clinicians who specialize in the treatment of that condition then become involved in treatment. This protocol was inspired by working with patients whose secondary psychotic disorders were not identified early on in their illness, leading to long-term negative consequences. While many academic medical centers have similar procedures there still exists a lack of awareness about the identifiable causes of secondary psychosis in many places around the world. Physicians, patients, and family members alike must be educated about these issues and advocate for standard assessment of secondary causes of psychosis to further our common goal of healing through correct diagnosis and treatment.

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VIDEO HIGHLIGHT

Schizophrenia Caregivers Initiative

CURESZ President Bethany Yeiser and Board Member Catherine Engle discuss the CURESZ Friendsz Caregivers Mentoring Initiative, then real Friendsz mentees and mentors share their personal experience with the program.

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.

"We are committed to helping individuals to cope with and recover from schizophrenia."

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