

ADOLESCENTS AND YOUNG ADULTS AT ULTRAHIGH RISK OF PSYCHOSIS: DETECTION, PREDICTION AND TREATMENT. A REVIEW OF CURRENT KNOWLEDGE

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SUMMARY

Background: The onset of psychosis is mostly preceded by a prodromal phase in which occur a series of various attenuated positive symptoms, negative symptoms and functional impairment. Recently, several longitudinal studies have evaluated the validity and prediction power of the “prodromal risk syndrome for psychosis”, which could lead to a better focused management of the patients at real risk of developing schizophrenia. At the same time, several authors have studied the pharmacological and non-pharmacological interventions for people at ultrahigh risk.

Methods and aims: The objective of this review is to establish the status of our current knowledge about what is the most sensitive and specific tool to predict high risk of psychosis in the young population and which treatments have currently proved to be the most effective in the risk versus benefits balance. We will try to answer to these questions by reviewing the international literature from 2005 until today.

Results: Recent studies show significant improvement in the identification of individuals at high risk of developing psychosis, using validated detection scales such as SIPS and CAARMS, multivariate neuroanatomical pattern classification and specific genetic factors. Cognitive Behavioral therapy, approach improving social functioning, and Long-Chain Ω -3 Fatty Acids appears to be promising alternatives to antipsychotics, for which the balance between benefice and adverse side effects seems questionable.

Conclusions: Detection of young people at ultrahigh risk of psychosis has significantly improved during the last 6 years. The challenge for the next decade will be to define a nosologic entity specific and sensitive enough to become a diagnostic category by itself, which could lead to specific guidelines for the preventive management of psychosis.

Key words: “Prodromal” patients - ultra high-risk – psychosis – prevention - early detection - treatment practice - early intervention

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INTRODUCTION

In Europe, psychotic disorders affect 1.2% of the general population between 18 and 65 years old, an estimate of 3.7 million citizens within any 12-month period. Psychosis is one of the most distressing and costly diseases, and schizophrenia is the 8th leading cause of disability-adjusted life years (DALYs) worldwide in 15 to 44 years of age (Schultze-Lutter et al. 2008, Rössler et al. 2005). Thus the detection and successful treatment of the clinical manifestations preceding the first psychotic episode appears to be an essential track that could lead to significant reduction of the severity of troubles linked to psychosis (Schultze-Lutter et al. 2008).

The prodrome of schizophrenia has initially been defined as “an early or premonitory manifestation of impending disease, before specific symptoms begin” thus retrospectively identified, when the disease is already diagnosed. Recently, authors who are interested in prevention of mental ill health have studied different criteria using prospective methods, defining “the prodromal risk syndrome for psychosis” (Woods et al. 2009).

This increasing interest in the detection and the management of the prodromal phase has several

reasons: First of all, the prodromal phase is characterized by many psychiatric symptoms and incapacities which could lead to severe functional impairment, stigmatizing disabilities and life-threatening consequences. Secondly, the persistence of those disabilities prior to the onset of full positive psychotic syndrome may lower the possibility of eventual recovery, as shown in studies about the influence of the duration of untreated psychosis (Schultze-Lutter et al. 2008, Marshall et al. 2005, Perkins et al. 2005, Fusar-Poli et al. 2009). Thirdly, the preventive treatment previous to transition to full-blown psychosis could minimize alterations in brain structure, as well as neurobiological changes, which could lead to substantial improvement of the prognosis (Nelson et al. 2008).

METHODS

We carried out a literature search using PUBMED and Google, selecting only Scholar’s articles, preferably with full text available, from 2005 until now, in order to identify and describe significant trials, systematic reviews and meta-analysis which have been carried on the subject of the early detection and intervention of the prodromal phase of psychosis.

RESULTS

Power of Prediction of the Clinical Criteria for Detection of Patients at High Risk

For an early detection of people at high risk of psychosis, complementary clinical approaches are usually followed:

The Ultra High Risk criteria (Shultze-Lutter et al. 2010, Nelson et al. 2008)

Using the PACE prodromal symptoms criteria (Table 1), early researches showed a rate of transition to full psychotic disorder ranging from 35-54% over a 12-month period. More recent studies (Yung et al. 2007, McGorry et al. 2008, Cannon et al. 2007) tends to show a lower rate of annual transition (20-35%), which could be due to earlier detection, improved efficacy of

intervention provided, but also to a “dilution” effect – a proportion of patient at real risk of psychosis being diluted by the detection of a greater portion of the population, thus finding more false positives. Nevertheless, there is a current tendency, in the available studies, for a 30-35 % risk of psychosis within 1 to 2 years of follow-up among UHR cases, a rate definitively higher than the incidence rate of psychosis in the general young population (Cannon et al. 2007). For instance, a large longitudinal North American study published in 2009 shows that 40% of the 377 patients assessed by the Structured Interview for Prodromal Syndromes (SIPS) as meeting criteria for prodromal syndromes, converted to fully psychotic illness during the 2.5 years of follow-up. The sensitivity of the baseline prodromal diagnosis for conversion to psychosis was 89% and the specificity was 60.2% (Woods et al. 2009).

Table 1. Personal Assessment and Crisis Evaluation (PACE) criteria

Require that a young person, aged between 14 and 30 years, who have a perceived need for care, meets criteria for one or more of the following groups:

- Attenuated Psychotic Symptoms (APS): have experienced attenuated positive psychotic symptoms (Magical thinking, paranoid ideation/mistrust, unusual perceptual experiences, body-related illusions, idea of reference...) during the past year.
- Brief Limited Intermittent Psychosis Symptoms (BLIPS): have experienced episodes of frank psychotic symptoms, no longer than a week, with spontaneous full recovery.
- Combination of Risk Factor (have a first degree relative with a psychotic disorder or meet diagnosis for schizotypal personality disorder) and Recent Functional Decline during the past year.

Shultze-Lutter et al. 2010, Nelson et al. 2008, Fowler et al. 2010)

Table 2. The Basic Symptoms Criteria

1. *Cognitive Perceptive Basic Symptoms (COPER)*: At least one of the following basic symptoms with at least weekly occurrence within the last 3 months + first occurrence at least 12 months ago:
 - 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;
 - derealization;
 - visual perception disturbances;
 - acoustic perception disturbances.
2. *Cognitive Disturbances (COGDIS)*: At least two of the following basic symptoms with at least weekly occurrence within the last 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.

(Koch et al. 2010)

Prediction algorithms incorporating combinations of 2 or 3 baseline variables (genetic risk for schizophrenia with recent deterioration in functioning, higher levels of unusual thought content, higher levels of suspiciousness, greater social impairment, history of substance abuse (see Velthorst et al. 2009)) result in dramatic increases in positive prediction power (ie, 68-80%), compared with SIPS criteria alone (35%) (Cannon et al. 2008).

The Basic Symptoms Criteria (Koch et al. 2010, Nelson et al. 2008)

The annual conversion rate for sample meeting basic symptoms criteria is around 25% (Koch et al. 2010),

and the rate of conversion reaches 70% in a study with a 110 patient's follow-up of 9.6 years, with a mean time to onset of 5.6 years (Nelson et al. 2008) (Table 2).

Some authors consider that the Basic Symptoms precede the onset of APS and BLIPS (see for instance the definition of the early (-E) and the late (-L) at-risk mental state (ARMS) of psychosis (Table 3) according to Comprehensive Assessment of At Risk Mental States (CAARMS) criteria (Koutsouleris et al. 2009), which is not confirmed by a 2010 German retrospective study exploring the time-related syndromic sequence preceding the onset of full-blown psychosis (Shultze-Lutter et al. 2010).

Table 3: EARLY and LATE At Risk Mental States criteria

ARMS-E: Individual With ARMS Without APSs and/or BLIPSs

1. Cognitive Perceptive Basic Symptoms (COPER)
and/or
2. Reduction in Global Assessment of Functioning Scale score (DSM-IV) of ≥ 30 points (within the past year) combined with ≥ 1 of the following trait markers:
 - First-degree relative with lifetime diagnosis of schizophrenia or a schizophrenia spectrum disorder
 - Prenatal or perinatal complications

ARMS-L: Individual With ARMS With or Without Basic Symptoms, With or Without Global Functioning and Trait Markers

1. Individuals had ≥ 1 of the following APSs within the past 3 months, appearing several times per week for a period of ≥ 1 week:
 - Ideas of reference
 - Odd beliefs or magical thinking
 - Unusual perceptual experiences
 - Odd thinking and speech
 - Suspiciousness or paranoid ideation*and/or*
2. Individuals had ≥ 1 BLIPS, defined by the appearance of 1 of the following psychotic symptoms for < 1 week (interval between episodes ≥ 1 week), resolving spontaneously:
 - Hallucinations
 - Delusions
 - Formal thought disorder
 - Gross disorganized or catatonic behavior

(Koutsouleris et al. 2009, Häfner et al. 2004)

Other Clinical Classifications

A study using magnetic resonance imaging-based neuroanatomical pattern classification showed promising results regarding the detection of people at risk of psychosis and the prediction of disease transition (Koutsouleris et al. 2009).

Efficacy of Medical and Non-Medical Treatment of the Prodromal Phase

Antipsychotics (Kelly et al. 2010, De Koning et al. 2009)

All the studies compared in a recent meta-analysis of treatments of the patients at Ultra High risks (Kelly et al. 2010) showed comparable efficacy, with a diminution of the transition rate about 15% in favor of the

antipsychotics, which reached statistical significance only in the studies using risperidone and amisulpride (McGorry et al. 2002, Ruhrmann et al. 2007), although the study using olanzapine (McGlashan et al. 2006) tended toward significance. The study using aripiprazole was excluded because there was no control group (Woods et al. 2007).

Considering adverse effects, amisulpride caused side-effects associated with the increase of the prolactin for 81% of the intervention group (vs 20.6% of the control group) (Ruhrmann et al. 2007); aripiprazole caused akathisia for 60 % of the patients (Woods et al. 2007); olanzapine (McGlashan et al. 2006) caused weight gain (61.3% vs 17.2%) and fatigue (29% vs 3.9%); and risperidone (McGorry et al. 2002) caused stiffness (12% vs 0%).

Antidepressants (Kelly et al. 2010)

Only one substantial study (Cornblatt et al. 2007) compared an intervention group of 20 UHR patients receiving antidepressants versus 28 receiving second-generation antipsychotics, showing similar efficacy but more drop-out in the second group, suggesting that it might be preferable to begin treating the prodromal phase with antidepressants; but the assignment to a group or the other was not randomized, which lower the power of those results.

Long-Chain Omega-3 Fatty Acids (Kelly et al. 2010, De Koning et al. 2009)

A randomized, placebo-controlled trial (Amminger et al. 2010) with a 12-week intervention and 40-weeks monitoring period showed a reduction of 22.6% of the cumulative risk of progression to full-threshold psychosis for the intervention group. Long-chain Ω -3 fatty acids also significantly reduced positive, negative and general symptoms and improved functioning, compared with placebo. The incidence of adverse effects did not differ between groups. Another earlier study showed similar results (Berger et al. 2007).

Cognitive-Behavioral Therapy (CBT) (Kelly et al. 2010)

A randomized study (Morrison et al. 2004) comparing CBT over 6 months with monthly monitoring in 58 patients meeting UHR criteria showed a 15% reduction of the rate of conversion to full blown psychosis. This significant benefit of the cognitive treatment seems to persist over the long term, as a three-year follow-up of this cohort tended to show (Morrison et al. 2007).

Integrated Care (Kelly et al. 2010)

Seventy-nine patients were randomized to integrated model treatment (Modified Assertive Community Treatment, Social skills training, and Psycho-education in multiple-family groups) or standard treatment (usual treatment at a community mental health center). At two-year follow-up, the proportion diagnosed with a psychotic disorder was 25.0% for patients randomized to integrated treatment compared to 48.3% for patients randomized to standard treatment (Nordentoft et al. 2006).

DISCUSSION

Recent studies show significant improvement in the identification of individuals at high risk of developing psychosis, using validated detection scales such as SIPS and CAARMS, multivariate neuroanatomical pattern classification and specific genetic factors, which lead to early intervention to prevent the emergence of florid psychosis. While the number of false positive remains important, those patients who may never develop full blown psychosis suffer nevertheless from invalidating symptoms which could deeply compromise their social integration and thus are in need for psychological and/or

psychiatric treatment. However, the risk subsists of unnecessary stigmatization that could aggravate the sense of being odd, especially with the adolescents.

Cognitive Behavioral therapy, approach improving social functioning, and Long-Chain Ω -3 Fatty Acids appears to be a promising alternative to antipsychotic treatments, for which the balance between beneficial and adverse side effects seems questionable, for a population without long term florid symptoms. Non-medical interventions are attractive because they target psychosocial deficits, which are usually pharmacological-resistant (Schultze-Lutter et al. 2008). More studies are required to determine the place of antidepressants and further larger randomized controlled trials analyzing risk-benefits and cost-benefits of early detection and early intervention have to be conducted in the nearer future.

CONCLUSION

The Ultra High-Risk or Prodromal Risk Syndrome tends to become a nosologic entity by itself. It describes a group of clinical symptoms which lead to social, psychological and neurocognitive impairments, thus in need for early detection and care.

As research proceeds, the challenge of the next decade will be to improve detection tools to define the "Psychosis Risk Syndrome" specifically and sensitively enough to become a diagnostic category by itself (Woods 2010, Shrivastava et al. 2011), which could lead to specific guidelines for the preventive management of psychosis.

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