"At risk mental state" for psychosis: identification and current treatment approaches

Andrew Thompson 1,2, Steven Marwaha, 1,2 Matthew R. Broome 1,3,4

1. Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick, Coventry, UK.

2. Early Intervention in Psychosis Service, Coventry and Warwickshire Partnership Trust, UK.

3. Department of Psychiatry, University of Oxford, Oxford, UK.

4. Early Intervention in Psychosis Service, Oxford Health NHS Foundation Trust, UK.

Address for correspondence: Dr Andrew Thompson, Division of Mental Health and Wellbeing, Warwick Medical School, Gibbet Hill, Coventry, CV47AL, UK. Tel: +44 (0)2476574387; Fax: +44(0) 02476528375. E-mail andrew.d.thompson@warwick.ac.uk

Biographies

Dr Andrew Thompson is an Associate Clinical Professor in Psychiatry at the University of Warwick and a Consultant Psychiatrist in the North Warwickshire Early Intervention in Psychosis Service. He previously worked at the PACE clinic in Melbourne, a research clinic for at risk for psychosis patients. His research interests include risk factor and biomarkers for developing psychosis. Dr Steven Marwaha is an Associate Clinical Professor at the University of Warwick and a Consultant

Psychiatrist in Coventry. His research interests are in early interventions for bipolar disorders and identifying risk states for bipolar disorder. Dr. Matthew Broome is a Senior Clinical Research Fellow at the University of Oxford and Honorary Associate Clinical Professor of Psychiatry at the University of Warwick. He works as a Consultant Psychiatrist in the Oxford Early Intervention in Psychosis Service. He previously worked at the OASIS at risk service in London and has an interest in the ethics of at risk states and biomarkers for predicting psychosis.

Declaration of Interest

None

Summary

The concept of "at risk mental state" for psychosis arose from previous work attempting to identify a putative psychosis prodrome. This article summarises the current criteria used to identify such individuals, such as the Ultra High Risk criteria, and the further identification of important clinical risk factors or biomarkers to improve prediction of who might develop a psychotic disorder. We also discuss the important ethical issues in classifying and treating such individuals, current treatment trials in this area and what treatment current services can offer to these patients.

Learning objectives

- Understand the development, refinement and use of tools attempting to identify a putative psychosis prodrome or "at risk mental state"

- Appreciate the ethical issues in identifying and treating individuals with an "at risk mental state" for psychosis

- Consider the treatment options in light of the ethical issues, the research trials and what current services can offer

Background

It has long been known that the majority of psychotic disorders do not develop *de novo*. There is invariably a period of non-specific or low-grade symptoms or "prodrome" prior to the onset of a frank psychosis. In medicine, a prodrome is an early symptom (or set of symptoms) that might indicate the start of a disease before specific symptoms occur. A common example would be measles, which is described as having a prodrome of 3-4 days consisting of non-specific symptoms such as fever, coryzal symptoms, conjunctivitis, and cough. This is then followed by the specific rash, making the definitive diagnosis possible.

Attempts to identify a prodrome in psychosis are not new. The notion of being able to prevent the onset of schizophrenia and other psychotic disorders by detecting and intervening in the prodromal phase has been a goal discussed for many years (Sullivan 1927). Chapman and others have previously outlined the developing symptoms of schizophrenia (Chapman 1966, Yung, 1996) retrospectively. They are often non-specific symptoms such as depression, anxiety and disturbance in sleep as well as psychotic symptoms which are not fully formed or fleeting. In this review we will summarise the work to date on attempts to prospectively identify the prodrome concentrating on the so called "at risk mental state" group, including the effectiveness of interventions. This is especially important to UK psychiatrists at present as the new mental health targets for psychosis include this group so services for these patients may become more widespread (Marwaha, 2015).

Identification of a putative prodrome

In the mid-1990's researchers attempted to characterize or identify a "putative prodrome" for psychosis prospectively. This was prompted by a critique of the DSM III prodrome category, the emerging early intervention in psychosis paradigm and further retrospective accounts of prodromal symptoms in first episode psychosis patients. This led to the idea that identifying an "At Risk Mental State" (ARMS) for psychosis, based on some of the reported prodromal symptoms, may be useful in order to predict subsequent development of a psychotic disorder. The goal was to identify a group at imminent high risk of developing a psychotic disorder, using a combination of genetic and clinical risk factors (Yung, 2003). Criteria have since been developed to attempt to identify this group such as the "Ultra High Risk" (UHR) criteria (Yung, 2004a) or the similar "Clinical High Risk" (CHR) (Miller, 2003) criteria; those meeting these criteria are deemed to have an "At Risk Mental State" (ARMS) for psychosis. In this article we will refer to this group as UHR as this was the initial criteria, developed in Melbourne, Australia and is most commonly used in the UK. The criteria were named Ultra High Risk to distinguish this help-seeking clinical group from other high risk populations such as those with a genetic risk. The UHR criteria in brief consist of three groups: (1) Attenuated Psychotic Symptoms (APS): Presence of attenuated (subthreshold for a diagnosis of a psychotic disorder) psychotic symptoms within the previous 12 months. (2) Brief Limited Intermittent Psychotic Symptoms (BLIPS): history of brief self-limiting psychotic symptoms in the previous 12 months, which spontaneously resolve (within 7 days). (3) Trait group (FH): genetic vulnerability to psychotic disorder (either schizotypal personality disorder or family history of psychotic disorder in a first degree relative) and a drop in functioning or persistent low functioning for at least one month within the previous 12 months (criteria shown in Box 1). Age is also a criteria, as this focuses on those in the

highest epidemiological risk period for development of psychosis. In Melbourne, the age range is currently 15-25 and most of the research cited below focuses on this youth population.

The initial studies using these criteria suggested that they identified a group with a high risk of transition to (development of) a full threshold psychotic disorder, defined as full psychotic symptoms occurring for over 1 week, which was taken as the threshold for when clinicians would generally start treatment. A recent meta-analysis of transition to a psychotic disorder from studies in this population, using a varieties of similar tools for measuring the at risk mental state, reported rates of 18% after 6 months of follow-up, 22% after 1 year, 29% after 2 years, and 36% after 3 years (Fusar-Poli, 2012). These risks are around 400 times the population risk of development of psychosis. The risks also appear to continue over a longer-term period (Nelson, 2013).

Rating scales have been developed and validated to assess and identify those who meet the UHR criteria. The most widely used scale is the Comprehensive Assessment of At Risk Mental Sates (CAARMS), (Yung, 2005) developed in Melbourne, although the similar Structured Interview for Prodromal symptoms (SIPS) and the associated Scale of Prodromal Symptoms (SOPS) (Miller, 2003) are more often used in the United States and some other international centres. These scales focus on the positive symptoms of psychosis (disordered beliefs, perceptions and speech) as the way of indexing risk clinically.

The basic symptoms and self-disturbance approach

A different approach to understanding and characterising the prodrome has been proposed by European research groups that highlight the importance of subtle subjective alterations in cognition, memory and thinking that may be manifest many years before the onset of a psychotic disorder (Huber, 1989); these have been termed "basic symptoms". Research groups have developed assessment tools to identify those presenting with such symptoms (e.g. the Schizophrenia Proneness Instrument (SPI-A) (Schultze-Lutter 2007)) and individuals meeting basic symptoms criteria also have a much higher risk of developing a psychotic disorder over a longer term period (if at least one of the 66 basic symptoms was present at baseline, a specificity of 0.59, a sensitivity of 0.98, a PPV of 0.70, and an NPV of 0.96 for developing schizophrenia at 9.6 year follow-up resulted) (Klosterkotter, 2001). Some research groups have combined the two concepts and classified those who meet these basic symptoms criteria as an early initial prodrome stage, with the UHR criteria identifying a late initial prodromal stage (Bechdolf, 2012). A further related set of criteria examine the disturbance of the sense of self in putatively prodromal patients using tools such as the Examination of ~~Anomolous~~Anomalous Self-Experience (EASE) (Parnas, 2005). We will concentrate on the UHR/ARMS concept in this article as it is more widely used in UK practice, although the approach does relatively neglect those presenting with cognitive problems or negative symptoms. At present, the assessment and criteria for identification of basic symptom and self disturbances require considerable training and are therefore less accessible to clinicians in practice but remains an interesting area of research development.

Problems with the UHR criteria and improving predictive power

Despite the initial enthusiasm with regard to the ability to prospectively identify high risk individuals there were criticisms, especially when intervention and treatment strategies were proposed for this group. Firstly, although the transition rates were high, it was still the case that more than half of the identified individuals would not develop psychosis in 12 months. This may not be an issue for some disorders but, for a potentially stigmatizing disorder such as psychosis, especially if treatment is considered, this is important. There were also reports that the rate of transition to psychosis may not be as high as first thought. This appears to be a particular problem in established clinics where the transition rates have declined over time (Yung, 2007). There are a number of explanations for this but one important factor is the population from which the sample is drawn. Similar to any diagnostic test, the positive predictive power of these criteria is affected by the population prevalence of the disorder. Therefore, if these criteria were applied to a non help-seeking population sample then they would (and do) have a lower predictive power than if they were used in a sample referred to an early psychosis clinic but not quite meeting the criteria for a psychotic disorder. This has been discussed in the literature (Yung, 2007). In response to this there have been attempts to see if the predictive power of these criteria can be improved either using clinical factors and/or biomarkers.

A study of 104 UHR individuals reported by the group in Melbourne investigated whether particular clinical or demographic factors, in addition to the UHR criteria, could be used to improve the prediction of which UHR individuals would develop a psychotic disorder (Yung, 2004b). Four baseline clinical predictors of transition to psychosis were identified: a combination of attenuated psychotic symptoms and

genetic risk; a long duration of symptoms prior to baseline; poor social functioning; and poor attention. A model requiring the presence of at least one of these four potential predictors gave a good predictive validity with a positive predictive value (PPV) of 80.8% and a sensitivity and specificity of 60.0% and 92.6% respectively. Belonging to at least one of the three inclusion groups and belonging to the Brief Limited Intermittent Psychotic Symptoms (BLIPS) group also increased the risk of transition.

The North American Prodrome Longitudinal Study (NAPLS) ~~consortium investigated~~consortium investigated the predictive power of a large number of variables using their pooled sample of 291 cases (Cannon, 2008). This was a particularly important study given that one of the methodological difficulties in UHR research to that point had been that of small sample sizes. They found that five variables were strong predictors of transition to psychosis and that when these variables were combined the PPV was as high as 81%, without a substantial compromise in sensitivity or specificity. These predictors had substantial, but not complete, overlap with the predictors found from the earlier Melbourne study described above. Three of the five variables were found to be associated with transition in a replication study: high unusual thought content scores on the rating scales; low functioning; and having genetic risk with functional decline (Thompson, 2011).

The EPOS group, again using multisite data, investigated predictors in a European sample. They reported a high positive predictive value (83.3%) for a 6 variable model

that included higher positive symptoms, bizarre thinking, sleep disturbances, schizotypal personality disorder, Global Assessment of Functioning (GAF) score and years of education. They also reported a different and innovative method of assessing "risk" in terms of using a prognostic index, which enables the risk of individual patients to be calculated (Rurhmann, 2010). The addition of UHR criteria and basic symptom criteria has also been shown to increase the predictive power for transition to psychosis as well as the related subjective symptoms of self-disturbance (Nelson, 2012).

Interestingly, in a study again from the PACE clinic in Melbourne, the initial judgments of experienced clinicians as to whether an individual meeting UHR criteria and admitted to the clinic would subsequently develop psychosis were adequate (a sensitivity of 0.80, specificity of 0.84, positive predictive value of 0.32) but not extremely accurate predictors so caution about the accuracy of clinical prediction based on "praecox feeling" was recommended (Nelson, 2010). In summary, it appears that additional specific clinical factors such as specific positive psychotic symptoms, poor functioning, negative symptoms and subtle disturbances in cognition or sense of self may improve the prediction of the UHR criteria further. Further categorizing these individuals with individual risk profiles is an area of research development.

Risk factors or biomarkers

A number of biomarkers or phenotypic markers have been investigated to see if they can increase the predictive ability of UHR criteria. Biomarkers of note include

structural imaging changes, such as parahippocampal grey mater volume (Mechelli, 2011) with studies synthesizing data from multiple sites confirming the role neuroanatomical changes may have in the prediction of psychosis (e.g. Koutsouleris, 2015). In addition, functional neuroimaging has also been utilized to predict psychosis – both in measuring *in vivo* neurochemistry as well as with task and resting state fMRI. Functional imaging changes which may predict psychosis include changes in prefrontal and cortical function on the verbal fluency task, and its relation to dopamine levels, (Allen, 2012, Fusar-Poli, 2011), improvement in left inferior frontal gyrus function correlated with reduction in prodromal symptoms longitudinally (Fusar-Poli, 2011), and, on functional analysis of networks, a change in the centrality of the anterior cingulate cortex in the network predicts those at risk who may go on to develop a psychotic illness (Lord, 2012). Using PET and MRS to study neurochemical changes, reduction in pre-synaptic dopamine levels (Howes, 2011) predicted transition and ~~lower levels of thalamic glutamate is~~lower levels of thalamic glutamate are associated with a poorer functional outcome (Allen, 2015). Electrophysiological markers such as p300, sensory gating and Mismatch Negativity (MMN) have all been shown to be impaired in those at risk for psychosis, with particularly strong evidence that MMN can predict onset of disorder (Bodatsch, 2015). Other biomarkers include inflammatory and oxidative stress markers and genetic variants such as the neuregulin gene (Keri, 2009). A recent study found 15 markers including inflammation, oxidative stress, hormones, and metabolic analytes potentially served as a blood assay to predict psychosis (Perkins, 2015). Phenotypic markers include social cognitive and neurocognitive deficits such as poor theory of mind, poor working memory or executive functioning and verbal fluency (Giuliano, 2012). However, none of these at present are used practically in routine clinic settings,

although research is on going to attempt to combine some of these markers with clinical factors to be of use to clinicians.

Intervention studies

There have now been a number of randomized clinical trials of interventions in the UHR group, ranging from antipsychotics to CBT, and omega 3 fatty acids, with the main aim to prevent or delay the onset of psychosis. These are shown in Table 1. For pharmacological interventions we have restricted included trials to placebo-controlled designs. There are currently three meta-analyses comparing these treatments on the outcome of transition to a full threshold psychotic disorder (Preti, 2010, Stafford, 2013, van der Gaag, 2013) suggesting there is some promise for all current interventions and the meta-analysis of Van de Gaag and colleagues reported a Number Needed to Treat (NNT) of 9 to prevent psychosis at 12 months. Early enthusiasm for the use of low dose antipsychotic was tempered by the non-trivial rates of side effects (weight gain with olanzapine and extra-pyramidal symptoms with risperidone) (McGlashan, 2006, McGorry, 2002) and the short-term reduction of the transition rate not being maintained over time (Phillips, 2007). Similarly, initial enthusiasm in small trials with CBT (Morrison, 2004) have been followed by less striking results (at least on transition rates) in larger trials (Morrison, 2012) although other trials have found more positive results on transition rates (van der Gaag, 2012). A single placebo controlled trial of omega three fatty acids (Amminger, 2010) was particularly promising but initial results from the first of two replication studies failed to find a significant positive effect in terms of transition to psychosis or symptom improvement (McGorry et al, 2015). Further non-randomized trials have suggested the benefits of antidepressant medications (Cornblatt, 2007) and Amisulpiride in a

non-placebo controlled design (Ruhrmann, 2007). The efficacy of other pharmacological interventions such as glycine and non-pharmacological approaches such as family therapy as treatments are currently being investigated. One issue with all trials that specifically target a diminished transition rate is whether the intervention results in a transition time shifted to after trial end or whether protection rendered is long term.

Evidence of a decreased rate of transition to psychotic disorder in recent years (Yung, 2007) has resulted in many more intervention trials in the UHR group possibly being underpowered. In a number of recent trials the standard befriending, supportive therapy, active monitoring or case-management strategies have fared as well as the intervention strategy when the outcome has been transition to a psychotic disorder. This has prompted some involved in these trials to suggest an alternative view to the studies simply being underpowered, that the relatively non-specific "control" interventions such as active monitoring and supportive therapy (that are not in fact treatment as usual but low grade interventions) may be effective in some individuals who meet the UHR criteria (Morrison, 2012), McGorry, 2013).

Ethical issues

It is worth highlighting again that the idea of treating psychotic symptoms very early in the prodrome and in UHR patients has been the subject of much discussion from both clinical and ethical perspectives (Yung, 2007). Some feel that the approach advocates treating people too early and labelling and/or potentially stigmatising individuals (Yang, 2013) when less than 50% will develop a psychotic disorder in the

short to medium term. These are the so-called ‘false positive’ at-risk individuals – i.e. those who are not prodromal for psychosis ultimately and therefore there is the risk of over-treatment. Also, where antipsychotics are used as an intervention, there is a risk of iatrogenic dopamine sensitization, symptom rebound on drug withdrawal and brain changes on exposure to neuroleptics. More recently, attention has turned to the persistence and development of other psychiatric disorders in this group and the poor functional outcome of these patients regardless of whether they develop psychosis (Lin, 2015). The percentage of patients meeting UHR criteria who meet the criteria for another mental disorder is high. This reinforces the idea that these individuals may be at risk for psychosis but are also certainly at risk of other poor outcomes (Lin, 2015). This has led to discussion about the need to target functioning as well as a defined psychosis threshold in this population.

There was much debate amongst all stakeholders during the preparation for the DSM-5 manual as to whether ARMS criteria should be including in the main body of the diagnostic manual. The debate centred on whether it was premature to include this as a disorder based on the current predictive validity of the criteria (Yung, 2010). A version of the UHR criteria termed “Attenuated Psychosis Syndrome”, was eventually included, but in section III or the conditions for further study section of DSM-5, indicating further study is needed prior to possible inclusion in the main document. Some have argued that the DSM 5 diagnosis of “Other Specified Schizophrenia Spectrum Disorder and Other Psychotic Disorders, 298.8 (F28 ICD-10)” includes the above as a disorder. The APS criteria are shown in Box 2 and will be subject to further field trials prior to the next revision of DSM.

A further ethical concern many clinicians working in this area routinely come into contact with is the tension between reassurance and normalization of the unusual experiences with the follow-up and monitoring present in high-risk services, and genuine appreciation of risk. The monitoring, and care offered, may themselves impact on anxiety, appraisals, etc., and thus may have the paradoxical effect of increasing, rather than decreasing, the rate of transition in an at risk group if not delivered in services with certain levels of skill and expertise. Expanding clinical awareness and service delivery may lead to this and other unwanted, and unforeseen, outcomes, one of which may be how the criminal justice systems decides to treat an offender who demonstrates the Attenuated Psychosis Syndrome: will it be viewed as a mental disorder, with all the attendant consequences to both to the patient, the courts, and the clinicians? Or will the legal system see it as the risk state it is? More subtle ethical issues lie around how one talks about risk with young people deemed to be at risk. As noted above, the majority of such individuals may not develop a frank psychosis if followed-up. Hence, should clinicians who work in early detection consider whether patients have a right not to know their prognosis? One could argue that given we have no specific treatments that have clearly demonstrated to have altered clinical course there may be no positive benefit in knowing. Further, there are the possible harms of self-stigmatization and fear from the potential diagnosis. Despite these issues, many would argue that if sensitive and appropriate interventions can delay or reduce the impact of developing psychosis, even in a minority of individuals, that this is warranted given the impact for most individuals of a psychotic disorder.

Current specialised UHR services

Although the concept of UHR or ARMS has been more widely accepted, there are few services that provide specific interventions to these patients in the UK. Service provision is mostly aligned to the Early Intervention in Psychosis (EIP) services and not stand-alone services. The OASIS service in South London and EDIT services in Birmingham and Manchester and the CAMEO service in Cambridge are notable exceptions of specific UHR teams. These services often have a strong research focus. Worldwide there has been considerable expansion of these services and this trend seems likely to continue. Specialised clinics offer CBT focused intervention along with case management and medical treatment of co-morbidities. An example of an approach from the specialized PACE clinic in Melbourne is shown in Box 3. These specialized clinics have been shown to be cost-effective, (Valmaggia, 2009) which has added to the argument for providing specific services for these patients. Assessment and treatment of UHR patients has been included as part of the new Department of Health waiting time standards for first episode psychosis (Department of Health, 2014).

What should a clinician do where no specialised services are available?

What are the options then for clinicians who see such patients in their clinic and do not have the option of referring them to a specialized service? Often the local EI team will have a policy on what treatment to suggest and may provide an assessment using the CAARMS or a similar tool. However, often this is a "watch and wait" approach and the level of specific intervention is minimal. The issue of risk needs to be handled sensitively as highlighted above. As a psychiatrist, the temptation might be to start someone with sub-threshold symptoms on a low dose of an antipsychotic, especially when other non-pharmacological interventions are not available. The current research

suggests that a) more than half of these patients will not develop a psychotic illness even in the long term and therefore we may be treating a high proportion inappropriately and not in fact delaying or reducing transition to psychosis b) whilst we have some indicators of those at highest risk our current tools and clinical predictors are less than perfect. On balance the suggestion is that antipsychotics should not be used in the first instance. Current Iinternational Early Psychosis guidelines also suggest that antipsychotics should not be first line but "if rapid worsening of psychotic symptoms occurs together with significant deterioration in functioning related to these symptoms and elevated risk to self or others, a low-dose atypical antipsychotic may be considered, in conjunction with close monitoring and support" (Early Psychosis Guidelines Writing Group 2010). This is also supported by the National Institute for Health and Care Excellence (NICE) adult Psychosis and schizophrenia in guideline (NICE, 2014), which states "Do not offer antipsychotic medication to people considered to be at increased risk of developing psychosis or with the aim of decreasing the risk of or preventing psychosis". Treating the common co-morbidities such as depression and anxiety, if at treatment thresholds, are definitely warranted and a more watchful waiting approach is advised, as diagnostic uncertainty is common. The beneficial effects of high dose omega three fatty acids initially seemed promising and relatively side-effect free but recent research does not appear to have replicated the initial promising findings. In services where specialised psychological interventions are available, CBT would be appropriate. CBT approaches in UHR often focus on other difficulties such as depression and anxiety rather than simply psychotic symptoms (see Box 3).

For some patients, often whose symptoms are exacerbated by stress or drug use, more practical solutions offered in the process of assessment or in care-coordination, or interventions for substance misuse can have beneficial effects.

The recent NICE guideline for adults with Psychosis and Schizophrenia now includes the following recommendations on treatment of at risk patients: 1) offer individual cognitive behavioural therapy (CBT) with or without family intervention; 2) offer interventions recommended in NICE guidance for people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse (NICE, 2014).

Conclusions

Attempts to prospectively identify individuals at very high risk of developing a psychotic disorder have considerably advanced the research knowledge on both the mechanism of development of psychosis and approaches to very early or indicated intervention. Whilst there was initial enthusiasm with regard the ability to identify and treat clinical presentations such as the UHR state, some caution with regard to the predictive validity and the consequences of using such labels in respect to this validity has been raised. Further refining of the criteria including both the use of biomarkers, phenotypes and clinical features represents the next step in the pathway towards the overall goal of altering the course of psychotic disorders.

Box 1: the Melbourne UHR criteria (from (Nelson, 2012))

The Melbourne Ultra High Risk Criteria: (1) Must Be Aged Between 15 and 25 Years; (2) Have Been Referred to a Specialized Service for Help; (3) Have Experienced a Drop in Functioning of At Least 1 Month Over the Last Year or Sustained Low Functioning and (4) Meet the Criteria for One or More of the Following 3 Groups

Group 1: Attenuated Psychotic Symptoms:

- Presence of at least one of the following symptoms: ideas of reference, odd beliefs or magical thinking, perceptual disturbance, paranoid ideation, odd thinking and speech, odd behavior, and appearance
- Frequency of symptoms: at least several times a week
- Recency of symptoms: present within the last year
- Duration of symptoms: present for at least 1 week and no longer than 5 years

Group 2: Brief Limited Intermittent Psychotic Symptoms (BLIPS)

- Transient psychotic symptoms
- Presence of at least one of the following: ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, odd thinking, or speech
- Duration of episode: less than 1 week
- Frequency of symptoms: at least several times per week
- Symptoms resolve spontaneously
- Recency of symptoms: must have occurred within the last year

Group 3: Trait vulnerability group

- Schizotypal personality disorder in the identified individual or a first-degree relative with a psychotic disorder

Box 2: The Criteria for Attenuated Psychosis Syndrome from the DSM5 research appendix section III – disorders for further study

Box 2: Criteria for Attenuated Psychosis Syndrome in DSM 5

All 6 of the following

- A. At least one of the following symptoms are present in attenuated form with relatively intact reality testing, but of sufficient severity and/or frequency to warrant clinical attention:
- 1. delusions/delusional ideas
- 2. hallucinations/perceptional abnormalities
- 3. disorganized speech/communication
- B. Symptoms in Criterion A must be present at least once per week for the past month.
- C. Symptoms in Criterion A must have begun or worsened in the past year.
- D. Symptoms in Criterion A are sufficiently distressing and disabling to the individual and/or legal guardian to lead them to seek help.
- E. Symptoms in Criterion A are not better explained by any other DSM-5 diagnosis, including Substance-Related Disorders.
- F. Clinical criteria for a Psychotic Disorder have never been met.

Box 3: Treatment approach from Specialised UHR services (the Melbourne group) - adapted from the PACE group manual (PACE writing group, 2012)

1) Assessment, formulation and engagement

2) Psychoeducation

3) Individual case management – includes

- Ongoing monitoring of the client's mental state and risks.
- Ensuring the client and family or carers are appropriately informed about the nature of the mental health issues and their treatment.
- Reducing the trauma or anxiety associated with any necessary inpatient admissions.
- Facilitating adequate treatment for comorbid disorders.
- Assisting in reducing any adverse impact of the illness on the client's psychosocial environment, for example in relationships, accommodation, education, employment, financial security.
- Fostering the recovery of the client, reintegration into society, and restoration of a normal developmental trajectory.
- Risk assessment and management

4) Family interventions

5) CBT using a stress vulnerability model

- stress management
- positive symptoms
- depression/negative symptoms
- basic symptoms
- co-morbidities

6) Appropriate medical treatment of co-morbidities (e.g. depression, anxiety disorders)

References

Addington J, Epstein I, Liu L, et al, (2011) A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis. *Schizophrenia Research;* **125**: 54-61

Allen P, Luigjes J, Howes OD, et al. (2012) Transition to psychosis associated with prefrontal and subcortical dysfunction in ultra high-risk individuals. *Schizophrenia Bulletin*; **38**: 1268-76.

Allen P, Chaddock CA, Egerton A, et al. (2015) Functional outcome in people at high risk for psychosis predicted by thalamic glutamate levels and prefronto-striatal activation. *Schizophrenia Bulletin*; **41**: 429-39.

Amminger GP, Schafer MR, Papageorgiou K, et al. (2010) Long-chain {omega}-3 fatty acids for indicated prevention of psychotic disorders: A randomized, placebo-controlled trial. *Archives of General Psychiatry*; **67**: 146-54.

Amminger GP, Schafer MR, Schlogelhofer M, et al (2015) Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. *Nature Communications*; **6**: 7934.

Bechdolf A, Wagner M, Ruhrmann S, et al. (2012) Preventing progression to first-episode psychosis in early initial prodromal states. *The British Journal of Psychiatry*; **200**: 22-9.

Bodatsch M, Brockhaus-Dumke A, Klosterkotter J, et al. (2015) Forecasting psychosis by event-related potentials-systematic review and specific meta-analysis. *Biological Psychiatry*; **77**: 951-8.

Cannon TD, Cadenhead K, Cornblatt B, et al. (2008) Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Archives of General Psychiatry*; **65**: 28-37.

Chapman J (1966) The early symptoms of schizophrenia. *British Journal of Psychiatry*; **112**: 225-51.

Cornblatt BA, Lencz T, Smith CW, et al. (2007) Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents. *Journal of Clinical Psychiatry*; **68**: 546-57.

Department of Health (2014) *Achieving Better Access to Mental Health Services by 2020*. London: Department of Health.

Early Psychosis Guidelines Writing Group. (2010) *Australian Clinical Guidelines for Early Psychosis*. 2nd Edition ed. Melbourne: Orygen Youth Health.

Fusar-Poli P, Broome MR, Matthiasson P, et al. (2011) Prefrontal function at presentation directly related to clinical outcome in people at ultra high risk of psychosis. *Schizophrenia Bulletin*; **37**: 189-98.

Fusar-Poli P, Bonoldi I, Yung AR, et al. (2012) Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Archives of General Psychiatry*; **69**: 220-9.

Giuliano AJ, Li H, Mesholam-Gately RI, et al. (2012) Neurocognition in the psychosis risk syndrome: a quantitative and qualitative review. *Current Pharmaceutical Design*; **18**: 399-415.

Howes O, Bose S, Turkheimer F, et al. (2011) Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. *Molecular Psychiatry*; **16**: 885-6.

Huber G, Gross G (1989) The concept of basic symptoms in schizophrenic and schizoaffective psychoses. *Recenti Prog Med*; **80**: 646-52.

Keri S, Kiss I, Kelemen O (2009) Effects of a neuregulin 1 variant on conversion to schizophrenia and schizophreniform disorder in people at high risk for psychosis. *Molecular Psychiatry*; **14**: 118-9.

Klosterkotter J, Hellmich M, Steinmeyer EM, et al. (2001) Diagnosing Schizophrenia in the Initial Prodromal Phase. *Archives of General Psychiatry*; **58**: 158-64.

Koutsouleris N, Riecher-Rossler A, Meisenzahl EM, et al. (2015) Detecting the psychosis prodrome across high-risk populations using neuroanatomical biomarkers. *Schizophrenia Bulletin*; **41**: 471-82.

Lin A, Wood SJ, Nelson B, et al. (2015) Outcomes of nontransitioned cases in a sample at ultra-high risk for psychosis. *American Journal of Psychiatry*; **172**: 249-58.

Lord LD, Allen P, Expert P, et al. (2012) Functional brain networks before the onset of psychosis: A prospective fMRI study with graph theoretical analysis. *Neuroimage Clinical*; **1**: 91-8.

Marwaha S, Thompson A, Upthegrove R, Broome, MR. (2015) 15 Years on - Early Intervention for a new generation. Submitted for Publication.

McGlashan TH, Zipursky RB, Perkins D, et al. (2006) Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis.. *American Journal of Psychiatry*; **163**: 790-9.

McGorry PD, Yung AR, Phillips LJ, et al. (2002) Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis

in a clinical sample with subthreshold symptoms. *Archives of General Psychiatry*; **59**: 921-8.

McGorry PD, Nelson B, Phillips LJ, et al. (2013) Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: twelve-month outcome. *Journal of Clinical Psychiatry*; **74**: 349-56.

Mechelli A, Riecher-Rossler A, Meisenzahl EM, et al. (2011) Neuroanatomical abnormalities that predate the onset of psychosis: A multicenter study. *Archives of General Psychiatry*; **68**: 489-95.

Miller TJ, McGlashan TH, Rosen JL, et al. (2003) Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophrenia Bulletin*; **29**: 703-15.

Morrison AP, French P, Walford L, et al. (2004) Cognitive therapy for the prevention of psychosis in people at ultra-high risk: Randomised controlled trial. *British Journal of Psychiatry*; **185**: 291-7.

Morrison AP, French P, Stewart SLK, et al. (2012) Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. *British Medical Journal*; **344**.

National Institute for Health and Care Excellence. (2014) *Psychosis and Schizophrenia in Adults: Treatment and Management. NICE Clinical Guideline 178*. (http://www.nice.org.uk/guidance/cg178/evidence/cg178-psychosis-and-schizophrenia-in-adults-full-guideline3).

Nelson B, Yung AR (2010) Can clinicians predict psychosis in an ultra high risk group? *Australian and New Zealand Journal of Psychiatry*; **44**: 625-30.

Nelson B, Thompson A, Yung AR (2012) Basic self-disturbance predicts psychosis onset in the Ultra High Risk for psychosis "prodromal" population. *Schizophrenia Bulletin*; **38**: 1277-87.

Parnas J, Handest P, Jansson L, et al. (2005) Anomalous subjective experience among first-admitted schizophrenia spectrum patients: empirical investigation. *Psychopathology*; **38**: 259-67.

Perkins DO, Jeffries CD, Addington J, et al. (2015) Towards a psychosis risk blood diagnostic for persons experiencing high-risk symptoms: preliminary results from the NAPLS project. *Schizophrenia Bulletin*; **41**: 419-28.

Phillips LJ, McGorry PD, Yuen HP, et al. (2007) Medium term follow-up of a randomized controlled trial of interventions for young people at ultra high risk of psychosis. *Schizophrenia Research*; **96**: 25-33.

Preti A, Cella M (2010) Randomized-controlled trials in people at ultra high risk of psychosis: A review of treatment effectiveness. *Schizophrenia Research*; **123**: 30-6.

Ruhrmann S, Bechdolf A, Kuhn KU, et al. (2007) Acute effects of treatment for prodromal symptoms for people putatively in a late initial prodromal state of psychosis. *British Journal of Psychiatry (Suppl)*; **51**: s88-95.

Ruhrmann S, Schultze-Lutter F, Salokangas RK, et al. (2010) Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Archives of General Psychiatry*; **67**: 241-51.

Schultze-Lutter FA, J; Ruhrmann, S; Klosterkotter, J. (2007) *Schizophrenia Proneness Instrument, Adult Version (SPI-A).* Rome: Giovanni Fioriti Editore s.r.l.

Stafford MR, Jackson H, Mayo-Wilson E, et al. (2013) Early interventions to prevent psychosis: systematic review and meta-analysis. *British Medical Journal*; **346**.

Sullivan HS (1927) The onset of schizophrenia. *American Journal of Psychiatry*; **6**: 105-34.

Thompson A, Nelson B, Yung A (2011) Predictive validity of clinical variables in the "at risk" for psychosis population: International comparison with results from the North American Prodrome Longitudinal Study. *Schizophrenia Research*; **126**: 51-7.

Valmaggia LR, McCrone P, Knapp M, et al. (2009) Economic impact of early intervention in people at high risk of psychosis. *Psychological Medicine*; **39**: 1617-26.

van der Gaag M, Nieman DH, Rietdijk J, et al. (2012) Cognitive behavioral therapy for subjects at ultra high risk for developing psychosis: a randomized controlled clinical trial. *Schizophrenia Bulletin*; **38**: 1180-8.

van der Gaag M, Smit F, Bechdolf A, et al. (2013) Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups. *Schizophrenia Research*; **149**: 56-62.

Yang LH, Anglin DM, Wonpat-Borja AJ, et al. (2013) Public stigma associated with psychosis risk syndrome in a college population: implications for peer intervention. *Psychiatric Services*; **64**: 284-8.

Yung AR, McGorry PD (1996) The initial prodrome in psychosis: Descriptive and qualitative aspects. *Australian and New Zealand Journal of Psychiatry*; **30**: 587-99.

Yung AR, McGorry PD (2007) Prediction of psychosis: setting the stage. *The British Journal of Psychiatry*; **191**: s1-s8.

Yung AR, Phillips LJ, Yuen HP, et al. (2003) Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophrenia Research*; **60**: 21-32.

Yung AR, Phillips LJ, McGorry PD. (2004a) *Treating schizophrenia in the prodromal phase*. London: Taylor & Francis.

Yung AR, Phillips LJ, Yuen HP, et al. (2004b) Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophrenia Research*; **67**: 131-42.

Yung AR, Yuen HP, McGorry PD, et al. (2005) Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Australian and New Zealand Journal of Psychiatry*; **39**: 964-71.

Yung AR, Yuen HP, Berger G, et al. (2007) Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? *Schizophrenia Bulletin*; **33**: 673-81.

Yung AR, Nelson B, Thompson AD, et al. (2010) Should a "risk syndrome for psychosis" be included in the DSMV? *Schizophrenia Research*; **120**: 7-15.