Ethical Implications for Clinical Practice and Future Research in "At Risk" Individuals

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Abstract

The last 15 years have witnessed a shift in schizophrenia research with increasing interest in earlier stages of illness with the hope of early intervention and ultimately prevention of psychotic illness. Large-scale longitudinal studies have identified clinical and biological risk factors associated with increased risk of psychotic conversion, which together with symptomatic and demographic risk factors may improve the power of prediction algorithms for psychotic transition. Despite these advances, 45–70% of at risk subjects in most samples do not convert to frank psychosis, but continue to function well below their age matched counterparts. The issue is of utmost importance in light of the upcoming DSM-V and the possible inclusion of the attenuated psychotic symptoms syndrome (APSS) diagnosis, with clinical and ethical implications. Clinical considerations include feasibility of reliably diagnosing the at risk state in non-academic medical centers, variable psychotic conversion rates, a non-uniform definition of conversion and extensive debate about treatment for individuals with an ill-defined outcome. On the ethical side, diagnosing APSS could lead to unnecessary prescribing of antipsychotics with long-term deleterious consequences, slow research by providing a false sense of comfort in the diagnosis, and have psychosocial implications for those who receive a diagnosis. Thus it may be prudent to engage at risk populations early and to use broad-spectrum treatments with low risk benefit ratios to relieve functional impairments, while simultaneously studying all subsets of the at risk population.

Keywords

Prodromal; Ethics; Nonconverters; DSM-V; At Risk; Schizophrenia

BACKGROUND

The last 15 years have witnessed a shift in schizophrenia research with increasing interest in earlier stages of illness. The focus on early psychosis was precipitated by the finding that

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longer duration of untreated psychosis is correlated with poor outcomes, poor response to antipsychotics, higher symptom burden, depression and poor functional outcomes [1–3].

Therefore, researchers in the field began to study the period of time just prior to onset of frank psychosis. The terms "ultra high risk"," clinically high risk" or "at risk" were used to describe subjects at imminent risk of developing a psychotic disorder, and the era of longitudinal studies to identify risk factors for conversion to psychosis began [4–7]. Even at the earliest stages of research, investigators recognized that studying the pre-psychosis or prodromal period has important ethical implications [8, 9]. What is an optimal definition of being "at risk", how would having a label impact the subject, and would there be future problems related to insurability? Concerns about low or variable psychotic transition rates, treating false positive cases with medications with long-term adverse effects, and conversely, treating false negatives with placebo were raised. On the whole, it was felt that treating younger, less symptomatic patients increased potential negative impact on the individual's life [9]. The question of confidentiality and informed consent became even more problematic for younger subjects, some as young as 12 or 13 years old. It was also recognized that an exit strategy was needed (if and when to stop treatment) [10, 11].

The initial focus of prodromal studies was to validate the at risk criteria and to characterize the subset of patients who progressed to a frank psychotic illness. In this regard, initial studies showed variable rates of conversion ranging from 10% to 70% depending on the sample size, inclusion criteria and length of follow-up[5, 12–15]. In more recent, large scale, multi-center studies, the rates of conversion are closer to 30% over a 2 – 3 year period [16–19]. Thus, substantial efforts have been devoted to identify specific factors to improve the sensitivity of the current at risk criteria.

Clinical and demographic variables associated with increased risk of psychotic transition include pre-morbid functional status [5, 20–22], family history of psychosis, severity of specific attenuated psychotic symptoms [5, 23, 24] (disorganized thoughts, suspiciousness, and referential thoughts), co-morbid depression [23, 25, 26], and substance abuse [5, 27]. The NAPLS (North American Prodrome Longitudinal Studies) Consortium found that of 291 at risk subjects, 35% became psychotic within 2.5 years, but those with delusional-like experiences, decline in social functioning, family history of psychosis and/or drug abuse were most likely to convert to psychosis. A combination of any 3 of these criteria increased the positive predictive power to 80%, suggesting that it may be possible to develop an "at risk algorithm" that can be used to identify those at highest risk [5]. Interestingly, a recent decline in functional status is not only a risk factor for later conversion to psychosis but recent reports show the persistence of functional deficits even in those individuals who do not develop a psychotic episode [28].

WHAT ABOUT THE NONCONVERTERS?

The vast majority of at risk individuals do not convert to psychosis, yet there is evidence of deficits in global functioning within that group. Emerging findings of persistent functional abnormalities in those at risk individuals who do not convert highlights the importance of focusing on the "false positive" sample who never develops a psychotic illness, a group that

has been poorly characterized in most studies. In fact, little is known about the natural course of illness in the "nonconverters". Some questions to consider include 1) Do most of the nonconverters continue to maintain the at risk state or convert to other illnesses, such as affective or anxiety disorders? 2) Is there a subset of patients who remit and no longer meet criteria for the at risk state? 3) What factors, if any lead to remission or prevention of progression to psychosis? Exploring answers to these and other related questions has the potential to provide a richer understanding of both disease promoting and disease preventing factors, not just in psychosis, but other illnesses as well.

Thus, we briefly reviewed the literature with a focus on non-converters in studies of at risk populations. In addition we have summarized findings of vulnerability markers in the prodrome to highlight the significance and contribution of neurobiological markers in understanding the pathophysiology of the disorder, its treatment and implications for prevention. Finally, we attempt to provide a bigger picture of the schizophrenia prodrome by inter-weaving current knowledge of conversion rates and neurobiological markers and their clinical and ethical implications. Thus we provide some of the arguments for and against the inclusion of such a disorder in the DSM-V, and some of the ethical and practical implications. This is especially timely with a new revision of the Diagnostic and Statistical Manual of Psychiatric disorders on the horizon, and renewed interest in including the "at risk" state as a diagnosis.

Seven longitudinal studies have been conducted in the last decade that provide follow-up information on the status of at risk subjects who do not convert to psychosis in their samples [12, 13, 15, 32–35]. We examined these studies and focused on the non-converted subset of patients. Conversion rates and characterization of that subset of patients has been presented in numerous reviews [36, 37] previously.

We previously reported[12] one-year outcomes on a sample of 50 subjects, 10 (20%) of whom were lost to follow-up. Of the remaining 40 subjects, 6 (15%) converted to psychosis 20 (50%) continued to meet at risk criteria, 6 (15%) no longer met at risk criteria and 8 (20%) had not converted but their at risk status was unknown because they were assessed by phone interview. Although 6 subjects no longer met the at risk criteria at follow-up interview, 3 had an Axis I mood disorder (Bipolar Disorder, Major Depression), 1 had a diagnosis of Attention Deficit Disorder that had been present at baseline and 2 had no Axis I disorder at follow-up. One subject without a clear Axis I disorder at follow-up had intermittently met "at risk criteria" throughout the year and had not received pharmacologic treatment. The other 5 subjects who no longer met at risk criteria had been on psychotropic medication (e.g., antidepressant or mood stabilizer) during the last year, including 1 subject who had been on an antipsychotic since entry into the study. Based on our assessments, it is difficult to state that any of our subjects had truly "remitted" given that all but one was receiving psychotropic medication.

Klosterkotter's *et al.*'s [13] original study began with 385 subjects, but only 160 were available for follow-up. Of the 160 subjects, 79 (49%) converted to psychosis and met criteria for the diagnosis of schizophrenia, paranoid type, with mean transition time of 4.3 years and 6.7 years in women and men, respectively. Of the patients who did not develop

schizophrenia, 48 (30%) continued to meet at risk criteria, whereas 33 (21%) had complete resolution of their initial symptoms. Within the group that achieved remission, subjects either remitted within weeks of initial presentation, or after several fluctuations in symptoms, although their treatment status was not discussed.

Similarly, in Miller *et al.*'s [36] validity study, 13 subjects who met at risk criteria (12 subjects had attenuated positive symptoms and one had brief intermittent psychotic syndrome) were followed over 12 months. Seven subjects (54%) developed psychosis, 4 (31%) continued to meet at risk criteria and 2 (15%) subjects had remission of symptoms. The authors noted that none of the subjects in the non-converted group were on antipsychotic medications during the follow-up period.

In Lencz. *et al.*'s study [31], 42 subjects who met at risk criteria were initially enrolled. Of these subjects, 34 were available for mean follow-up of 24.7 (+15.9) months. Nine subjects (26.5%) converted to psychosis. Of the 25 subjects (74%) who did not convert, 12 (35.3% of the outcome sample) continued to meet at risk criteria. The authors noted that 4 of the subjects in the non-converted group experienced remission of positive symptoms for a time before returning to baseline. The remaining 13 (38.2%) experienced remission of attenuated positive symptoms, although use of antipsychotics in this group was not discussed.

Mason *et al* [15] enrolled 130 subjects, and reported on a subset (n=74) that had completed follow-up assessments by a predetermined date. The mean follow-up period was 26.3 months (±9.2). Some patients received psychotropics other than antipsychotics, unless they converted to psychosis, and many received psychosocial interventions. Thirty-seven (50%) subjects converted to psychosis 20 (27%) had no diagnosis, 16 (18%) had other non-psychotic diagnoses (mainly depression), and 4 (5%) had other disorders. The authors did not report whether non-converted subjects continued to meet at risk criteria, or if any subjects achieved remission.

Yung *et al.* [33] reported on a sample of 104 subjects. None of the subjects received antipsychotics; however, subjects were permitted to receive other psychotropic medications and/or psychosocial interventions at their discretion. In total, 41/104 (39.4%) subjects converted to psychosis. Of the remaining 68 (65%) subjects, 30 (29%) had no diagnosis at 12 months, 31 (30%) had other non-psychotic diagnoses (mainly mood and anxiety disorders) and 7 (7%) cases known to be not psychotic at 12 months were missing a final diagnosis. The authors did not report whether non-converted subjects continued to meet at risk criteria, or if any subjects achieved remission.

More recently, Addington *et al.* [28], focused exclusively on the non-converters within the NAPLS dataset, who did not receive antipsychotics at any time during the study. During one year of follow-up, the 111 "non-converters" showed significant improvements in negative and positive symptoms. However, nearly half the subjects continued to experience at least one positive attenuated symptom, and all subjects showed significantly reduced social and role function compared to normal controls [28].

To summarize, non-conversion rates range between 45–70% in most studies. The group of non-converters is comprised of subjects who continue to meet at risk criteria, may have

converted to other non-psychotic disorders, or achieved remission of presenting symptoms. However, since most studies use naturalistic treatment, the effects of treatment on outcomes are not well described. It is often unclear whether subjects in remission are on antipsychotic or other psychotropic medications, or what non-pharmacologic interventions have been instituted. One is also left wondering whether there are "protective factors" that facilitate remission in a subset of patients. For instance, are certain clinical and demographic variables, and biomarkers, associated with a milder course of illness? Or does the sample represent true false positives? Improving our understanding of the subset of patients that undergo remission may shed light on the pathophysiology of psychotic transition.

The fact that at risk subjects go on to develop other non-psychotic syndromes including mood, anxiety and substance use disorders, speaks to the need for large longitudinal studies, with extensive follow-up of all subjects to determine risk for specific outcomes. A recent report by Cornblatt and colleagues [37], for example, suggests that the prodrome for bipolar disorder is identical and indistinguishable from the schizophrenia prodrome. It is plausible that the at risk state represents a developmental stage of heightened neural restructuring, a process that coupled with a vulnerable brain, allows the expression of multiple disease phenotypes, including disorders of cognition, mood, or anxiety. Perhaps, the phenotype expressed depends on the degree of damage inflicted on a particular neural network [38]. In such a conceptualization, syndromes may be thought of as a collection of differentially impaired neural networks. Therefore, a predominantly psychotic transition with some mood features, or a predominantly mood disorder transition with some psychotic features, may be quantitative differences in impairment in respective neural networks, rather than unrelated disease processes. In fact, this approach is in line with the recent NIMH Research Domain Criteria Project (RDoC), which suggests that psychiatric diagnoses be based on observable behavior and neurobiological measures, rather than phenomenology, in an effort to bridge the gap between neurobiological research and diagnoses [38].

VULNERABILITY MARKERS IN THE STUDY OF THE PRODROME

Several lines of evidence suggest that pathogenic processes in schizophrenia are active for many years during the vulnerable period when the brain is still developing, before the onset of the florid psychiatric illness [41, 42]. The prevailing neurodevelopmental hypotheses suggest that environmental insults, in combination with a genetic predisposition to abnormalities of early brain development, produce the neuronal phenotype that manifests as schizophrenia. One way to assess this proposed vulnerability in an at risk population is by assessing measures of brain function that are shown to be abnormal in patients with chronic disease. In this regard, schizophrenia patients, their unaffected relatives, schizotypal subjects and subjects at risk for psychosis have been shown to have deficits in attention and information processing on a variety of biological measures [43–46], many of which are associated with functional outcome [47, 48]. Thus, vulnerability markers provide a potential means of improving the sensitivity of the existing clinical and demographic criteria and help to characterize neurodevelopmental pathology in early stages of the illness. Neurobiological measures (versus clinical characteristics) may identify simpler, empirically-derived endophenotypes and genetic markers with more specific pathophysiological and functional outcome correlates in the at risk sample. The specific abnormalities that are quantified with

vulnerability markers represent potential targets for treatment development that can lead to personalized treatment in the prodromal phase of illness.

Neurocognitive deficits are prominent across schizophrenia spectrum groups [49–52] and are apparent in childhood in people who go on to develop schizophrenia [53]. When compared to healthy subjects, subjects at risk for psychosis have neurocognitive deficits across multiple domains that are intermediate to those observed in patients with schizophrenia. In addition, at risk subjects who later convert to psychosis have greater verbal learning and IQ impairment at baseline evaluation compared to those individuals who remain "at risk" at follow-up [48, 54–57]. Neurocognitive deficits are also predictive of poor social functioning at follow-up despite improvement in positive symptoms in at risk subjects [30].

There have been relatively few structural neuroimaging studies in individuals at risk for schizophrenia [58] and it has been difficult to draw firm conclusions from a cross sectional design. A recent report by Mechelli *et al.* [59, 60], that combined data across 5 centers, found that individuals at high risk for psychosis show alterations in regional gray matter volume regardless of whether they subsequently develop the disorder, but reduced left parahippocampal volume was associated with the later onset of psychosis. Longitudinal studies have shown progressive loss of gray matter in medial temporal, inferior temporal, parietal, orbitofrontal and anterior cingulate regions in at risk individuals who later convert to psychosis indicating the potential significance of neurodevelopmental change over time as a risk factor for psychosis [61, 62].

Functional imaging studies in at risk populations are also rare [36, 63]. In general, at risk individuals show abnormal activation patterns in brain regions similar to chronic patients, in areas implicated in executive and emotional systems [36]. Although not yet linked to later psychotic conversion, a handful of studies have investigated neurochemical changes underlying functional imaging abnormalities in at risk subjects. Alterations in both dopaminergic and glutamatergic function has been recently documented in at risk individuals [64–66]. Furthermore, there appears to be a direct link between neurocognitive functioning and neurochemical alterations [67, 68]. One study has shown progressive increase in striatal dopamine synthesis in subjects who later develop psychosis [69].

Electrophysiological studies have identified abnormalities in event related potentials including P300 amplitude and latency, P50 and N100 suppression, mismatch negativity as well as prepulse inhibition of startle in at risk samples. Importantly, the duration mismatch negativity paradigm [70] and startle prepulse inhibition [71] have each been associated with risk for psychotic conversion [45, 71–76].

Despite recent advances in our understanding of neurobiological abnormalities and associated neural networks in the at risk population, the practical utility of these markers in at risk algorithms remains less developed. Current research paradigms will need to be simplified significantly in order to be useful diagnostic tools in the office setting. For instance, shorter, more reliable neurocognitive assessment instruments, more basic, easily administered electrophysiological paradigms, and more specific assessments of brain

structure, function and neurochemistry will need to be developed prior to use as diagnostic tools.

Along with the translation of research gains into diagnostic tools with practical utility, strategies will need to be developed to address the ethical and psychosocial implications of diagnosing the at risk state. Some of the most salient issues related to the ongoing debate of inclusion of an "*attenuated psychotic symptoms syndrome*" (APSS) in the DSM-V [77, 78] are discussed below.

ETHICAL AND PRACTICAL IMPLICATIONS OF INCLUDING AN APSS IN THE DSM-V

At present, there is some momentum for including an APSS diagnosis in the DSM-V [77, 78]. In this regard, Fusar-Poli and McGuire (personal communication) have recently assessed the validity of transition rates in subjects at risk for psychosis in a meta-analysis (unpublished data). Despite the fact that the studies vary in the method of subject ascertainment and definition of the at risk state and transition to psychosis, the studies support the validity of the criteria and are consistently associated with an increased risk of transition to psychosis. In their recent article, Carpenter and van Os[76] present a dynamic debate on the validity of the APPS diagnosis, especially outside academic medical centers, whether it will facilitate treatment or lead to unnecessary use of medications, whether it will stimulate or hamper research, and the psychosocial implications for those who are given the label of APPS [77].

In addition, many of the early "prodromal researchers" have provided varied perspectives. In a recent article Yung *et al.* [81] discuss the risks in "reification" and "codification" of the UHR criteria in the diagnostic scheme of DSM-V when the risk syndrome and its endpoint have not been validated. On the other hand, Woods *et al.* [78, 80] suggest that codification will enhance treatment and preventive research [80]. Shrivastava *et al.* [75] have articulated their concerns in a recent article and identified four areas of concern 1) Extension of pathology to normal behaviors without clear distinction between the two states 2) High false positive rate 3) Increased use of antipsychotic medications and 4) Labeling young people with transient symptoms as disordered. The authors suggest that inclusion of the at risk syndrome in the main text may be premature, but inclusion in the research appendices may provide momentum for more research. On the other hand, it has been suggested that codification of the at risk criteria may actually reduce research in the area [81] as it may give a false degree of comfort with the current definition.

One major difficulty with the inclusion of the risk syndrome in the appendix is that the diagnostic instruments used for the assessment require extensive training to achieve high reliability [83]. The nuances of the diagnosis are challenging in the research setting and field trials have not yet been performed in the community setting. Additionally, diagnostic creep may occur resulting in lowering of the at risk threshold and subsequent reduction in transition rate [84]. Inclusion in the DSM V, even in the appendix, is likely to lead to greater pharmacologic intervention since it provides a diagnosis, suggesting need for treatment, in the eyes of the clinician. The rate of antipsychotic treatment of children and adolescents, for

non-psychotic indications, has increased over the last decade [9] and the inclusion of the APPS criteria could contribute to this trend. There is some evidence to suggest that antipsychotics may have a deleterious effect on the brain [82] in addition to the known metabolic side effects in pediatric populations [83].

The risk syndrome has been likened to staging systems used in medical illness such as cardiovascular disease and cancer. For instance, the progression from cervical dysplasia to cervical carcinoma is well studied, and thus detection and treatment of cervical dysplasia can prevent the onset of carcinoma. The success of this approach depends on two factors, 1) well-documented progression of disease and 2) clear definition of outcome. In contrast, the progression of disease is not as clear for at risk subjects, where the majority maintains at risk symptoms, and some achieve remission. On the second point, the outcomes in at risk subjects are more varied and range from conversion to psychosis, to other serious mental disorders of mood, anxiety or substance use. Thus, any diagnostic and treatment schemes will need to account for lack of specificity of the at risk state for a particular illness and the overall low risk of conversion to a psychotic illness. Although the high sensitivity of the criteria increases the probability of identifying those who need treatment, it also risks treatment in those who do not need it. Thus, labeling individuals with a psychosis spectrum diagnosis may facilitate treatment, yet this approach also risks premature diagnosis and treatment in those who don't need it.

A related additional consideration is the definition of "transition to psychosis", the threshold at which an individual is considered to have developed "psychosis" is arbitrary, whose diagnostic and prognostic value remains undetermined[79]. Within each prodromal group, there are those who convert to psychosis, but maintain function, just as many patients that don't cross to psychosis, but continue to suffer significant functional impairments [35]. Thus, validation of the "risk syndrome" and the definition of "psychotic conversion" are both first principles that need to be addressed urgently, prior to inclusion of the risk syndrome in the DSM-V.

Nonetheless, in conventional clinical practice, subjects who present with at risk features are not usually taken on by psychiatric services. Thus, defining the at risk state as a new diagnostic category may encourage clinicians to identify and manage these help seeking individuals. A broadly defined "risk syndrome" that does not label the individual as pre-psychotic yet recognizes the heightened risk of current and future disability, could make resources available to treat the emerging disability, and not just reduce the likelihood of psychotic transition. Thus, treatment can also ameliorate the presenting symptoms and problems, which are often of greater concern to the subject than their long term risk of transition. Moreover, when at risk subjects are engaged early and then later develop psychosis, the delay before the latter is treated can be markedly reduced, and the first episode may be less traumatic.

Finally, the predictive accuracy of at risk criteria depends on its prevalence in the population sampled and thus the population from which the sample is drawn [86]. To date, transition rates have largely been derived from samples of help-seeking subjects who were engaged by specialized early intervention services. These individuals are often referred to these services

because of a suspicion that they are at risk for psychosis and thus would be expected to have relatively high base rates of being at risk. The prevalence in community samples is still unknown, and it is possible that there are individuals in the community who would meet at risk criteria but do not seek clinical help. If so, the predictive value of the at risk criteria may be considerably lower [86], closer to community prevalence rates estimated [16].

WHAT TREATMENTS MAY BE JUSTIFIED GIVEN OUR CURRENT LEVEL OF UNDERSTANDING OF THE AT RISK STATE.

Thus any treatment recommendations will need to balance two factors: 1) the heterogeneity of diagnostic outcomes in a given at risk population and that 2) many individuals continue to experience functional disability, or are truly at imminent risk of developing serious, chronic mental illnesses. Thus ideal treatments would meet the following criteria:

1. Be broad-spectrum treatments that can be beneficial across diagnostic categories, rather than syndrome specific treatments.

2. Have a low propensity for long-term side effects since many subjects will require treatment for long periods of time, and may never convert to a mental disorder.

3. With increased understanding of neural networks, network specific interventions may be considered to target specific functionally impairing domains.

Thus, general use of antipsychotics should be avoided in this population as a common practice; the risk-benefit ratio of antipsychotic medication treatment for this new clinical entity will not become clear until multiple clinical trials with rigorous methodology are conducted.

On the other hand, the omega 3 fatty acids present a promising treatment option. In a recent study by Amminger *et al* that followed 81 at risk subjects for 12 months, there was a markedly lower conversion rate in the treated versus placebo group [87]. Equally important, the study showed reduced positive and negative symptoms, and improved global function in the active treatment group. The omega 3 fatty acids presumably lead to increased levels of glutathione, which bolsters the brain's antioxidant defense and provides neuroprotection. It is especially noteworthy that the omega 3 fatty acids have also shown positive effects in major depression, bipolar disorder, borderline personality disorder, incarcerated young males, developmentally disordered children and autism spectrum disorders [88]. Nevertheless, this treatment study should be replicated before omega 3 fatty acids are considered a first-line pharmacological intervention for this particular population. Other pharmacologic interventions under investigation (in need of well planned clinical trials) include acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine), NMDA receptor antagonists, and anti-inflammatory agents, for their broad spectrum neuroprotective effects.

Psychosocial interventions ranging from a case management approach, to psychoeducation, to family therapy (FT) and cognitive behavioral therapy (CBT) have been shown to improve outcomes in early psychosis [90]. These treatments are broad-spectrum and have a favorable risk/benefit ratio considering those who do not develop mental illness. Another modality

with positive benefits includes cognitive remediation. In a meta-analysis of 26 studies, McGurk *et al.* [90] concluded that cognitive remediation combined with psychiatric rehabilitation, produces moderate improvements in cognitive performance and improves functional outcomes.

An entirely novel line of treatments utilizes technological advances, to provide cognitive remediation using individualized repetitive computer based learning trials has also been developed. In a recent trial, Genevsky *et al* showed significant improvements in working memory, verbal learning and memory and general cognition in patients with schizophrenia, along with neurobiological markers suggestive of learning induced cortical plasticity [91].

Thus, by integrating our current understanding of neural and molecular mechanisms of psychosis and functional impairment, treatment models should target rehabilitation of disordered neural networks using non-pharmacologic approaches which could be facilitated by neurocognitive enhancers [92].

CONCLUSIONS

Recent advances in our understanding of the earliest stages of psychosis have led to better identification of clinical, demographic, neurocognitive and biological risk factors prior to the onset of frank psychosis and new insights into the neurodevelopmental antecedents of psychotic illness. Although the at risk criteria are sensitive to predicting chronic illness and functional disability, they still lack diagnostic specificity for inclusion in the DSM-V as a "psychosis risk syndrome". Even if field trials were to support the reliability of the syndrome in community clinics, we do not have specific treatments for a heterogeneous group of individuals with unknown outcome. At present, broad spectrum treatment interventions with low risk to benefit ratios that focus on improving functional outcome are indicated. As we move forward, increasing our database of information about the non-converted, remitted and non-schizophrenia spectrum disordered subjects may shed some light on the pathophysiology of psychosis as well as other mental disorders. In addition, since most help-seeking individuals continue to suffer from functional disability, perhaps the focus of diagnosis and treatment can shift towards addressing the impairments. Such a framework will move the field closer to neural and molecular based diagnostic schemes, with treatments targeted towards neural networks or molecular targets, rather than phenomenologically described psychiatric syndromes.

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