

Assessment and treatment of individuals at high risk for psychosis

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ARTICLE

SUMMARY

Early detection and specialised early intervention for people at high risk for psychotic disorders have received growing attention in the past few decades, with the aim of delaying or preventing the outbreak of explicit psychotic symptoms and improving functional outcomes. This article summarises criteria for a diagnosis of high psychosis risk, the implications for such a diagnosis and recommendations for treatment.

LEARNING OBJECTIVES

After reading this article you will be able to:

- recognise signs and symptoms indicating increased psychosis risk
- understand uses and limitations of screening for high psychosis risk, and interpretation of results
- recognise evidence-based treatment options for patients at clinical high risk for psychosis.

DECLARATION OF INTEREST

C.A. has received non-financial support from Sunovion and Lundbeck in the past 36 months.

KEYWORDS

Psychotic disorders; schizophrenia; early treatment; at risk mental state; clinical high risk.

increased focus on early detection and treatment of psychotic disorders, boosted by a seminal study that reported a prodromal phase with attenuated or unspecific symptoms and/or functional decline several years in advance of a first psychotic episode in the majority of patients (Häfner 1998). In the late 1990s, operationalised criteria were developed to identify individuals at increased risk for psychotic disorders. The present review aims to provide a summary of major terms, concepts and recommendations with respect to diagnosis and treatment of such individuals. The case vignettes are fictitious but based on our clinical experience.

Diagnosis

The terms ‘clinical high risk’ and ‘at-risk mental state’ are used to describe signs and symptoms indicative of a high risk for psychotic disorders (Fusar-Poli 2013a). Two sets of criteria are used for diagnosis: ultra-high-risk and basic symptom criteria (Schultze-Lutter 2015).

Ultra-high-risk criteria

Ultra-high-risk criteria require the presence of at least one of the following: (a) attenuated positive symptoms, i.e. symptoms such as hallucinations and delusions that occur in the presence of more or less intact reality testing (case vignette: Box 1); (b) brief limited intermittent psychotic symptoms (BLIPS), i.e. full-blown positive symptoms that spontaneously remit after a short time (case vignette: Box 2); and (c) genetic high risk accompanied by functional decline (see Table 1 for detailed definitions and criteria).

The most widely used psychometric instruments for diagnosis of ultra-high-risk criteria to date are the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan 2010) and the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung 2005). Both instruments include a cut-off threshold for the definition of overt psychosis based on symptom frequency, duration and severity.

It should be noted that there are some differences in the way ultra-high-risk criteria are operationalised by the SIPS and CAARMS (Table 1). However, a recent study (Fusar-Poli 2016a)

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First received 8 Sep 2018

Final revision 19 Dec 2018

Accepted 16 Jan 2019

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Schizophrenia and schizophrenia spectrum disorders are one of the worldwide leading causes of chronic disability in young people (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). Although about 40% of patients can be described as having a good symptomatic outcome, impairments in everyday functioning often persist even with successful pharmacological treatment of psychotic symptoms (Emsley 2009); only about 1 in 7 patients experience ‘true’ recovery, i.e. symptom remission accompanied by adequate social functioning (Jaaskelainen 2013).

It has long been acknowledged that timely treatment in the early stages of psychotic disorders can improve clinical and functional outcomes, prevent negative social consequences of psychosis such as social isolation, unemployment and homelessness, and reduce the risk of self-harm and violence (Oliver 2018). Awareness of this fact has led to an

BOX 1 Case vignette: Anna – diagnosis of attenuated positive symptoms

Anna is 16 years old and has dropped out of high school. Her mother arranged an appointment at an early psychosis service, after searching information about her daughter's symptoms online. Anna reports seeing faces and shadows and hearing footsteps on the staircase, as well as a voice whispering her name, almost every day for the past 6 months. She is aware that her experiences are not real; she was not certain at first, but she tried to record the appearances with her mobile phone and she found out that she could not. However, they make her afraid, and she cannot sleep at night. When asked what she thinks causes the appearances, she says 'there must be something wrong with my head'. She was prescribed quetiapine 50 mg/day 3 weeks ago, but she did not notice any improvement.

Anna dropped out of school at the age of 15 after failing eighth grade (UK year 9) twice. Since then, she has had a few part-time jobs.

In the past few months, she has been spending most of her time at home watching TV and sleeping. Anna's mother reports that Anna has been withdrawn, oppositional and argumentative for the past couple of years; she does not seem to care about anything anymore, and she hardly talks to her parents. Anna describes a growing sense of hopelessness and worthlessness; in the past few weeks, she has had little energy and spent most of her time at home watching TV and sleeping. She has often contemplated suicide but has never tried to harm herself.

Discussion

Anna suffers from visual and auditory hallucinations. Although reality testing is intact, her experiences do cause some concern and have an impact on her sleep. Their frequency is sufficient for a diagnosis of attenuated psychotic symptoms, given that the symptoms have been present for less than a year.

BOX 2 Case vignette: Mike – diagnosis of brief limited intermittent psychotic symptoms (BLIPS)

Mike, a 19-year-old apprentice carpenter with no previous psychiatric history, was referred for emergency psychiatric assessment by his general practitioner after receiving a fine for fare evasion. Mike reported that he had fled home 3 days ago because he thought he was being persecuted. After seeing a stranger on the bus, who appeared at his place of work to visit his manager 2 days later, he started noticing people on the street and being convinced that they were following him and talking about him. He felt threatened, especially after seeing a hearse driving by, so he went to the train station, jumped on the next departing train and spent 3 days travelling around. He returned home when he started feeling safe again.

At the time of assessment, a week after the incident, Mike did not express any ideas of

reference or persecutory delusion. He dismissed his previous ideas as 'absurd' and was worried that they meant that he was going crazy, so he agreed to a full diagnostic evaluation. He reported smoking cannabis fairly regularly, about once or twice a week, but not in the week prior to the episode. There were no other relevant findings from his psychiatric or family history, physical examination, laboratory tests and neuropsychological evaluation.

Discussion

Mike suffered from full-blown psychotic symptoms (complete loss of reality testing) but they lasted less than a week and remitted spontaneously and fully without antipsychotic treatment. Hence, he meets criteria for BLIPS.

showed that there is substantial diagnostic agreement between the two instruments, most differences having no major consequences in clinical practice. A notable exception is operationalisation of BLIPS: the SIPS includes an urgency exclusion criterion (symptoms associated with severe disorganisation or with danger to self and others are considered to exceed the threshold for psychosis irrespective of

their duration), and thus some patients meeting this criterion in the CAARMS may be categorised as exhibiting a first psychotic episode in the SIPS (Fusar-Poli 2016a).

Basic symptoms

Basic symptom criteria represent a distinct approach in the diagnosis of high psychosis risk, in that they only consider symptoms *subjectively* experienced (i.e. the emphasis is on the patient's distress rather than observation by others) (case vignette: Box 3). They include disturbances of perception, cognition and language, and are thought to indicate an earlier prodromal stage than ultra-high-risk criteria (Klosterkötter 2011). Because they do not necessarily coexist with ultra-high-risk symptoms, they are used in some centres, especially in German-speaking countries, to complement assessment of suspected high-risk individuals.

Basic symptoms are assessed using the Schizophrenia Proneness Instrument, which has separate adult (SPI-A) (Schultze-Lutter 2007) and child and adolescent (SPI-CY) versions (Schultze-Lutter 2010). Two partially overlapping criteria sets are used for diagnosis of the high-risk state (Schultze-Lutter 2008) (Box 4).

Prognostic considerations – how to interpret a clinical high-risk diagnosis

The probability of psychotic transition in individuals meeting high-risk criteria has been estimated to be about 36–37% in recent meta-analyses and appears to reach its peak in the first 2–3 years of follow-up (Fusar-Poli 2013a; Schultze-Lutter 2015); most of these individuals will develop a schizophrenia spectrum disorder (Fusar-Poli 2013b).

From the above figures it becomes clear that, although these patients are at considerably higher risk for the development of a psychotic disorder than the general population, approximately two-thirds of them will not develop such a disorder. It should always be kept in mind that the diagnostic instruments mentioned above have high sensitivity (96%) but only modest specificity (47%) (Fusar-Poli 2015a), and thus are more useful in ruling out psychosis risk than in predicting an actual future transition to psychosis (Fusar-Poli 2016b).

The effect of screening strategy

In recent years, a notable decline in transition rates has been observed in high-risk individuals, which cannot be fully accounted for by the effects of earlier treatment (Nelson 2016). It has been suggested that the declining transition risk may represent a 'dilution effect' due to the application of the clinical high-risk concept to unsuitable

TABLE 1 Ultra-high-risk criteria and comparison of the Structured Interview for Prodromal Syndromes (SIPS) and Comprehensive Assessment of At-Risk Mental States (CAARMS)

	CAARMS	SIPS
General criteria		
Symptoms relevant for diagnosis	Unusual thought content Non-bizarre ideas Perceptual abnormalities Disorganised speech	Unusual thought content/delusional ideas Suspiciousness/persecutory ideas Grandiose ideas Perceptual abnormalities, hallucinations Disorganised communication
Substance-induced symptoms	Exclusion criterion if symptoms occur only during peak intoxication	Exclusion criterion if strong connection to symptoms
Presence of comorbid psychiatric diagnoses	–	Exclusion criterion if symptoms are better accounted for by another psychiatric disorder
Attenuated positive symptoms (APS): Presence of positive psychotic symptoms (see above, symptoms relevant for diagnosis) in attenuated form. Severity is rated on the basis of subjective distress, impact on daily life and functionality, attribution of meaning to abnormal experiences and extent of loss of reality testing		
Duration	≥1 week	
Onset	≤5 years ago <i>and</i> presence of symptoms in the past 12 months	<1 year ago or severity increase of ≥1 point in the past year <i>and</i> presence of symptoms in the past month
Frequency	>3–6 times per week for <1 h or >1 time per month for >1 h	>1 time per week in the past month for several minutes
Additional criteria	Functional decline as defined below	–
Brief limited intermittent psychotic symptoms (BLIPS): Overt, full-blown psychotic symptoms (see above, symptoms relevant for diagnosis) that spontaneously remit after a short period of time. The main benchmark for classification of psychotic symptoms as full-blown is extent of loss of reality testing (for formal thought disorder, appearance with minimal pressure, and response to structuring of the interview)		
Duration	≤1 week	≤3 months
Onset	≤5 years <i>and</i> presence of symptoms in the past 12 months	<3 months
Frequency	3–6 times per week for >1 h, or daily for <1 h (if less → APS)	>1 time per month for several minutes
Additional criteria	Functional decline as defined below Spontaneous remission without antipsychotics Past psychotic episode is an exclusion criterion	Seriously disorganised or dangerous symptoms are an exclusion criterion (and count as overt psychosis instead) Past psychotic episode is an exclusion criterion
Genetic risk with functional decline: <i>Either</i> presence of a psychotic disorder in a first-degree relative <i>or</i> presence of a schizotypal personality disorder according to DSM-IV criteria in the patient, accompanied by significant decline in social or occupational functioning		
Definition of functional decline	30% drop in SOFAS score over at least 1 month compared with the past year, or chronically low functional level (SOFAS score <50 for more than 1 year)	Decline of at least 30% in GAF score compared with the past year

GAF, Global Assessment of Functioning; SOFAS, Social and Occupational Functioning Assessment Scale.

populations. It has been established that the prognostic accuracy of high-risk criteria is strongly dependent on the pre-test risk of the population studied (Fusar-Poli 2015a), which is higher for help-seeking individuals referred to early intervention centres (15%) compared with, for example, primary care patients (0.045%) (Fusar-Poli 2015a, 2016b). Thus, low-threshold referral strategies and outreach campaigns targeting the general population may result in limited prognostic usefulness of specialised early assessment. In its guidance on the early detection of the high-risk state, the European Psychiatric Association acknowledges that substantial pre-assessment ‘risk enrichment’ is needed for early intervention services to have clinical utility, and suggests that the above criteria for assessment of high risk for psychosis should only be applied to individuals already distressed by mental problems and seeking help for them, or to those seeking clarification of their current risk in the context of, for example, a genetic predisposition for psychotic disorders (Schultze-Lutter 2015).

Children and adolescents: special considerations

In young children, the prevalence of psychotic symptoms such as auditory hallucinations may be as high as 9%, but more often than not they have no clinical relevance and remit spontaneously (Schimmelmann 2013). Moreover, a recent telephone survey of adolescents reported a point prevalence for attenuated positive symptoms of around 13.8%, but in most cases these were not frequent enough to meet criteria for psychosis risk (Schultze-Lutter 2017). Therefore, particular caution is advised when assessing children and young adolescents for early signs of psychosis, and interpretation and communication of results should be carried out by trained professionals experienced in psychosis risk screening (Schimmelmann 2013). In older adolescents, there are more similarities to clinical presentations of high risk in adults, but with a more fluctuating course (Schimmelmann 2007).

Predictors of transition to psychosis

Given the above-mentioned limitations of screening instruments, a large body of research has been

BOX 3 Case vignette: Claire – diagnosis of basic symptoms

Claire is a 17-year-old high school pupil. In the past few weeks, she has been experiencing increasingly distressing symptoms that occur at least once a week. While reading books, for example, she noticed that she does not understand the meaning of words and passages as effortlessly as before and needs to reread them. She also has difficulty finding the right words and putting them in order to make meaningful sentences. At times, she loses her train of thought or her mind is flooded by insignificant thoughts, which makes it impossible to concentrate. More than a year ago she started to experience visual disturbances. Colours of objects seem brighter, and she feels that she cannot always rely on her perception of distance or movement; for example, sometimes she thinks objects are moving, although in reality they are not. She also sometimes has the impression that people are talking about her

or looking at her, although at the same time she knows that this is actually not possible. She has asked her family and friends if she seems odd or changed in any way, but they have not observed any changes.

Discussion

Claire experiences several cognitive basic symptoms: disturbance of receptive and expressive speech, thought interference, thought blockage, unstable ideas of reference. Moreover, she experiences one perceptual basic symptom (visual perception disturbances). Because she experiences these symptoms as a deviation from her usual state and they cause her distress, they meet the general criterion for basic symptoms. The fact that the symptoms are not observed by others is not relevant for diagnosis, as the definition of basic symptoms relies exclusively on subjective experience.

devoted to identifying specific variables, or combinations of variables, that could be used to improve prediction of the risk of psychotic transition at the level of the individual patient.

Several studies have investigated whether specific combinations of prodromal symptoms are predictive of increased transition risk. Although individual results vary, greater severity of psychosis risk symptoms at baseline appears to be a consistent predictor of increased transition risk (Mechelli 2017). Moreover, patients meeting both ultra-high-risk and basic symptom criteria have been reported to be at increased transition risk compared with those meeting only one set of criteria (Ruhrmann 2010).

Apart from symptoms, variables such as environmental, cognitive, neuroimaging and electrophysiological measures (Fusar-Poli 2013a; Schmidt 2017) have also been suggested to be useful in predicting psychotic transitions. Several studies apply machine learning algorithms to large datasets in order to provide individualised estimates of transition risk (Klosterkötter 2005; Schmidt 2017; NAPLS 2018; PRONIA 2018) or functional outcomes (Koutsouleris 2018) in high-risk individuals. The ultimate goal is the development of individualised ‘risk calculators’ (Cannon 2016; Fusar-Poli 2017a). However, predictive tools need to be validated in independent samples and different clinical contexts, as their performance depends on several factors, such as recruitment strategies, sample characteristics and instruments used for assessment. Since high-quality validation studies are largely lacking (Studerus 2017), the applicability of existing

BOX 4 Sets of criteria for diagnosis of high-risk state using basic symptoms on the Schizophrenia Proneness Instrument

To be rated as basic symptoms, symptoms must be experienced with full insight (i.e. as a change from the individual’s usual state) and cause significant subjective distress.

Cognitive disturbances (COGDIS)

Presence of least two of the following symptoms in the past 3 months:

- Inability to divide attention
- Thought interference
- Thought pressure
- Thought blockages
- Disturbance of receptive speech
- Disturbance of expressive speech
- Unstable ideas of reference
- Disturbance of abstract thinking
- Captivation of attention by details of the visual field

Cognitive-perceptual disturbances (COPER)

Presence of at least one of the following symptoms for at least 12 months:

- Thought interference
- Thought perseveration
- Thought pressure
- Thought blockages
- Disturbance of receptive speech
- Decreased ability to discriminate between ideas and perception, fantasy and true memories
- Unstable ideas of reference
- Derealisation
- Visual perception disturbances
- Acoustic perception disturbances

risk prediction tools is currently still limited to the research setting.

Transition to psychosis – not the only outcome of interest

Although most studies so far have focused on transition to psychosis as the major outcome of interest in high-risk individuals, more recent research indicates that other clinical measures may also be meaningful and relevant to treatment. A number of studies investigating the clinical course of high-risk patients who do not transition to psychosis indicate that at least a third of these individuals persistently or recurrently experience attenuated psychotic symptoms in the long term (Simon 2013; Michel 2018). Moreover, the majority of these patients have non-psychotic psychiatric disorders such as substance-related, affective or anxiety disorders (Lin 2015;

Michel 2018) and exhibit long-term functional impairments compared with healthy controls (Polari 2018). These observations are relevant to treatment. For example, it has been suggested that attenuated psychotic symptoms may also occur in the context of other clinical disorders, such as depressive and anxiety disorders, as a sign of increased severity (van Os 2017); in such patients, treatment of the primary disorder might lead to remission from the high-risk state.

Treatment

As detailed above, patients screening positive for clinical high risk for psychosis experience significant distress and often functional impairment as well, irrespective of whether they will convert to psychosis or not. Therefore, the aim of treatment is not only to prevent transition to psychosis, but also to improve comorbid disorders such as depression, anxiety and substance use, as well as to prevent functional impairments or improve existing functioning (Schmidt 2015; Addington 2017; Fusar-Poli 2017b). Specialised early intervention services work towards these goals by adopting an integrated multidisciplinary approach that typically includes a combination of elements such as symptom monitoring and management, improvement of social skills and cognition, psychoeducation, treatment of comorbidities, crisis management, family intervention and support, and psychosocial support for housing, educational or vocational problems (case vignettes: Box 5, Box 6, Box 7).

Specialised early intervention services have been shown to reduce the occurrence of psychotic transition (van der Gaag 2013) in high-risk individuals; in patients with a first psychotic episode, they contribute to reduction of the duration of untreated psychosis (i.e. the time between onset of symptoms and the beginning of treatment) (Oliver 2018) and reduce the need for in-patient treatment and compulsory admissions (Fusar-Poli 2016c). These benefits have been acknowledged by several national and international guidelines, which consider assessment by a specialised early intervention service as an

BOX 5 Case vignette: Mike – clinical course of BLIPS

Mike received a few psychoeducation sessions, in which a crisis plan for future episodes was developed. He was advised to abstain from cannabis, but he continued smoking it occasionally. He came to his follow-up appointments every 3–4 months for about a year and kept in touch over the telephone for another few months, but he did not feel the need to make any further appointments.

BOX 6 Case vignette: Anna – clinical course of attenuated positive symptoms

Anna was diagnosed with a major depressive episode. Quetiapine was discontinued, and she was offered psychoeducation about attenuated positive symptoms and cognitive-behavioural therapy. However, after missing several therapy appointments, she was started on an antidepressant. Her mood improved somewhat, suicidal ideation disappeared and she was able to keep her appointments more reliably. She reported feeling less frightened by her hallucinations and later that they had disappeared altogether. A few joint sessions with her parents were held to relieve family tensions. Anna is currently being helped by a social worker to find a supported apprenticeship.

integral part of early psychosis treatment (National Institute for Health and Care Excellence 2014; Schmidt 2015; Addington 2017). Specific psychotherapy programmes, such as cognitive-behavioural therapy protocols and family interventions, have also shown some promising results in the treatment of clinical high-risk individuals (Schmidt 2015; Devoe 2019). However, a recent meta-analysis (Davies 2018a) did not find any evidence favouring specific interventions over needs-based interventions for the prevention of transition to psychosis.

Cannabis use

Although a causal relationship has not been conclusively established, several epidemiological studies suggest that regular or heavy cannabis use may increase the risk for the development of psychotic disorders over and above the effects of acute intoxication, especially in predisposed individuals, users of potent strains of cannabis or those with an early onset of use (Gage 2016; Murray 2016). Moreover, cannabis use has been related to worse symptomatic outcomes and accelerated loss of grey matter volume in individuals with schizophrenia (Iseger 2015). All

BOX 7 Case vignette: Claire – clinical course of basic symptoms

Claire had an appointment with an early psychosis detection service after she talked to the school social worker about her very distressing experiences. She had an extensive diagnostic assessment in which she was relieved to talk about her problems and to obtain professional help on how to cope with her cognitive disturbances and how to understand her perceptual disturbances. She agreed on regular monthly follow-ups in order to reassess her disturbances.

MCQ answers

1 b 2 d 3 e 4 d 5 b

BOX 8 Dos and don'ts in clinical practice**Do**

- Refer for specialist assessment and treatment early when you suspect high risk for psychosis
- Offer treatment for any depression, anxiety or substance misuse, and psychosocial support
- Be optimistic – keep in mind that only about a third of high-risk patients will make the transition to psychosis

Do not

- Screen for psychosis risk if the individual is not distressed by mental problems, unless they are seeking advice on their current risk in the context of a genetic predisposition
- Communicate suspicions of high psychosis risk to children and adolescents or their families: interpretation of screening results in this age group is complicated and should be left to trained professionals with expertise in high-risk diagnosis
- Use antipsychotics for subthreshold symptoms, or symptoms of unconfirmed severity, before exploring other options

of these effects appear to be mediated by tetrahydrocannabinol (THC) (Iseger 2015; Gage 2016). Therefore, both high-risk and first-episode patients should be encouraged to reduce or abstain from cannabis use.

Interestingly, the observed negative consequences of THC do not extend to cannabidiol (CBD), which instead has been suggested to have antipsychotic effects (Iseger 2015; Khoury 2017). Two small randomised controlled studies have suggested that CBD might be effective in the treatment of positive symptoms in individuals with schizophrenia (Leweke 2012; McGuire 2018), but a third study failed to replicate these findings (Boggs 2018). So far, there are no published studies on the clinical efficacy of CBD in high-risk or first-episode patients; however, a recent neuroimaging study of single-dose CBD in high-risk patients suggested a positive effect on the function of brain regions associated with the clinical high-risk state, such as the parahippocampal area, striatum and midbrain (Bhattacharyya 2018). Thus, and given its favourable adverse effect profile (Iseger 2015), CBD presents a promising area for future research.

Pharmacological interventions

Several atypical antipsychotics have shown efficacy in reducing conversion rates in clinical high-risk patients (Schmidt 2015). However, available meta-analyses suggest that treatment with antipsychotics is not superior to psychological interventions in terms of conversion rates (Schultze-Lutter 2015;

Davies 2018a), reduction of attenuated positive symptoms (Davies 2018b; Devoe 2019) or functional outcomes (Schmidt 2015). Therefore, current international guidelines (Schmidt 2015; Addington 2017) recommend the least restrictive approach, i.e. psychological interventions, as the first-line treatment, while treatment with antipsychotics is reserved for patients who do not respond to psychological interventions or who show severe and/or progressive high-risk symptoms. In these cases, antipsychotic medication should be used to achieve sufficient clinical stability for psychosocial interventions; long-term preventive treatment with antipsychotics is currently not recommended (Schmidt 2015).

Apart from antipsychotics, other pharmacological or neuroprotective agents have shown promise in the treatment of high-risk patients, particularly N-methyl-d-aspartate (NMDA) receptor modulators such as d-serine and glycine for the treatment of positive and negative symptoms (Woods 2014; Dong 2015) and antidepressants for prevention of psychotic transitions (Cornblatt 2007; Fusar-Poli 2015b); however, further evidence is needed before a reliable recommendation can be provided. Promising results that were initially obtained for omega-3 fatty acids (Amminger 2010, 2015) could not be replicated in a larger randomised controlled trial (McGorry 2017; Nelson 2018).

Summary

Almost three decades have passed since the introduction of operationalised criteria for the identification of individuals at high risk for psychosis. Clinical experience and a large number of studies have established the usefulness of the concept of high psychosis risk and led to its inclusion in international guidelines. However, clinicians should be aware of the limitations of psychosis risk assessment and the particularities of treatment in high-risk individuals (Box 7); early referral to a specialised early intervention service will be advantageous in most cases.

References

- Addington J, Addington D, Abidi S, et al (2017) Canadian treatment guidelines for individuals at clinical high risk of psychosis. *Canadian Journal of Psychiatry*, **62**: 656–66.
- Amminger GP, Schäfer 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 G, Schäfer M, Schlögelhofer M, et al (2015) Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. *Nature Communications*, **6**: 7934.
- Bhattacharyya S, Wilson R, Appia-Kusi E, et al (2018) Effect of cannabidiol on medial temporal, midbrain, and striatal dysfunction in people at clinical high risk of psychosis: a randomized clinical trial. *JAMA Psychiatry*, **75**: 1107–17.
- Boggs DL, Surti T, Gupta A, et al (2018) The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia: a randomized placebo controlled trial. *Psychopharmacology*, **235**: 1923–32.

- Cannon TD, Yu C, Addington J, et al (2016) An individualized risk calculator for research in prodromal psychosis. *American Journal of Psychiatry*, **173**: 980–8.
- Comblatt 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.
- Davies C, Cipriani A, Ioannidis J, et al (2018a) Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis. *World Psychiatry*, **17**: 196–209.
- Davies C, Radau J, Cipriani A, et al (2018b) Efficacy and acceptability of interventions for attenuated positive psychotic symptoms in individuals at clinical high risk of psychosis: a network meta-analysis. *Frontiers in Psychiatry*, **9**: 187.
- Devoe DJ, Farris MS, Townes P, et al (2019) Attenuated psychotic symptom interventions in youth at risk of psychosis: a systematic review and meta-analysis. *Early Intervention in Psychiatry*, **13**: 3–17.
- Dong C, Haschimoto K (2015) Early intervention for psychosis with N-methyl-d-aspartate receptor modulators. *Clinical Psychopharmacology and Neuroscience*, **13**: 328–9.
- Emsley R (2009) Early response to treatment predicts remission and recovery at 3 years in people with schizophrenia. *Evidence-Based Mental Health*, **12**(2): 43.
- Fusar-Poli P, Borgwardt S, Bechdolf A, et al (2013a) The psychosis high-risk state: a comprehensive state-of-the-art review. *Archives of General Psychiatry*, **70**(1): 107–20.
- Fusar-Poli P, Bechdolf A, Taylor MJ, et al (2013b) At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. *Schizophrenia Bulletin*, **39**: 923–32.
- Fusar-Poli P, Cappucciati M, Rutigliano G, et al (2015a) At risk or not at risk? A meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction. *World Psychiatry*, **14**: 322–32.
- Fusar-Poli P, Frascarelli M, Valmaggia L, et al (2015b) Antidepressant, antipsychotic and psychological interventions in subjects at high clinical risk for psychosis: OASIS 6-year naturalistic study. *Psychological Medicine*, **45**: 1327–39.
- Fusar-Poli P, Cappucciati M, Rutigliano G, et al (2016a) Towards a standard psychometric diagnostic interview for subjects at ultra high risk of psychosis: CAARMS versus SIPS. *Psychiatry Journal*, **2016**: 1–11.
- Fusar-Poli P, Schultze-Lutter F (2016b) Predicting the onset of psychosis in patients at clinical high risk: practical guide to probabilistic prognostic reasoning. *Evidence-Based Mental Health*, **19**: 10–5.
- Fusar-Poli P, Díaz-Caneja CM, Patel R, et al (2016c) Services for people at high risk improve outcomes in patients with first episode psychosis. *Acta Psychiatrica Scandinavica*, **133**: 76–85.
- Fusar-Poli P, Rutigliano G, Stahl D, et al (2017a) Development and validation of a clinically based risk calculator for the transdiagnostic prediction of psychosis. *JAMA Psychiatry*, **74**: 493–500.
- Fusar-Poli P, McGorry PD, Kane JM (2017b) Improving outcomes of first-episode psychosis: an overview. *World Psychiatry*, **16**: 251–65.
- Gage SH, Hickman M, Zammit S (2016) Association between cannabis and psychosis: epidemiologic evidence. *Biological Psychiatry*, **79**: 549–56.
- GBD 2016 Disease and Injury Incidence and Prevalence Collaborators (2017) Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*, **390**: 1211–59.
- Häfner H, Maurer K, Löffler W, et al (1998) The ABC schizophrenia study: a preliminary overview of the results. *Social Psychiatry and Psychiatric Epidemiology*, **33**(8): 380–6.
- Iseger TA, Bossong MG (2015) A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophrenia Research*, **162**: 153–61.
- Jaaskelainen E, Juola P, Hirvonen N, et al (2013) A systematic review and meta-analysis of recovery in schizophrenia. *Schizophrenia Bulletin*, **39**: 1296–306.
- Khoury JM, Neves MdCLd, Roque MAV, et al (2017) Is there a role for cannabidiol in psychiatry? *World Journal of Biological Psychiatry*, Feb 20: doi: 10.1080/15622975.2017.1285049 [Epub ahead of print].
- Klosterkötter J, Ruhrmann S, Schultze-Lutter F, et al (2005) The European Prediction of Psychosis Study (EPOS): integrating early recognition and intervention in Europe. *World Psychiatry*, **4**: 161–7.
- Klosterkötter J, Schultze-Lutter F, Bechdolf A, et al (2011) Prediction and prevention of schizophrenia: what has been achieved and where to go next? *World Psychiatry*, **10**: 165–74.
- Koutsouleris N, Kambeitz-Ilankovic L, Ruhrmann S, et al (2018) Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: a multimodal, multisite machine learning analysis. *JAMA Psychiatry*, **75**: 1156–72.
- Leweke FM, Piomelli D, Pahlisch F, et al (2012) Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational Psychiatry*, **2**: e94.
- 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.
- McGlashan T, Walsch B, Woods S (2010) *The Psychosis-Risk Syndrome. Handbook for Diagnosis and Follow-up*. Oxford University Press.
- McGorry PD, Nelson B, Markulev C, et al (2017) Effect of ω -3 polyunsaturated fatty acids in young people at ultrahigh risk for psychotic disorders: the NEURAPRO randomized clinical trial. *JAMA Psychiatry*, **74**: 19–27.
- McGuire P, Robson P, Cubala WJ, et al (2018) Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. *American Journal of Psychiatry*, **175**: 225–31.
- Mechelli A, Lin A, Wood S, et al (2017) Using clinical information to make individualized prognostic predictions in people at ultra high risk for psychosis. *Schizophrenia Research*, **184**: 32–8.
- Michel C, Ruhrmann S, Schimmelmann BG, et al (2018) Course of clinical high-risk states for psychosis beyond conversion. *European Archives of Psychiatry and Clinical Neuroscience*, **268**: 39–48.
- Murray RM, Quigley H, Quattrone D, et al (2016) Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry*, **15**: 195–204.
- NAPLS (2018) *NAPLS – The North American Prodrome Longitudinal Study*. Yale University Campus Press (<https://campuspress.yale.edu/napls>). Accessed 17 July 2018.
- National Institute for Health and Care Excellence (2014) *Psychosis and Schizophrenia in Adults: Treatment and Management* (NICE Clinical Guideline CG178). NICE.
- Nelson B, Yuen HP, Lin A, et al (2016) Further examination of the reducing transition rate in ultra high risk for psychosis samples: the possible role of earlier intervention. *Schizophrenia Research*, **174**: 43–9.
- Nelson B, Amminger G, Yuen H, et al (2018) NEURAPRO: a multi-centre RCT of omega-3 polyunsaturated fatty acids versus placebo in young people at ultra-high risk of psychotic disorders – medium-term follow-up and clinical course. *NPJ Schizophrenia*, **4**: 11.
- Oliver D, Davies C, Crossland G, et al (2018) Can we reduce the duration of untreated psychosis? A systematic review and meta-analysis of controlled interventional studies. *Schizophrenia Bulletin*, **44**: 1362–72.
- Polari A, Lavoie S, Yuen HP, et al (2018) Clinical trajectories in the ultra-high risk for psychosis population. *Schizophrenia Research*, Feb 18: doi: 10.1016/j.schres.2018.01.022 [Epub ahead of print].
- PRONIA (2018) *PRONIA – Personalised Prognostic Tools for Early Psychosis Management*. PRONIA (<https://www.pronia.eu/the-project>). Accessed 17 July 2018.
- 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.
- Schimmelmann BG, Conus P, Cotton S, et al (2007) Pre-treatment, baseline, and outcome differences between early-onset and adult-onset psychosis in an epidemiological cohort of 636 first-episode patients. *Schizophrenia Research*, **95**: 1–8.
- Schimmelmann BG, Walger P, Schultze-Lutter F (2013) The significance of at-risk symptoms for psychosis in children and adolescents. *Canadian Journal of Psychiatry*, **58**: 32–40.

Schmidt SJ, Schultze-Lutter F, Schimmelmann BG, et al (2015) EPA guidance on the early intervention in clinical high risk states of psychoses. *European Psychiatry*, **30**: 388–404.

Schmidt A, Cappucciati M, Radua J, et al (2017) Improving prognostic accuracy in subjects at clinical high risk for psychosis: systematic review of predictive models and meta-analytical sequential testing simulation. *Schizophrenia bulletin*, **43**: 375–88.

Schultze-Lutter F, Addington J, Ruhrmann S, et al (2007) *Schizophrenia Proneness Instrument, Adult Version*. Giovanni Fioriti Editore.

Schultze-Lutter F, Ruhrmann S (2008) *Früherkennung und Frühbehandlung von Psychosen*. UNI-MED.

Schultze-Lutter F, Koch E (2010) *Schizophrenia Proneness Instrument, Child & Youth Version (SPI-CY)*. Giovanni Fioriti Editore.

Schultze-Lutter F, Michel C, Schmidt SJ, et al (2015) EPA guidance on the early detection of clinical high risk states of psychoses. *European Psychiatry*, **30**: 405–16.

Schultze-Lutter F, Michel C, Ruhrmann S, et al (2017) Prevalence and clinical relevance of interview-assessed psychosis-risk symptoms in the young adult community. *Psychological Medicine*, **48**: 1167–78.

Simon AE, Borgwardt S, Riecher-Rössler A, et al (2013) Moving beyond transition outcomes: meta-analysis of remission rates in individuals at high clinical risk for psychosis. *Psychiatry Research*, **209**: 266–72.

Studerus E, Rameyead A, Riecher-Rössler A (2017) Prediction of transition to psychosis in patients with a clinical high risk for psychosis: a systematic review of methodology and reporting. *Psychological Medicine*, **47**: 1163–78.

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.

van Os J, Guloksuz S (2017) A critique of the “ultra-high risk” and “transition” paradigm. *World Psychiatry*, **16**: 200–6.

Woods SW, Kantrowitz JT, Javitt DC (2014) NMDAR-based treatments for patients at clinical high risk for psychosis. *Biological Psychiatry*, **1**: 11S.

Yung AR, Yung AR, Pan Yuen H, 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.

MCQs
Select the single best option for each question stem

1 Which of the following does not count towards a diagnosis of clinical high risk for psychosis?
 a suspiciousness
 b negative symptoms
 c hallucinations
 d disorganised speech
 e subjective disturbance of receptive speech.

2 The parents of a 13-year-old girl seek advice after she tells them that, if she concentrates hard, she can perceive the edges of a picture moving. She is not distressed or alarmed by this experience; on the contrary, she seems to enjoy it. On the basis of this information only, should you refer them to a specialised early psychosis service for evaluation?
 a yes, because visual perception disturbances are one of the COPER criteria
 b yes, because psychosis screening in adolescents should always be carried out by trained professionals
 c no, not before you establish whether the time criterion for COPER (at least 12 months) is met
 d no, because there is no subjective distress and therefore the general criteria for basic symptoms are not met
 e no, not before you establish whether the symptom is substance-related.

3 Which of the following statements regarding clinical high risk for psychosis is correct?
 a the majority of these patients will experience a psychotic episode in the future
 b psychosis risk in these patients is substantially increased compared with the general population
 c many of these patients suffer from other psychiatric disorders such as depression
 d all of the above
 e b and c.

4 Which of the following are evidenced-based treatments for high-risk patients?
 a treatment in a specialised early intervention service
 b antipsychotics
 c antidepressants
 d a and b
 e all of the above.

5 Which of the following is not true regarding high-risk criteria?
 a their prognostic usefulness is dependent on referral practices
 b the diagnostic instruments have a low sensitivity and high specificity and, hence, they are good predictors of a future transition to psychosis
 c most patients who develop a psychotic disorder meet criteria for high risk in the prodromal phase
 d patients meeting high-risk criteria often exhibit long-term functional impairments
 e they should be interpreted with caution in children and adolescents.