

The COVID-19 Pandemic Introduces Diagnostic and Treatment Planning Complexity for Individuals at Clinical High Risk for Psychosis

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COVID-19 has led to a great deal of general suffering and an increased prevalence of psychiatric illness worldwide. Within the area of psychosis-risk syndromes, a highly heterogeneous clinical population, the picture is quite nuanced as the social restrictions resulting from the pandemic have reduced stress for some and increased it for others. Further, a number of pandemic-related societal and cultural changes have obfuscated the diagnostic and treatment landscape in this area as well. In this opinion article, we describe several prototypical cases, representative of presentations seen in our clinical high-risk (CHR) research programs. The cases highlight considerable clinical variability and, in addition, speak to the current complexities faced by diagnosticians and treatment providers. In addition to discussing these issues, this piece introduces potential solutions highlighting the promise of incorporating data-driven strategies to identify more homogenous CHR subtypes and employ precision medicine.

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The COVID-19 pandemic has dramatically altered daily life for most people around the globe. In addition to the burden of physical symptoms that can range from mild to deadly, we are learning that there are also serious implications for mental health. Within the past year, there have been numerous case reports on the association between COVID-19 and the emergence of psychosis and several empirical reports showing worsening symptoms of psychosis in the general population or those with diagnosed psychotic disorders.^{1–11} The effects of the pandemic on psychosis-risk syndromes are less clear. Given

that chronic stress and social isolation are known to increase the risk for conversion¹² and these are worsening during the pandemic, it is logical to expect that psychosis risk may be increasing throughout the world currently. However, the attenuated psychosis syndrome is clinically and etiologically heterogeneous¹³ and what might serve as a risk factor for some with prodromal syndromes (eg, increased loneliness and social disconnection) could even be a protective factor for others (eg, decreasing the frequency of stressful social interactions and exposure to psychosis inducing environmental cues). Developing a clearer understanding of the effects of the COVID-19 pandemic on trajectories of clinical outcomes during and after the pandemic is of considerable clinical importance, as it will guide more focused risk assessment and prevention/intervention efforts over coming years and offer a window for better understanding etiological mechanisms of psychosis.

In this *Translation* opinion article, we highlight clinical profiles we have been observing within our 3 clinical high-risk early identification and prevention programs during the pandemic and reflect upon issues related to early identification and diagnosis of these profiles during the COVID-19 pandemic. We also discuss these case examples to illustrate the considerable potential of employing statistically derived subgrouping to inform individualized medicine practices in this context.

Several notable patterns have emerged when working with psychosis-risk patients and research participants during the COVID-19 pandemic. Specifically, we have noticed that there are widely divergent responses as well as subsequent impacts on clinical phenomenology and course. This is very much in line with a growing consensus that clinical heterogeneity among psychosis-risk

syndromes is the rule and not the exception, and that it remains a substantial barrier to the progression of this field.¹² As noted, COVID-related stress, social isolation, and existential crises have apparently exacerbated positive, negative, and general psychopathology in some cases.^{2-6,8-11} In our own clinics we have observed that the increased reliance on digital technologies for social communication and information access during the pandemic has also exacerbated emerging suspiciousness, ideas of reference, anxiety, depression, and internalized stigma. Multiple environmental factors may therefore be interacting to increase psychopathology and risk for conversion.

However, some individuals meeting the criteria for a psychosis-risk syndrome appear to be thriving; social isolation may serve as a buffer for those with pronounced distress during social interactions or those whose delusions or hallucinations are triggered by social cues in the environment (eg, ideas of reference, persecution, mind reading). Though the reasons behind this are still not entirely clear, there are a number of plausible explanations for this observation. Before the pandemic, adolescents and young adults experiencing common psychosis-risk symptoms that impact social functioning (eg, social anxiety, attenuated delusions, asociality, anhedonia), may have felt pressure to engage in unwanted social and role activities or experienced marked distress when doing so. Social stressors may be particularly salient in this population, as the adolescent and young-adult period is characterized by greater demands for social engagement, increasingly dynamic and complex social skills, relationships, and occupational pursuits that set the stage for the subsequent life course.^{14,15} However, during the COVID-19 pandemic, when quarantine and social distancing have become the norm, some individuals who meet CHR criteria have reported feeling the pressure or related distress to be dramatically reduced. Others who experienced reduced social activity prior to the pandemic due to apathy (ie, lack of interest) appear relatively unaffected by the pandemic—their daily social and role behaviors have been minimally changed since before the pandemic. Asociality may be increasing due to reduced opportunity for social contact, but these individuals do not exhibit a global worsening in negative symptoms and functioning remains comparable to prepandemic levels.⁸

In the context of assessment and treatment planning/evaluation, we will need to reset the benchmarks we use to track participant-initiated interactions with friends, exercise, and engagement with group activities in the classroom or at work. The “new” normative reduction in social interactions is also playing havoc with the way we conceptualize and track what is “normal” social and academic/role behavior. This issue makes anchors used in current negative symptom and social/role function scales less appropriate for the current context since they are referenced to the general population during nonpandemic

times; they must be interpreted with caution and comparisons to prepandemic times may be inaccurate, with social impairments being artificially inflated in pandemic ratings. Confusion in assessment may also impact prediction. For example, in the NAPLS2 risk calculator,¹⁶ the severity of “unusual thought content/delusional ideas” and “suspiciousness/persecutory ideas” are highly weighted in predicting conversion and the predictive power of the severity of these symptoms may change if a reliable and valid assessment is difficult to achieve as a result of social distancing during the pandemic.

These types of issues provide a helpful backdrop for considering the potential clinical utility of employing latent class and cluster analysis analytic approaches to identify more homogenous subgroups of clinical high-risk patients. Generally speaking, these approaches use iterative methods to calculate solutions that maximize within-group similarity while simultaneously maximizing between-group differences on whichever indicators are entered into the model. Here, the models are flexible and can accommodate a wide range of biological, behavioral, and clinical information. This approach has been applied to psychosis-risk syndromes and proved promising.¹⁷⁻²⁰ For example, Ryan et al.¹⁸ applied cluster analysis to domains of attenuated symptoms using the NAPLS1 and NAPLS2 datasets and found evidence for 3 distinct subgroups that replicated across datasets. Critically, the clusters had distinct demographic profiles (eg, one subgroup was more likely to be female), levels of genetic loading (a greater number of affected first-degree relatives was observed in another group), and rates of conversion (one group had a trend toward higher levels of conversion). These data-driven subtypes may provide a useful heuristic for clinicians to conceptualize heterogeneous clinical high-risk cases that are differentially impacted by the pandemic.

While there have not yet been the types of empirical studies needed to provide the requisite level of confidence necessary for clinical decision making, the COVID-19 pandemic and related complications provide an excellent framework for illustrating how latent classification analysis approaches may prove to be invaluable in gauging the impact of the COVID-10 pandemic on phenomenology and treatment planning. This approach may be particularly useful when combining them with existing structured interviewing instruments and weighing the subsequent information in light of clinical inference tools (eg, attention to base-rates²¹). For example, the method may be useful for determining the relative predictive power of various symptoms in the risk of ultimate transition to psychosis. Consider a hypothetical case where a patient has reported a significant drop in regular bathing or putting on new clothes in the past several months. Is this someone who might be at heightened risk for a progressive illness or transitioning to formal psychosis? How does a provider weigh what in nonpandemic times would be a clear sign

Table 1. Clinical subtypes may provide invaluable clues for assessment, prediction, and treatment planning when working with psychosis-risk syndrome individuals and the related challenges during the COVID-19 pandemic

Prototype clinical presentation(s)	COVID-19/quarantine-related issue and clinical quandaries	Relevant subtype	Subtype clarity contributions	Citation
<p>Case 1: An adolescent male patient treated for a CHR syndrome is able to attend remote tele-psychiatry sessions regularly, communicates clearly, and has been shown stable attenuated positive symptoms. But recently, the patient endorsed a decrease in hygiene, indicating behaviors of now showering only every other week, and not consistently wearing clean clothes for his remote classes.</p>	<p>During the pandemic, cultural norms about dressing, as well as other aspects of hygiene, have shifted.</p> <p>Risk for conversion question: A decline in self-care can be a sign of emerging psychosis, particularly in an adolescent. Should this case be prioritized for more intensive intervention at a time when resources are limited as caseloads increase?</p>	<p><i>Impaired Hygiene Subtype</i></p>	<p>In the NAPLS 1 sample, 11% of CHR participants showed poor hygiene as a defining symptom. This patient likely meets for the subtype as it is also defined by an intact communication ability such as staying on track and participating in give and take (those in this group scored among the lowest on disorganized communication). This is also consistent with the biological sex of the participant (which is more frequent in this subgroup than others). This has relevance to the clinical quandary, as although deteriorating hygiene is an important risk indicator in and of itself, trend level findings indicate that the specific hygiene subtype is at lower odds of transition than other prominent clinical subtypes among those with CHR syndromes.</p>	<p>Ryan et al.¹⁷</p>
<p>Case 2: A patient successfully treated for Major Depressive Disorder is now in partial remission. However, a few months into the pandemic, the patient began sharing a theory that the government invented the pandemic because masses would eventually be susceptible to taking a vaccine that had mind-control properties.</p>	<p>This theory is widely circulated on the Internet, and it is possible the patient participates in sub-cultures where this is a commonly held view.</p> <p>Diagnostic question: What is the likelihood of a psychosis-risk syndrome diagnosis here?</p>	<p><i>Odd and Euthymic Subtype</i></p>	<p>Truly bizarre ideations are rare in the psychosis-risk stage (occurring more often in formal psychosis), but these symptoms can happen—albeit at an attenuated level. In the NAPLS 2 sample, 5% of 737 participants that fell into a subgroup defined by the marked presence of bizarre symptoms. So, the patient may be a candidate for this group. However, the other defining feature of the empirically derived subgroup is a lack of apparent distress. So, this patient would not meet criteria for this subgroup as this person indicated high levels of distress.</p>	<p>Ryan et al.¹⁷</p>

Table 1. Continued

Prototype clinical presentation(s)	COVID-19/quarantine-related issue and clinical quandaries	Relevant subtype	Subtype clarity contributions	Citation
<p>Case 3: A patient diagnosed with a psychosis-risk syndrome attends a treatment planning meeting and endorses significant avolition. She has indicated she does not have time (she is looking for a new job) or resources (she was waiting tables and her restaurant is shut down, and her health insurance is canceled) to dedicate to anything but the most “essential” treatments. While it is clear she is not formally psychotic, it is difficult to get a full clinical picture of comorbidities or other clinically relevant factors.</p>	<p>The patient is suffering from significant avolition and has limited time and financial resources (particularly due to COVID-19 related lay-offs). The patient is very hesitant to travel for treatment given she relies on public transportation (COVID-restrictions have limited the number of seats and her local municipal guidelines have discouraged non-essential travel).</p>	<p><i>Volition Subtype</i></p>	<p>This would lend weight to the possibility that this patient is developing ideas that are “normative” in sub-cultures in the anti-vaccine/conspiracy culture movement. Of course, it is always possible that a person can experience bizarre symptoms without falling into a subgroup, and referral for a more formal structured assessment would also be indicated).</p>	<p>Gupta et al.¹⁹</p>

of decompensation, when a large proportion of the population is now working from home/not leaving the home, and hygiene norms have changed? Table 1 highlights this prototypical case in more detail and provides information about how the use of empirically derived subtypes might guide decision-making during a difficult clinical quandary. The method can also yield clues for diagnosis. For example, consider a long-standing patient, treated for depression, who has begun to express a seemingly bizarre delusion during the pandemic. How do you determine if the person might meet the criteria for a psychosis-risk syndrome when a large subgroup of the general population is also espousing and acting upon similar illogical views on the Internet? Here again, the table highlights how subtyping can be highly informative. This method is also relevant for treatment planning. Given both time and financial resources are limited during the pandemic and traveling to in-person options might be dangerous or impossible, how can a provider predict behaviors and anticipate prognosis in a way that maximizes limited resources but has the greatest chance for impact? The table describes a third prototypical case where a new clinical high-risk patient is showing avolition as a primary clinical feature during a treatment planning session.

While these vignettes describe hypothetical cases informed by clinical observations, the type of data necessary for informing true translational applications is not far off. Indeed, this information is currently being collected in a number of ongoing psychosis-risk syndrome studies, continuing remotely during pandemic.^{22–24} There are many promising directions investigators can take to tailor the modeling to the COVID-19 pandemic, or future disasters as well. For example, studies might use the type of symptom or biological variables noted above, but also include new factors such as the degree of change in pre–post COVID-19 symptoms and behaviors, pandemic-related distress (eg, hardships relating to the loss of a loved one, loss of job), COVID-19 exposure, etc. Further, while highly disruptive, the pandemic has also led to situations that catalyze innovations and drive progress. For example, some of our patients and participants are frightened to travel, cannot travel, or have been mandated not to travel; provider time and availability are taxed to its most extreme. But in response to these challenges, tele-psychotherapy for psychosis-risk syndromes, an area that until now has seen precious little development, now shows promise.²⁵

We are now moving into a period where the quarantine restrictions are being lifted and in-person social and work activities are returning. These patients and participants will be challenged with an entirely new set of obstacles and opportunities as well. In addition, it is also clear that there is a palpable risk of new pandemic surges. During the coming years, clinicians and researchers alike will be faced with the challenge of providing services and understanding clinical risk in a

shifting landscape. A move toward embracing heterogeneity and modeling complexity of this unique clinical population can only serve to help us to succeed in these endeavors in the years ahead.

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