211:Early Psychosis: Detection and Treatment

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There are no conflicts of interest to report.

Guest bios:

Monica E. Calkins, PhD

Monica E. Calkins, PhD, is the HeadsUp Co-Director who oversees outreach, education, training, and Coordinated Specialty Care program evaluation and fidelity. Dr. Calkins grew up in Philadelphia, attending Philadelphia public schools and earning a bachelor's degree from Temple University. She earned a doctorate in clinical science and psychopathology research from the University of Minnesota and completed a postdoctoral fellowship at the University of Pennsylvania before joining its faculty, currently Professor of Psychology in Psychiatry. Dr. Calkins' research and clinical work focuses on early identification and intervention in psychotic disorders, and she has authored more than 200 scholarly publications in this area. Her work and mission is to improve the lives and experiences of young people with psychosis and their families.

Christian Kohler, MD

Christian Kohler, M.D., is the co-director of HeadsUp. Dr. Kohler grew up in Austria and obtained a doctorate in medicine from Innsbruck University. He completed residencies in psychiatry at Wright State University and neurology at the University of Cincinnati, and subsequently a postdoctoral fellowship at the University of Pennsylvania. Dr. Kohler has been on the faculty at the University of Pennsylvania since the late 1990s and is currently professor of psychiatry and neurology. He has participated in research on emotional processing, brain-related studies and novel treatments resulting in over 100 publications to date. Dr. Kohler has extensive experience in the treatment of severe mental illness and, in particular, of young persons with recent onset of psychosis—a challenging and rewarding area to pursue improvement in clinical symptoms and functioning.

Dan Wolf, MD, PhD

Dan Wolf, MD, PhD is the HeadsUp Telehealth Director, as well as a practicing psychiatrist and brain imager specializing in psychosis treatment and research. He completed medical and neuroscience training at Yale University, residency training in psychiatry at Harvard University, postdoctoral training in neuropsychiatry at the University of Pennsylvania, and has been a faculty member at the University of Pennsylvania since 2008.

Elisa Nelson, PhD

Dr. Elisa Nelson is a psychologist in the Psychosis Evaluation and Recovery Center (PERC) at the University of Pennsylvania (Penn). She completed her postdoctoral training in Recovery-Oriented Cognitive Therapy (CT-R) for individuals with serious mental health conditions at Penn. She has supported individuals in coordinated specialty care programs in the

early stages of psychosis for several years. She is currently researching CT-R concepts and ways this approach can be adapted to support families in this setting.

Introduction: What is early psychosis and why is it an important topic?

More common than we may think, psychosis is not an illness but a broad clinical term that embodies a range of symptoms in which our thoughts, perceptions, behaviors or feelings become disrupted. Psychosis can trigger misinterpretation or confusion when interacting with the world, which can feel disorienting and cause distress.

Psychosis is sometimes related to a serious mental health disorder, but experiences of psychosis can occur for other reasons, such as with substance use or with certain medical conditions.

Schizophrenia

Schizophrenia is one condition associated with psychosis experiences. No two people living with schizophrenia have the exact same experiences, but there are six primary categories of symptoms that people living with schizophrenia experience in some combination: (1) hallucinations—perceiving things, in any one of the five sensory modalities (hearing, seeing, tasting, smelling, touching), that other people don't hear, see and so on. In schizophrenia, auditory hallucinations such as hearing voices when no one is speaking are common, but people with schizophrenia can have other types of hallucinations as well. (2) delusions—which are very firmly held beliefs with full conviction that things are happening to the person or in the world that are not happening in reality. A person may believe that others are trying to hurt them or follow them, or that events in the world occur in reference to them (like people talking in public are talking about them). The person might also have unusual beliefs like other people can hear their thoughts, or that others are controlling their thoughts or actions against their will. (3) "negative" symptoms—include difficulties in experiencing emotions, like feeling loss of interest, pleasure, motivation, or difficulties in expressing emotions (like appearing to show no emotions on the face). (4) disorganized speech—meaning the speech lacks the typical organization we see in others. A person may go off track when talking, leading others to have trouble following what they are saying, or in extreme cases, the person may even be incoherent to others. (5) disorganized behavior—includes a range of behaviors including extremely poor hygiene, or dressing in a highly unusual manner. (6) catatonic behavior—a marked decrease in responding to the environment. A person, for example, may be mute or immobile.

These symptoms are accompanied by a significant decline in the person's ability to function—socially, jobs, school, with family—or in younger people, they can lead to challenges achieving typical functioning. In schizophrenia, at least two of the six symptoms mentioned last at least

one month, but frequently longer, with an overall duration of at least 6 months. If the symptoms do not last a minimum of six months, or the person only has one symptom that is not interfering in their life, other disorders would be considered. For a diagnosis of schizophrenia, other medical causes of the symptoms, including substance use, are ruled out.

It is important to note that the symptoms typically associated with schizophrenia can also manifest in other mental health disorders. In the DSM-5, these symptoms are addressed under a broader category called 'Schizophrenia Spectrum and Other Psychotic Disorders,' which includes conditions linked to substance use, catatonia, and psychotic disorders due to medical conditions. Moreover, psychosis symptoms such as hallucinations and delusions can also occur in mood disorders; individuals with bipolar disorder or major depressive disorder might experience these symptoms during severe mood episodes. Consequently, the presence of psychosis symptoms alone is not diagnostic of schizophrenia.

Schizophrenia affects about 1% of the population—that is 1 out of every 100 people—and approximately 4% of the population experiences the broader category of psychosis spectrum disorders. Thus, these conditions are more common than many people realize. The onset of schizophrenia usually occurs between the ages of 16 and 30, meaning that often the symptoms begin during the critical developmental period of adolescence or early adulthood. We use the term “First Episode Psychosis” (FEP) to refer to the initial onset of threshold psychosis symptoms described above.

Clinical High Risk and Attenuated Psychosis

Clinical high risk, or “attenuated psychosis,” refers to symptoms a person experiences that research has shown increase the person’s risk of developing a threshold psychosis disorder like schizophrenia. Those symptoms include what we call “subthreshold” or “attenuated” versions of the symptoms discussed above. For example, a person might start to think or wonder whether people are following them, but they are not as convinced as they would be if they have a threshold delusion. Yet, this experience is troubling and can become quite distressing or interfere with the person's school or work or social relationships. In the subthreshold form of hallucinations, a person might hear unusual sounds or whispers, but they know they are not real—the person lacks the full experience of a true perception as they would for a hallucination.

This clinical high risk stage is important for two main reasons. First, clinically, these symptoms can be very early warning signs of a person developing a psychotic disorder, so they present a real opportunity to seek clinical care before the symptoms have progressed to a much more severe level. One important thing to note here is that some people might experience these kinds of symptoms, and then the symptoms go away on their own, and some people can experience them at this low level without ever transitioning to a psychotic disorder. The challenge is that we cannot currently predict for any given individual what is going to happen. And if those symptoms do not progress, studies have shown that they still might be associated with depression, anxiety,

substance use, and poorer overall functioning. Therefore, they are still important to recognize and potentially address through clinical care. Since we cannot tell what the course of any individual's symptoms will be, or how they might impact the individual, it is important that young people are supported and encouraged to talk about their mental health experiences with trusted people—parents, teachers, primary care providers, faith leaders—and seek professional help early. Second, these early symptoms are also a window into the changes in the brain that are happening very early in the course of illness. As we will discuss in more detail below, as researchers, this gives us the opportunity to investigate those changes and ultimately develop better medications or other interventions that we hope can one day be able to improve the course of symptoms, or maybe even prevent schizophrenia and other psychotic disorders altogether.

Recovery: The Coordinated Specialty Care Treatment Model

For individuals who have experienced a first-episode of psychosis or clinical high risk symptoms, Coordinated Specialty Care (CSC) is the gold standard treatment. CSC is a recovery-oriented treatment that approaches care from a team perspective, allowing specialists and clinicians to work together to determine the best course of treatment for the patient while also enlisting the help of family and community support. It involves a dedicated multi-disciplinary team of specialists who provide case management, psychotherapy, medication management, supported employment and education, peer support, and family support and education. CSC-type interventions were first developed in Australia and Europe and have been more widely implemented in the U.S. since 2015 through support of the Substance Abuse and Mental Health Services Administration (SAMHSA). As of 2019, there are CSC programs in all 50 states.

In Pennsylvania, there are currently 17 CSC programs for first episode psychosis (FEP), including three in Philadelphia—the program at Penn, which is the Psychosis Evaluation and Recovery Center (PERC), the PEACE program, and one of the newest programs at Children’s Hospital of Philadelphia.

Our CSC programs provide services to young people who have experienced a recent first episode of psychosis (usually within the past one to two years) and generally engage young people in care for two years, some with the option to participate in step-down care after the first two years. We also have two CSC programs dedicated to youth with clinical high risk symptoms, including the PERC program at Penn, and the Hope Team at the University of Pittsburgh (a partner of Penn).

211:Early Psychosis: Detection and Treatment

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HeadsUp

This work is part of several larger efforts. In 2017, the Pennsylvania Office of Mental Health and Substance Abuse Services (OMHSAS) funded the Pennsylvania Early Intervention Center, now called HeadsUp, to provide fidelity, program evaluation, and training to support Pennsylvania CSC programs. The mission of HeadsUp is to help end the stigma around psychosis through education, advocacy and support. On the HeadsUp website, there is information and resources about early psychosis, including a locator of Pennsylvania CSC programs (Find a Center). Anyone concerned about a young person experiencing early psychosis symptoms is encouraged to reach out to HeadsUp (headsuppaorg@gmail.com) or contact a nearby program.

HeadsUp provides ongoing training and support to the FEP clinicians across Pennsylvania in implementation of Recovery-Oriented Cognitive Therapy (CT-R). CT-R is an evidence supported approach for individuals with serious mental health conditions that uses individualized strategies to support the person in activating adaptive beliefs more often. When the individual has access to this mindset they can better collaborate with their providers on ways to navigate challenges and pursue meaningful life ambitions. In addition to working with individual program participants, clinicians engage family members. Family interventions have been linked to important outcomes (i.e., increased engagement in care, increased retention in services, decreased rate of relapse, reduction in symptoms, improved family interactions) Claxton el al.,, 2017; Lucksted et al., 2016). However, a study surveying FEP family members noted that families experience hesitation about getting involved and express concern about the best strategies to support their loved one in care (Lucksted et al., 2016). To address these needs, some Pennsylvania CSC programs offer support to families in the form of CT-R-based family groups. The purpose of these groups is to empower families by sharing information and strategies and connecting families to other families for support and understanding.

The growth of CSC has been a huge advancement in the field, and many studies have now shown improved outcomes in individuals engaged in 6-24 months of CSC, compared to treatment as usual. However, a large Danish study called OPUS examined ten-year outcome data, which unfortunately did not support sustained clinical and functional improvements in individuals with CSC compared to usual care, highlighting the need for additional longer-term treatment and outcome studies. Our programs have frequently discussed the challenges of identifying post-CSC treatment options for our participants to best support them as they transition out of our CSC programs.

Finally, in the United States, CSC programs remain rare in many regions and are inaccessible to many individuals experiencing a first episode of psychosis. For example, in Pennsylvania, there are still many regions of our commonwealth not yet served. Of the programs available, only 3 are dedicated Clinical High Risk (CHR) programs. At HeadsUp, we also have an “Early Psychosis Mentor” free consultation service for Pennsylvania providers working with individuals

experiencing a first episode of psychosis (more information about this can be found on our website. We also conduct provider training to help improve competency and knowledge of providers outside the CSC programs. We hope that through such efforts, we can continue to grow the accessibility, utility, and success of early psychosis care in our region.

Identification, Screening and Referral in Early Psychosis: How to tell if someone is experiencing psychosis and what to do about it

It is not uncommon for individuals who experience psychosis symptoms to do so for some time prior to presenting for clinical care. Early symptoms are distressing and can interfere with a young person's life goals. The longer these symptoms go untreated, called the Duration of Untreated Psychosis (or DUP), the harder it may be to recover, contributing to mood symptoms and cognitive dysfunction. The World Health Organization (WHO) recommends a DUP of less than 3 months. However, the DUP in the U.S. averages between 1 and 3 years (in Pennsylvania, the average is about 1 year). This critical delay is due to multiple factors, including limited mental health literacy in the general public, societal stigma about schizophrenia, and the absence of routine or universal screening.

All individuals who come in contact with adolescents and young adults—whether personally or professionally—are in a position to observe a youth who is beginning to experience psychosis. Although relatively less common than other mental health conditions such as depression and anxiety, the consequences can be extremely significant for the individual and their family. Schizophrenia-related disorders are the most highly stigmatized and misunderstood mental health conditions around the world, meaning that young people and others might be afraid to disclose their symptoms or seek help. We, therefore, promote increased mental health literacy about psychosis to raise awareness and knowledge about what psychosis spectrum disorders are and are not.

Mental Health Stigma

Mental health stigma is a tremendous problem, not just for schizophrenia—which is highly stigmatized—but for all mental health disorders. Stigma includes prejudice (negative attitudes and emotions towards certain groups), often stemming from stereotypes (beliefs about people based on their membership in a particular group). This can lead to discrimination, which is the unfair treatment of people because of the group to which they belong. For individuals and their families, stigma can lead to embarrassment or fear of seeking help if needed, distrust of treatment providers and treatment, impacted relationships with family and friends, personal distress, low self-esteem and self-stigma. It can also exacerbate illness and lead to difficulties

with reintegration and recovery, including treatment and medication adherence, denial of symptoms, limited social contacts and fear of job/housing applications.

For society, stigma fosters misunderstanding of mental illness, including myths about the tendency of those with mental illness to be violent or dangerous, which can facilitate fear, avoidance, or rejection of those with mental illness. All of this can affect public funding for research and services for mental health disorders, as well as the legal treatment of people with mental illness. For many people in our society, the media is a main source of information about mental health, but because media portrayals are pervasive, frequently inaccurate, and contain stigmatizing elements, the media is also a primary source of the perpetuated negative public attitudes and stereotypes about mental health disorders. Even professionals and other adults in positions to help young people who are beginning to experience psychosis are exposed to these same negative media portrayals, often leading them to hold the same misinformed and stigmatizing views. Therefore, it is critically important that we advance awareness and knowledge of psychosis spectrum disorders not just in the general public, but also for professionals who interact with youth—teachers, primary care providers, faith leaders, parents, and even the mental health providers who have little prior experience with psychosis.

Screening

In a collaboration with Children's Hospital of Philadelphia, the Penn psychosis research group conducted a large study, the Philadelphia Neurodevelopmental Cohort, led by Drs. Raquel Gur and Hakon Hakonarson, where close to 10,000 young people were screened for a range of mental health conditions, including subthreshold psychosis symptoms. The study found them to be relatively common, occurring in 12% of youth aged 11-21. Yet, these symptoms are not asked about in routine clinical care. Depression, anxiety, and suicidality are now routinely screened for in youth primary care, which is a tremendous step forward for youth mental health, in general, but psychosis is generally not included for a variety of reasons. To address this, HeadsUp has developed several brief screeners specifically about subthreshold psychosis. There are several available on the clinicians' section of the HeadsUp website. The PRIME-5 is a brief 5-item screening tool that we have "age normed" so that users can know whether the experiences being reported are typical for other young people the same age. We have also developed flowchart algorithms available at that link, with separate versions customized for school professionals, primary care providers, and community mental health providers, which can be used to assist decision making in the referral process.

One of our goals, shared by others around the world, is to get the PRIME-5 screeners into primary care, into the schools, and everywhere young people are in order to get more people asking kids about these symptoms. This is especially important for young people who have historically been underserved in traditional community care for psychosis, including Black and indigenous people of color, Asian, Latinx and LGBTQ+ populations. To fill these gaps, the field advocates for increased awareness, education, psychosis screening, and to normalize asking

about and thinking about psychosis. In the end, breaking the stigma of mental illness, and its impact on young people, is an ongoing process in which we can all help. We have high hopes that one day we will talk about and approach psychosis spectrum disorders and their treatments the same way we talk about other medical conditions, like heart disease.

Psychopharmacological Considerations in Early Psychosis: Medication Management for Youth and Young Adults

General Considerations

Psychosis symptoms (hallucinations, delusions, disorganized behavior, and disorganized speech) commonly coexist with anxiety, mood symptoms, and unpredictable behavior in first episode psychosis (FEP). Therefore, multiple medications, including antipsychotics, antidepressants, and mood stabilizers are commonly used in treating young people living with FEP. In early psychosis, insight regarding the need for treatment and medication adherence are significant challenges that interfere with access to care and adequate treatment otherwise (Mervis et al., 2021). This is a sensitive time period, as delay in treatment of even a few months, and increased duration of untreated psychosis, are related to worse long-term outcomes. Early treatment adherence should be pursued by mutually identifying target symptoms to be addressed in treatment (i.e., shared decision-making). Persons living with FEP are more sensitive to antipsychotics and psychosis symptoms, and they may respond rapidly to low doses of antipsychotic medications (Kohler et al., 2022). Persons living with FEP are also more sensitive to side effects, in particular acute extrapyramidal symptoms and weight gain. Therefore, neither first-generation antipsychotics (FGAs) nor olanzapine are preferred first-line medications in FEP. Remission rates in FEP can be 60-80%, and this should be the goal of initial treatment (Lieberman et al., 1993) and the greatest rate of improvement in positive and negative symptoms is generally seen within 6 months of treatment. Efficacy of a single medication on core psychosis symptoms should be determined over 6-8 weeks of treatment at an adequate dose. Partial treatment adherence/nonadherence is very common and it is important to track medication adherence to monitor for possible pseudo-resistance to antipsychotic treatment. Once psychosis symptoms have remitted, antipsychotic medication can be decreased to a maintenance dose that is based on the individual and, after a single episode, coming off the medication after 1-2 years can be pursued. Unfortunately, many young persons stop medication prematurely resulting in psychosis relapse and the need for more long-term, if not chronic, treatment.

211:Early Psychosis: Detection and Treatment

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Long-Acting Injectables (LAIs) and Clozapine

Long-acting injectables (LAIs) were historically used in people living with chronic serious mental illness (SMI) for symptom control. Over the past 15 years, second-generation antipsychotic (SGA) LAIs have been used more commonly in younger persons. LAIs offer the promise of symptom control for persons with chronic SMI and stabilization/remission during the early course of illness in persons who experience challenges with medication adherence. Nonetheless, LAIs remain underutilized, as about 30% of individuals are nonadherent with oral medications (Lieslehto et al., 2022), and LAIs are prescribed only to 10% of individuals, which is only a third of eligible persons (Reymann et al., 2022). Reasons for underutilization include patient preference and provider preference/comfort with this form of medication. It is important to engage in shared decision-making regarding the goals of treatment and the associated risks/benefits of medications. LAIs are contraindicated in persons who refuse or who feel coerced.

Like LAIs, clozapine is also underutilized in the United States. Provider comfort in prescribing and various logistical barriers lead to wide variation in use. For example, ~5% of antipsychotic prescriptions are for clozapine in the U.S., 25% in China, and 40% in Australia (Kelly et al., 2012). In addition, there is a notable underutilization of clozapine in the U.S. Black population. Too many people end up on single medication or polypharmacy with inadequate symptom improvement. Clozapine use is indicated after 2 trials of antipsychotics at adequate dosage and duration (preferably at least one trial of risperidone or olanzapine). Clozapine has a unique set of actions on multiple neurotransmitter systems, including modulation of cholinergic activity. A combination of these incompletely understood mechanisms likely explain clozapine superior efficacy in people who do not respond to first-line treatment (often referred to as “treatment resistant”). The downside is that clozapine is cumbersome to initiate and can cause significant side effects/risks, and therefore is not indicated as first-line antipsychotic medication.

Medication Management in CSC

The Coordinated Specialty Care (CSC) model is based on a team of providers who offer individualized services to the young person living with psychosis and, ideally, their family member(s). First episode psychosis (FEP) clinics are typically located separately from mental health centers or locations that serve persons with more chronic mental illness. The dedicated team, similar to what has been developed for Assertive Community Treatment (ACT) teams in persons with chronic SMI, allows for more personalized and collaborative or synergistic interventions both in-house and in the community to pursue clinical stabilization and translation of clinical improvement to interpersonal and academic/occupational functioning. For young persons living with FEP, it is essential to pursue stabilization of functioning with the prospect of achieving expected individual milestones of independent functioning, which is critical in this phase of life. Core services that CSC teams offer to individuals include psychotherapy (CT-R for psychosis), medication management, case management, supported employment and

education, and peer support services. All members of the CSC team communicate regularly with the program participant and with other members of the care team to best support the individual living with FEP. With respect to medication management, this allows for frequent and open communication around medication side effects/adherence, and quick feedback and intervention by the prescribing team member, as warranted. It is of high importance to also provide support and information on early psychosis to families, with the aim that they can better cope, assist their loved one experiencing psychosis, decrease stigma and self-blame, and connect with other families in the same situation for support. There are typically group-based services for young persons and for parents to increase knowledge, coping skills, and decrease the sense of isolation and stigma.

Impact of Substances on the Development of Psychosis

Experimentation with psychoactive substances is common during adolescence and early adulthood. With greater public acceptance and also legalization of possession and use, (i.e., cannabis), there has been more widespread use with little knowledge regarding potential adverse consequences beyond the acute effects of being under the influence. Cannabis is the most widely used and accepted psychoactive substance in the young adult age group. It is not uncommon for persons to use cannabis on a daily basis in the form of smoking, vaping, or edibles for different purposes, be it recreational or therapeutic (e.g., to reduce anxiety). While smoking and vaping cannabis produces an immediate psychoactive effect, edibles produce a much slower onset and longer-lasting effect. The type and procurement method of cannabis also has a role in effects (e.g., street-purchased versus dispensary cannabis in regard to quality control; delta 9 THC versus CBD content which have different effects on the brain; synthetic marijuana/K2/spice and delta 8 THC). Potential contamination of street-purchased and availability of delta 8 cannabis products (which can be misleadingly labeled) are problematic. Medical marijuana is widely available and, while not indicated in the FEP population, it represents a compromise of risk mitigation (i.e., knowledge that the product does not include contamination with other drugs or additional harmful pollutants).

Current evidence indicates that early use of cannabis during adolescence is associated with earlier onset of psychosis and that frequent use is also associated with psychosis onset—meaning these psychosis episodes can remain substance-induced and limited to the period around use, but can also produce psychosis onset and enduring or relapsing symptoms. Cannabis use is not only associated with emergence psychosis, but, in those with established psychotic disorder, can increase psychosis symptoms, worsen attention and motivation, and decrease the effectiveness of antipsychotic medications and overall treatment adherence. About 20% (more in some studies) of those who are initially diagnosed with a substance-induced psychosis eventually develop a chronic psychotic disorder that persists even if individuals stop

substance use (Myran et al. 2023). Current and recent cannabis use is very common in young persons who connect with FEP programs and is estimated to be around 30-50%.

The general acceptance of cannabis use, and in light of the grave situation associated with the national opioid epidemic, emphasis on cannabis use disorder remains relatively low but is of particular importance in this population. Common approaches in the FEP population include providing evidence-based information about the risks of cannabis for the individual living with FEP, motivational interviewing about the person's appraisal of their own goals and how cannabis may interfere with these goals, and incorporation of this topic into the different modalities of CSC interventions (CT-R, medication management, peer support, etc.) to provide a uniform message from different angles. Our experience is that cannabis use declines in the first 6 months of CSC treatment. CSC teams, in general, are not equipped to intervene in severe substance use disorder, cannabis or otherwise. When faced with persistent substance use disorder that interferes with treatment and functional goals, the provider team needs to consider referral to more intense and specialized substance use treatment, such as intensive outpatient care, partial hospitalization programs, or interpersonal psychotherapy programs.

Ketamine

Ketamine is a medication that has been widely used for anesthesia induction during surgery, due to its tolerability and short duration. It is also used as a street drug ("Special K"). At higher doses, ketamine blocks glutamate activation at the N-methyl-D-aspartate (NMDA) receptor complex in the brain. While it has found a place in clinical treatment of depression, its action is similar to PCP (phencyclidine, "angel dust") and it too is associated with producing psychosis symptoms. This is of particular importance in persons with psychosis experiences, as it can worsen symptoms and decrease medication efficacy.

Psilocybin

Psilocybin is another substance that has seen increased interest in both recreational use and therapeutic application for a variety of conditions, such as depression and anxiety. Psilocybin, like other hallucinogens, stimulates the brain 5HT2A serotonin receptor which is associated with producing psychedelic effects. Newer antipsychotics block activation of this receptor, consistent with the view that hallucinogens are, in part, doing the opposite of antipsychotics. In general, clinicians treating psychosis, as well as those researching therapeutic use of ketamine and psilocybin, consider these to be contraindicated in those with psychosis symptoms, or who are at high risk for psychosis.

A Look Ahead: What's the Future of FEP Care?

While improved screening, assessment, and treatment approaches already exist, these tools require greater dissemination and implementation. Even the best existing approaches are

insufficient to meet the ongoing need, while ongoing research is seeking further innovation and improvement to address gaps in care. A major barrier is that we currently lack the ability to predict which individuals identified as at-risk for psychosis will actually go on to develop psychosis, and in those who already have psychosis we have a poor ability to predict long-term outcomes or likelihood of responding to particular treatments. Another problem is that CSC care generally only lasts for 2 years and studies suggest that the benefits are not necessarily sustained long-term. Yet, we have no means, at this time, of knowing who will need more intensive/costly sustained CSC. Currently, risk for developing schizophrenia is determined primarily on the presence of subthreshold/attenuated symptoms of psychosis. Such approaches identify a group of clinical high risk (CHR) individuals who do have markedly elevated risk (20-30-fold above the general population). However, even in this CHR group, only a minority of individuals (~20-30%) will ever develop schizophrenia or any full-blown psychotic disorder (though most remain impaired, regardless).

This creates a set of interrelated problems for the field. First, the feasibility of testing proposed interventions to prevent transition to psychosis is greatly reduced since the majority of people who might enter such clinical trials are not going to transition to psychosis. Imagine a hypothetical study of 200 individuals at CHR divided equally into treatment and placebo groups (100 per group), with a hypothetical treatment that reduced risk of transition by 10% in those who would in fact otherwise transition. If the enrolled CHR group had a 90% chance of developing psychosis without treatment, the transition/non-transition numbers would be 90/10 in the untreated group, and 81/19 in the treated group. If instead, the CHR group had a 20% risk of transition (consistent with current identification abilities), the numbers would be 20/80 in the untreated group and 18/82 in the treated group, a much smaller overall effect that is harder to detect reliably. Essentially, inclusion of individuals who will not actually develop psychosis in prevention studies dilutes any prevention effect. (This also exposes will-not-convert individuals to risks without benefit, though that is not necessarily the case if focus is on outcomes other than transition.) This means that our inability to identify very high risk groups leads to a requirement for very large sample sizes in clinical trials, which makes these studies much more difficult and expensive to conduct and, thus, less likely to be undertaken.

The lack of efficacious preventative treatments, in turn, complicates the pragmatics and ethics of screening for CHR. Potential distress and stigma associated with being identified as CHR are harder to justify if this identification does not lead to improved outcomes as a result of effective treatment. Better risk stratification and trajectory prediction can also help lead to stepped/targeted care, focusing the least intensive or risky approaches on those at lower risk, and escalating for those at higher risk.

Therefore, a major focus of ongoing research is to identify “biomarkers”—measures that capture variation in biological factors such as genetics, hormones, brain function and brain structure—which might help improve risk prediction. A group at the Penn led an early effort to examine markers of psychosis risk in the general youth population, called the Philadelphia

Monica E. Calkins, PhD, Christian Kohler, MD, Dan Wolf, MD, PhD, Elisa Nelson, PhD, Joanie Burns, DNP, David Puder, MD

Neurodevelopmental Cohort (referenced above), which identified clinical, cognitive, and imaging phenotypes in at-risk youth that were similar (though less severe) to those seen in schizophrenia. The North American Prodrome Longitudinal Study (NAPLS) brought together a consortium of CHR sites beginning in 2003, with a second phase (NAPLS2) beginning in 2008, and a third phase (NAPLS3) enrolling from 2015-2020. Data was collected from hundreds of individuals at CHR as well as control participants. Analysis of this data is ongoing. One major result of the NAPLS effort has been the development, validation, and dissemination of a risk calculator for transition to threshold psychosis in those already identified as at CHR. This calculator is currently based on factors which correlate to increased risk, such as more severe subthreshold positive symptoms, greater functional decline, lower cognition, younger age, more adverse life events, and positive family history of psychosis. The Penn psychosis research group, and others, have replicated the validity of this calculator, and Penn developed its own version from the community-based Philadelphia Developmental Cohort (Moore et al., 2022).

While this represents clear progress, the accuracy of such calculators is not yet high enough for clinical use, though they may already be useful for stratification in research studies. However, a tradeoff in any risk stratification is that the highest risk group is also the least common risk group, so that defining a risk group based on a very high risk threshold reduces the prevalence and hence the positive predictive value of this cutoff or “test.” It also reduces the proportion of those ultimately converting to psychosis who can be identified (sensitivity) which impacts utility and generalizability. NAPLS has also identified biological phenotypes (biomarkers) linked to higher conversion risk, including more rapid reduction in cortical thickness, higher cortisol, reduced evoked potentials (e.g., mismatch negative on EEG, visual evoked potentials), and higher polygenic risk score for schizophrenia. More rapidly declining cortical thickness, in turn, is related to elevations of inflammatory cytokines, and thalamo-cortical dysconnectivity in resting state fMRI, showing the promise for “branching out” from individual biomarkers to a broader understanding of pathophysiology and risk.

Personalised Prognostic Tools for Early Psychosis Management (PRONIA) is another multi-site effort, based in Europe and Australia, which enrolled participants (approximately 300 per group) from 2014-2019 across four groups including CHR, recent-onset psychosis, recent-onset depression, controls, with follow up to 1.5 years. PRONIA analysis is ongoing, and the main published results focus on identifying heterogeneity within and across these groups with respect to clinical, cognitive, and structural imaging phenotypes (Koutsouleris et al., 2021), with less focus to date on predicting transition.

These efforts have now set the stage for the recently begun Accelerating Medicines Partnership-Schizophrenia (AMP-SCZ) effort, which Penn is part of and currently enrolling participants. More definitive testing of the potential biomarkers found in the NAPLS study, as well as identification of other potential biomarkers, requires the application of multivariable statistical and machine learning models in large numbers of participants. AMP-SCZ is investing roughly $100 million over 5 years aiming to study over 1500 individuals at CHR for psychosis

and over 500 control participants across more than 40 sites, 13 countries, and 4 continents. This study is collecting a battery of biomarkers at baseline and 2 months, with further clinical and cognitive follow-up over 2 years. These include MRI for brain structure and function, EEG for brain activity, saliva for stress hormones, blood for genetics and inflammatory cytokines, audio and video recordings for speech and facial expression analysis, and longitudinal assessment of cognition and symptoms as well as smartphone measures of sleep, activity and experience surveys. This massive undertaking involves a collaboration between the National Institute of Mental Health (NIMH), the U.S. and European regulatory agencies (FDA and EMA), pharmaceutical companies (BI, Janssen, Otsuka), and nonprofit organizations (NAMI, APA, OneMind, Schizophrenia & Psychosis Action Alliance, Wellcome). In addition to identifying biomarkers predicting outcomes in those at risk for psychosis, AMP-SCZ is building the complex collaborative infrastructures needed for conducting CHR treatment and prevention studies incorporating these biomarkers. The first wave of proposals for this intervention work are already being considered and are expected to begin in the next year.

Early Psychosis Intervention Network (EPINET)

Finally, we want to highlight another major effort to improve early psychosis care that the group at Penn is part of called the Early Psychosis Intervention Network (EPINET). EPINET, funded by NIMH in 2019, brings together over 100 early psychosis clinics organized around 8 regional hubs now covering 17 U.S. states. In 2020, the PA programs joined with Maryland programs as a regional EPINET hub, called the Connection Learning Healthcare System. The mission of the hub is to engage patients and other stakeholders in a learning culture, using data to improve practice and identify areas of improvement, and to rapidly translate that knowledge into practice throughout Pennsylvania and Maryland. National EPINET forms a Learning Health System (LHS), meaning a care system that is capable of integrating internal and external data in an ongoing and iterative fashion to optimize outcomes. All of the psychosis clinics in EPINET collect a set of standard clinical measures using uniform methods. EPINET brings together clients and their families, clinicians, health care administrators, and scientific experts into an integrated data sharing and analysis framework to drive continuous collaborative learning and quality improvement for those experiencing early psychosis, and their families.

AMP-SCZ and EPINET are just the beginning. Looking further ahead, we can envision a future when the combination of clinical and biological assessments will provide highly accurate risk predictions, leading to stratified entry into targeted clinical trials and to stepped and targeted care in the context of a learning health care system that employs ongoing assessment and modification of care algorithms. This will require major improvements in scientific knowledge as well as systems of care, derived from work that will build on what is now underway.

Monica E. Calkins, PhD, Christian Kohler, MD, Dan Wolf, MD, PhD, Elisa Nelson, PhD, Joanie Burns, DNP, David Puder, MD

Conclusion

Experiences of psychosis are common. When these experiences lead to interference in achieving life goals and/or distress, individuals can benefit from seeking evidenced-based care. The gold-standard treatment for young people (~16-30) experiencing psychosis is the Coordinated Specialty Care model, which provides a wide array of integrated services in one location for ~2 years. The earlier individuals experiencing psychosis come to treatment, the better the outcomes. We are all allies in connecting these young people to care and services. Recovery is possible—people living with psychosis experiences can lead full, meaningful, and fulfilling lives.

Resources:

Accelerating Medicines Partnership-Schizophrenia (AMP-SCZ): www.ampscz.org

Cannabis and Psychosis Fact Sheet: https://medicine.yale.edu/psychiatry/step/early-intervention-services/cannabis%20use%20and%20psychosis_380524_284_53825_v2.pdf

Counterpoint. Early intervention for psychosis risk syndromes: Minimizing risk and maximizing benefit: https://pubmed.ncbi.nlm.nih.gov/32402605/

Development of the PSYCHS: Positive Symptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS: https://pubmed.ncbi.nlm.nih.gov/37641537/

Early Psychosis Intervention Network (EPINET) https://nationalepinet.org/

Find a Center: https://headsup-pa.org/find-a-center/

HeadsUp: https://headsup-pa.org/

Instagram: https://www.instagram.com/headsuppa/ ; @HeadsUpPA

LinkedIn: https://www.linkedin.com/company/headsup-pa/

Main email address: headsuppaorg@gmail.com

Prediction and Prevention in the Clinical High-Risk for Psychosis Paradigm: A Review of the Current Status and Recommendations for Future Directions of Inquiry: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.770774/full

211:Early Psychosis: Detection and Treatment

Monica E. Calkins, PhD, Christian Kohler, MD, Dan Wolf, MD, PhD, Elisa Nelson, PhD, Joanie Burns, DNP, David Puder, MD

Prediction Tool for Individual Outcome Trajectories Across the Next Year in First-Episode Psychosis in Coordinated Specialty Care: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9631229/

Predictors of transition in patients with clinical high risk for psychosis: an umbrella review: https://pubmed.ncbi.nlm.nih.gov/37640731/

Recommended Treatment For Psychotic Episodes Often Stymied By Insurance, Fragmented Mental Health System: https://www.npr.org/sections/health-shots/2024/01/02/1221097477/it-keeps-people-with-schizophrenia-in-school-and-on-the-job-why-wont-insurance-p

X (formerlyTwitter): https://twitter.com/HeadsUpPAorg; @HeadsUpPAorg

YouTube: https://www.youtube.com/channel/UCxqqq5NWJRbXiy6dH4aZ8mg; @HeadsUp PA

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211:Early Psychosis: Detection and Treatment

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211:Early Psychosis: Detection and Treatment

Monica E. Calkins, PhD, Christian Kohler, MD, Dan Wolf, MD, PhD, Elisa Nelson, PhD, Joanie Burns, DNP, David Puder, MD

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