Young people at ultra high risk for psychosis: research from the PACE clinic

Jovens em risco ultra alto de psicose: pesquisa na clínica PACE

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Abstract

Over the last fifteen years, attempts have been made to prospectively identify individuals in the prodromal phase of schizophrenia and other psychotic disorders. The ultra high risk approach, based on a combination of known trait and state risk factors, has been the main strategy used. The validation of the ultra high risk criteria allowed for predictive research in this population in an attempt to identify clinical, neurocognitive and neurobiological risk factors for psychosis onset. It also led to a series of intervention studies in this population, which have included the use of low dose antipsychotic medication, cognitive therapy, and omega-3 fatty acids. Although there is moderate evidence for the effectiveness of specific intervention strategies in this population, the most effective type and duration of intervention is yet to be determined. A current controversy in the field is whether to include an adaption of the ultra high risk criteria (the attenuated psychosis syndrome) in the next version of the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition).

Descriptors: Diagnosis; Psychotic disorders; Schizophrenia; Biomedical research; Cognitive therapy

Resumo

Nos últimos quinze anos, foram feitas tentativas para identificar prospectivamente indivíduos na fase prodrômica de esquizofrenia e outros transtornos psicóticos. A abordagem de risco ultra alto, baseada na combinação de fatores conhecidos de risco de traço e estado, tem sido a principal estratégia utilizada. A validação dos critérios de risco ultra alto levou em conta a pesquisa preditiva nessa população, em uma tentativa de identificar fatores de risco clínicos, neurocognitivos e neurobiológicos para o início de psicose. Também levou a uma série de estudos de intervenção nessa população, que incluíram o uso de medicação antipsicótica em baixa dose, terapia cognitiva e ácidos graxos ômega-3. Ainda que existam evidências razoáveis sobre a eficácia de estratégias de intervenção específicas nessa população, o tipo mais efetivo e sua duração ainda têm que ser determinados. Uma controvérsia atual no campo refere-se à inclusão de uma adaptação dos critérios de risco ultra alto (a síndrome de psicose atenuada) na próxima versão do Manual Diagnóstico e Estatístico de Transtornos Mentais (Quinta Edição).

Descritores: *Diagnóstico; Transtornos psicóticos; Esquizofrenia; Pesquisa biomédica; Terapia cognitiva*

Introduction

Early intervention in schizophrenia and other psychotic disorders has been a central issue in psychiatry over the last several decades[1]. While the focus was initially on the first episode of psychosis[2,3], it soon expanded to include the pre-onset phase of disorder. The onset of psychotic disorders is usually preceded by a prodromal period characterized by non-specific psychiatric symptoms, functional decline, and, closer to the onset of psychosis itself, attenuated or isolated psychotic symptoms[4-6]. Identifying cases during this phase of illness (the "prodrome") opens up important avenues in psychosis research and intervention. First, it may provide insight into the pre-onset and onset phase of the disorder, allowing for the identification of predictive variables and vulnerability markers. Second, it allows for the development of interventions that may delay, ameliorate or even prevent the onset of disorder. However, a major challenge has been to prospectively identify the prodrome, particularly given the non-specific nature

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of prodromal symptoms[7,8]. Typical prodromal symptoms, such as sleep disturbances, lowered mood, and anxiety[9,10], could be the result of a number of conditions, such as major depression, anxiety disorders, and even physical illness, and not necessarily indicate a psychotic prodrome. Even attenuated or isolated positive psychotic symptoms may not necessarily progress to a frank psychotic disorder, as these are known to occur prior to onset of non-psychotic disorders[11-13] and to be reasonably common in the general population[14-17].

Thus, although some people with an apparent "prodrome" do indeed progress to develop a psychotic disorder (the "true positives"), many do not. "False positives" are those who have no and will never develop psychotic disorders. These false positives need to be distinguished from those who would have developed a psychotic disorder if it had not been for factors that changed their illness trajectory, such as intervention, stress reduction, or cessation of illicit drug use. We have called this latter group "false false positives"[18,19]. Theoretically, false false positives would share genotypes and endophenotypic markers with true positives whilst phenotypically resembling false positives.

An implication of these conceptual and terminological issues is that "prodrome" is necessarily a retrospective concept. An individual presenting with prodromal symptoms of sleep disturbances, lowered mood, and even attenuated psychotic symptoms may be a true positive, false positive or a false false positive case when followed up over time. The danger of using non-specific symptoms to identify the prodrome is that many will be false positives. The challenge has therefore been to develop criteria that are able to detect people with a high likelihood of developing psychosis, that is, to maximize the true positives and minimize the false positives. One strategy to achieve this aim was the development of the ultra high risk (UHR) criteria (with the term "ultra" being used to distinguish the criteria from the genetic "high risk" approach). These criteria use a sequential screening approach or "close-in strategy"[20] requiring the combination of multiple risk factors, with the effect of concentrating the level of risk in the selected group. The strategy prioritizes specificity over sensitivity, with the possibility that people genuinely at risk may not be identified. The UHR criteria use the risk factor of age (adolescence and young adulthood), given that this is the age range of highest incidence of psychotic disorders[21]. Age is combined with clinical risk factors, such as functional decline and prodromal symptoms, particularly those that occur close to the onset of frank psychosis, such as attenuated and isolated psychotic symptoms. Additionally, presumed genetic risk combined with functional deterioration or chronic low functioning is a criterion.

The original UHR criteria required that a young person aged between 14 and 30 being referred for mental health problems met criteria for one or more of the following groups: (1) Attenuated Psychotic Symptoms Group (APS): those who have experienced subthreshold, attenuated positive psychotic symptoms during the past year; (2) Brief Limited Intermittent Psychotic Symptoms Group (BLIPS): those who have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated (i.e., without treatment); and (3) Trait and State Risk Factor Group: those with a first degree relative with a psychotic disorder or the identified patient has a schizotypal personality disorder in addition to a significant decrease in functioning or chronic low functioning over the previous year. Detailed descriptions of the operationalized UHR criteria can be found elsewhere[19,22,23]. The UHR criteria have been adapted and adopted around the world and have been variably termed the ultra high-risk (UHR)[22], clinical high risk (CHR)[24], at risk mental state (ARMS)[25,26] or prodromal criteria[27,28]. They have been tested over the last 15 years and have been found to predict onset of first episode psychosis at rates several hundred-fold above that of the general population[22,23,27]. The highest period of risk is the first year after identification but the data indicate that risk extends beyond this point[27,29,30].

Another approach to overcoming the non-specific nature of prodromal symptoms has been to use the "basic symptoms" described in German psychiatry[31,32]. In brief, these symptoms refer to subjectively felt anomalies of experience in the cognitive, affective, and physical domains that are thought to reflect the underlying (i.e., basic) disturbance in schizophrenia. Certain basic symptoms have been found to be predictive of schizophrenia in a clinical sample[33] and have led to the development of a checklist of nine symptoms suggestive of a schizophrenia prodrome: inability to divide attention, thought interference, thought pressure, thought blockages, disturbance of receptive speech, disturbance of expressive speech, disturbances of abstract thinking, unstable ideas of reference and captivation of attention by details of the visual field[32]. High risk criteria require the presence of at least two of these symptoms. In recent studies these criteria have been combined with the UHR criteria[34], an approach that has been found to be useful in defining a more narrow and homogenous high risk group[35].

These validated strategies of identifying help-seeking people at high risk of schizophrenia and other psychotic disorders have led to the establishment of numerous clinical services to provide care for UHR patients and to serve as research platforms to further develop knowledge in the area[36]. The Personal Assessment and Crisis Evaluation (PACE) clinic in Melbourne, Australia, was the first clinic of this type [25].

Predictive research

The introduction of the UHR criteria provided the opportunity to prospectively study clinical and other variables that predict psychosis onset, providing a research paradigm for studying risk factors for psychotic disorders. In the North American Prodromal Longitudinal Study (NAPLS)[27,37], baseline variables that uniquely contributed to the prediction of psychosis over a 2.5 year follow up period included a genetic risk for schizophrenia with recent deterioration in functioning, higher levels of unusual thought content, higher levels of suspicion/paranoia, greater social impairment, and a history of substance abuse. Prediction

algorithms combining 2 or 3 of these variables resulted in significant increases in positive predictive power compared with the UHR criteria alone. These predictors have been replicated in an independent sample from the PACE clinic[38].

Other short term predictors of onset of psychosis in UHR samples have been long duration of symptoms prior to treatment[22]; positive psychotic phenomena such as unstable ideas of reference and visual and auditory perceptual disturbances[39]; unusual thought content, suspiciousness, and conceptual disorganization[22,40]; negative symptoms, including impaired concentration and attention, subjectively abnormal emotional experiences, impaired energy, and impaired tolerance to stress[41]; marked impairment in role functioning, anhedonia, and asociality[39]; blunted affect[39,41] and social withdrawal[40,42]; schizotypal features[39]; basic symptoms, particularly cognitive, language, perception and motor disturbances[32,33]; depression[22,42]; poor functioning[22,39,43]; and substance abuse[40]. A recent PACE study with a large sample of 817 subjects found that the BLIPS group was the UHR group with the highest risk of transition[44]. Neurocognitive and neurobiological variables have also been investigated. Overall neurocognitive deficits, particularly in the verbal domain, have been found to predict transition to psychosis[45-49]. Other neurocognitive predictors of transition are reduced verbal learning and memory[45,46,50-52] and verbal fluency[46,51,53], in particular semantic verbal fluency[53]. Lowered processing speed on visual tasks has been demonstrated[46,47,54] and two groups have found that visual memory performance was associated with transition to psychosis[50,51].

In terms of neurobiological variables, we have found significant reductions in grey matter within medial temporal and orbitofrontal regions on the left hemisphere, as well as the anterior cingulate bilaterally, in UHR patients who progressed to psychotic disorder[55]. These findings were supported by a study in a separate sample at another research centre[56] and in a third sample, ascertained through a genetic risk model[57]. These studies have since been refined[58-60], such that we have now been able to show significantly more rapid reductions in UHR individuals progressing to psychosis than were seen in those who did not. These changes do not seem to be limited to grey matter. In a similar approach to our initial study[55], we have shown that white matter also shows changes in the transition from UHR to full-threshold psychosis[61].

Intervention studies

The other focus of UHR research has been to investigate intervention strategies for this population. The main aims of intervention in the high risk phase are: (1) to prevent, delay or reduce the severity of the onset of psychosis; and (2) to treat current problems, such as comorbid depressive or anxiety symptoms or syndromes. A secondary aim is to ensure that, should transition occur, the individual is already well engaged with treatment so that duration of untreated psychosis (DUP) is minimized and a non-traumatic entry into a service for first episode psychosis is facilitated.

A number of intervention studies in this population have been published to date. The first such study was conducted in the PACE clinic and compared combined cognitive behavior therapy (CT) and low dose atypical antipsychotic medication (risperidone) with usual case management. The rate of transition to psychosis in the treatment group was significantly lower than in the control group after the 6-month treatment phase. However, at 12-month follow up, there was no difference in transition rates unless participants were fully compliant with the anti-psychotic medication[62]. Medium term follow up (mean of 3.5 years) showed no significant difference between the treatment groups in terms of transition rate, level of symptomatology or functioning[30].

This study was followed by a study from New Haven, USA, comparing 12 months of antipsychotic medication (olanzapine) with placebo[63]. There was a trend towards the treatment group showing a reduction in transition rate, although this did not reach statistical significance. This may have been due to under-powering of the study.

A third trial was a psychological therapy intervention conducted in Manchester, UK, in which subjects were randomized to receive either CT or monitoring of mental state for 6 months. The group that received CT had a significantly lower rate of transition to full threshold psychotic disorder and a significantly greater reduction in psychiatric symptoms at 12 months[64]. This trial of CT is complemented by the study of Bechdolf et al.[65] that reported that CT for patients in the early initial prodromal state (EIPS), as identified by the presence of basic symptoms, was superior to supportive counseling in reducing progression to sub-threshold psychotic symptoms and to full threshold psychosis over 24 months.

An intervention trial in Vienna, Austria, examined the effect of 12 weeks of omega 3 fatty acids (fish oil) in the UHR group[66]. At the end of the 12-week treatment phase the intervention group had a significantly lower transition rate compared to the placebo control group. This significant effect persisted at 12-month follow up, with the finding that 2 of 41 individuals (4.9%) in the treatment group developed psychosis compared to 11 of 40 (27.5%) in the control group (p=0.007). The treatment group also had significantly reduced positive symptoms (p=0.01), negative symptoms (p=0.02), general psychiatric symptoms (p=0.01) and improved functioning (p=0.002) compared with the placebo group. This study is currently being replicated on a larger scale in a multisite study led by the PACE clinic.

Finally, an interim report on another intervention trial conducted at the PACE clinic has recently been published. This study compared CT plus risperidone, CT plus placebo, and supportive therapy plus placebo[67]. There was a 12-month treatment phase and a 12-month follow up phase. The interim paper reports data from 6 months of follow up. There were no significant differences between the groups in transition rates at this follow up point. This may have been because the transition rate in the control group (supportive therapy plus placebo) was much lower than expected - at the 6-month follow up point only 7.1%

of the control group (2 out of 28) had developed psychosis. Alternatively, the findings may indicate that these 3 treatments are equally effective in delaying transition to psychosis in the UHR population, especially when patients are identified early in the course of symptoms (see below).

Open label trials of aripiprazole[68] and amisulpride[69] have also been conducted in UHR cohorts. In the aripiprazole trial, 15 UHR patients were treated with a flexible dose regime of 5-30 mg/day for 8 weeks[68]. Improvements on clinical measures were evident by the first week and no participants transitioned to psychosis. Similar findings were seen in the amisulpride trial[69]. This trial with a cohort of 124 patients considered to be in the late initial prodromal stage (LIPS) involved randomizing participants to needs-focused intervention with or without amisulpride (50-800 mg/day) for 12 weeks. At the end of the treatment period, the amisulpride group showed significantly greater improvements in positive, negative and general symptoms, as well as in overall functioning, than the control group. Adverse events were minor, with prolactinaemia and a small weight gain being the most important.

Recently, there has been interest in the possibility of using antidepressants to reduce risk of psychosis in high-risk samples[70,71]. Cornblatt et al.[71] reported a naturalistic study of young people with prodromal symptoms treated either with antidepressants or antipsychotics. Twelve (43%) of the 28 patients who had been prescribed antipsychotics went on to develop psychosis in the following 2 years, whereas none of the 20 patients treated with antidepressants subsequently developed psychosis. Similar results were reported by Fusar-Poli et al.[70] on the basis of a file audit. These results need to be interpreted with caution due to the uncontrolled nature of the studies: there may have been differences in baseline symptoms, functioning or other variables between treatment groups, and non-adherence was far more prominent amongst patients prescribed antipsychotics than patients prescribed antidepressants.

In a recent review paper, Preti and Cella[72] report that transition rates in specific intervention groups across the studies are 11%, compared to 31.6% for control groups. Receiving any of the specific interventions was associated with lower risk of developing psychotic disorders compared with no treatment or treatment as usual. The evidence to date indicates that the effects of specific treatments are not stable after the intervention is stopped and that treatment delivered over a limited time period (e.g., 6 months or less) may only achieve a delay in psychosis onset[30]. A medium term follow up of the Manchester CT trial found that the difference in transition rate between the CT group and the control group was not maintained at 3-year follow up, unless some baseline cognitive factors were controlled for[29].

These results indicate that specific intervention in the UHR population is effective in at least delaying psychosis onset. However, due to the heterogeneity of treatments trialed to date, further research is required to determine the most effective type and duration of intervention for this group. Further developing this knowledge base would be a useful contribution towards the elucidation of a working clinical staging model[73,74]. The findings regarding the efficacy of more benign treatments such as cognitive therapy and fish oil support the staging model, which posits that early stages of illness should be responsive to less invasive treatments[75].

Recent issues

Low transition rates have been observed at the PACE clinic and other UHR clinics in more recent years[76]. One-year transition rates have been in the order of 10-20%, rather than the 30-40% rates observed in the earlier studies. We have previously speculated on the possible reasons for this[77]. It seems that, as the work of the "at risk" clinics has become well known, the formal and informal use of the UHR criteria has increased and patients are being referred earlier[76]. Thus, psychotic-like experiences (PLEs) are being detected earlier and possibly when previously they may not have been. This could result in earlier referrals to PACE and in the referral of individuals who would not have been referred previously. For those referred earlier in the course of their symptoms, onset of psychosis would be expected to occur later than 6 or even 12 months (i.e., a 'lead time' bias may be operating). Alternatively, it may be that very early detection enables intervention to be more effective in delaying or even preventing onset of psychosis. This is consistent with the staging model in psychiatry, which proposes that the earlier a disorder is identified, the more benign the treatment and the better the outcome[78,79]. For those who would previously not have been detected and referred it means that more false positives may be included in UHR cohorts. It is known that PLEs are common in the community and are often not associated with distress or help-seeking[14-17,80,81]. It is possible that through increasing potential referrers' and the community's awareness about PLEs and their relationship to full blown psychotic disorders, the work of the PACE clinic may have inadvertently resulted in a greater proportion of people who were never truly at risk of psychotic disorder being referred to clinical services. It is not yet clear when PLEs in community cohorts signal increased risk for psychosis or non-psychotic disorders or when they are benign phenomena not associated with increased risk[17]. The lowered transition rate and possible change in referral practices highlight another important issue in UHR research. The predictive validity of UHR criteria depends on the sample to which they are applied. The UHR criteria will have low predictive power in samples with a low rate of transition to psychotic disorder, such as the general population, and will have higher predictive power in an enriched clinical population[77].

A current controversy in the UHR field is whether an adaptation of the UHR criteria should be included as a

diagnosis in the next version of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Different terms have been suggested for this new diagnosis, including "psychosis risk syndrome", "risk syndrome for first psychosis", and, most recently, the "attenuated psychosis syndrome"[82,83] (see Table 1). The diagnosis would be a "transitional" diagnosis in that it would be intended to be used for a limited period of time and be supplanted by other DSM diagnoses later, should their criteria be met. In this sense, it would be akin to "mild cognitive impairment" as a prodromal risk syndrome for dementia[84].

Some of the benefits of including the attenuated psychosis syndrome in DSM-V include: early intervention to prevent later psychosis; encouraging attention and resources to be directed to an important clinical population; highlighting epidemiological work that demonstrates that attenuated psychotic symptoms are prevalent in the general population, and may be associated with both current morbidity and risk for illness; and aligning psychiatry more closely with other fields of medicine that identify risk factors for the purposes of instituting preventative interventions[85]. Authors in favor of including the attenuated psychosis syndrome in DSM-V argue that a clinical need exists for these patients, as evidenced by the help-seeking status of individuals and families. Furthermore, individuals with this syndrome may not attract a satisfactory diagnosis under DSM-IV that adequately addresses their needs. Thus, they may have difficulty accessing care and

receiving reimbursement under medical insurance schemes. DSM-IV does not account for these patients because the trait-like personality diagnoses, such as schizotypal personality disorder, do not fit the state-like and duration aspects of the attenuated psychosis syndrome criteria and the symptoms are not severe enough to attract a full psychotic diagnosis. These cases may eventually meet criteria for other diagnoses, such as psychotic or mood disorders, or may simply recover and not attract a definitive diagnosis. Woods and colleagues[86] present data indicating that clinicians can select DSM-IV diagnoses for attenuated psychosis syndrome patients when required to do so for reimbursement purposes, but that the clinicians are not satisfied that these DSM-IV diagnoses accurately capture the clinical picture of the patients. Therefore, these authors argue that there is a gap in the current DSM for the attenuated psychosis syndrome that is not currently addressed by other diagnostic categories and which allows for various outcomes in identified individuals.

A number of points have been made against including the attenuated psychosis syndrome in DSM-V. First, there is the issue of the potentially high number of false positives diagnosed with the syndrome[85,87]. This high number of false positives may be due to the inherent problem of false positives in those identified as being at risk compounded by the problem of misdiagnosis in non-expert settings[85]. In addition, the base rate of psychosis may be lower in populations outside tertiary research settings, particularly in primary care and the

Table 1

Proposed DSM-V criteria for the attenuated psychosis syndrome

All six of the following:

a) Characteristic symptoms: at least one of the following in attenuated form with intact reality testing, but of sufficient severity and/or frequency that it is not discounted or ignored;

   (i)   delusions
   (ii) hallucinations
   (iii) disordered communication

b) Frequency/Currency: symptom or symptoms meeting criteria A must be present in the past month and occur at an average frequency of at least once per week in the past month;

c) Progression: symptoms meeting criteria A must have begun or worsened in the past year;

d) Distress/Disability/Treatment Seeking: symptoms meeting criterion A are sufficiently distressing and disabling to the patient and/or parent/guardian to lead them to seek help;

e) Symptoms meeting criterion A are not better explained by any other DSM-V diagnosis, including substance-related disorder;

f) Clinical criteria for any DSM-V frank psychotic disorder have never been met.

Source: http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=412

general population, thus increasing the false positive rate, as noted above[12,87-89]. This concern has led to the inclusion of the caveat that the attenuated psychotic symptoms must be associated with distress, disability, and help-seeking. However, this addition is also problematic as help-seeking is dependent on a number of non-illness factors, including availability of services and cultural and sub-cultural attitudes to seeking help.

While identifying false positives is not inherently problematic and may be acceptable in other areas of medicine (e.g., heart disease), opponents of the inclusion of the attenuated psychosis syndrome argue that its risk-benefit ratio is not favorable due to a number of unintended consequences: the high risk of stigma (both by self and other) and discrimination, including from health insurance companies[87,90]; the possibility of exacerbating the already evident trend of treatment with antipsychotic medications for patients with attenuated psychotic symptoms in the absence of good evidence for this[85,87,91-93]; and the low benefits resulting from case identification given the lack of a clear evidence base for effective interventions[85,88]. It is also possible that the attenuated psychosis syndrome would suffer from the phenomenon of "diagnostic creep" – that is, the threshold for a diagnosis gradually shifting in response to clinical practice, political lobbying, and other social forces[87]. An example of this would be a scenario of a clinician providing a patient with a diagnosis of attenuated psychosis syndrome in order to access treatment and gain insurance coverage, even though the patient technically falls just below the attenuated psychosis syndrome threshold. The "creep" might also occur in the other direction, i.e., patients previously diagnosed with schizophreniform or delusional disorder may be given a diagnosis of attenuated psychosis syndrome instead. This problem, according to Ross[92], might be particularly salient given the lack of a clear operational definition of "attenuated" symptoms in the proposed criteria. He argues that the degree of "attenuation" that is allowed before an individual is below threshold for the attenuated psychosis syndrome will result in low reliability in clinical settings.

Summary

The UHR criteria were introduced to identify young people with a high risk of imminent onset of psychotic disorders, i.e., as possibly being in the prodromal phase of illness. Early studies provided evidence for the validity and reliability of the criteria. A number of clinical, neurocognitive, and neurobiological predictors of transition to psychosis in this population have been identified. However, there is a need for further refinement of risk factors to decrease the number of false positives identified with the UHR approach, particularly given the declining transition rate observed in recent years. Intervention research has indicated that specific intervention strategies are effective in reducing transition rates in the UHR population, at least over the short term. Further research is required to determine the most effective type and duration of intervention for this group. Given the evidence that many

benign therapies such as CT, fish oil, and even supportive therapy are as effective as antipsychotics in reducing the risk of transition to psychotic disorder, anti-psychotics are not recommended for this population[94,95]. A current controversy in the field is whether to include an adaptation of the UHR criteria in DSM-V in the form of the diagnosis of attenuated psychosis syndrome.

Disclosures

Writing group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Alison R Yung	University of Melbourne	Janssen-Cilag (investigator initiated)*					
Barnaby Nelson	University of Melbourne						

* Modest
** Significant
*** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

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