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Early Interventions for Clinical High-Risk State for Psychosis

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ABSTRACT

The aim of this review was to discuss early intervention options for clinical high-risk states of psychosis, the limitations of the high-risk concept, and the importance of population-based approaches in preventing psychosis. Interventions for individuals at high risk of psychosis can be classified into two main categories: pharmacological and non-pharmacological. When selecting any of these intervention options, it should be taken into account that only a small proportion of individuals in the high-risk group will have a transition to clinical psychosis. Therefore, it is necessary to avoid aggressive interventions. Pharmacotherapies, particularly antipsychotics, are generally not considered as a treatment of choice for individuals at high risk of psychosis due to their potential side-effect profiles, whereas cognitive behavioral therapies and family-oriented therapies are the leading alternatives with virtually no side effects. However, meta-analyses have shown that none of the interventions are specifically more effective than needs-based treatment (including placebo) in preventing transition to psychosis. These interventions might not be effective in preventing transition to psychosis; however, they may improve the outcomes of psychosis. Accumulating evidence suggests that the targeted prevention approaches focusing on the clinical high risk of psychosis concept have major limitations in terms of the impact on reducing psychosis incidence in the general population compared to the population-based approaches. Recently, psychosis-focused prevention approaches have been replaced by easily accessible youth mental health centers that provide services for transdiagnostic conditions. Future studies on the efficacy of these community-based youth mental health services may provide guidance on how to prevent psychosis.

Keywords: Schizophrenia, psychosis, early intervention, cognitive behavioral therapy, antipsychotic, high risk

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INTRODUCTION

Efforts to prevent transition to psychosis in individuals at high risk of psychosis have been an active research field over the last 25 years. The main goal of early interventions for psychosis is to identify high-risk groups to reduce the rates of transition to clinical psychosis. This paper summarizes the early intervention options for groups at high risk of psychosis and discusses the limitations of the concept of high risk of psychosis as well as why early diagnosis and interventions focused on the high risk of psychosis are not successful at the community level. Finally, the role of community-based youth mental health services in preventing psychosis is reviewed.

Identification of Individuals at High Risk of Psychosis

Following developments in the medical world, the concept of "high risk of psychosis" or "a clinical high-risk state for psychosis" emerged for the prevention of "transition" to psychosis within the framework of studies on the prevention of schizophrenia (1, 2), and various approaches have been suggested for the evaluation of the stage before transition to psychosis. The first of these was the stratification approach described by Bell in 1992 (3). Other approaches are based on the basic symptoms and clinical high risk (4). The Bonn Scale for the Assessment of Basic Symptoms (BSABS) is used to identify individuals who may clinically have a transition to schizophrenia approximately over 5 years through the evaluation of many domains from thoughts, language, perception, to motor disorders, physical sensory disorders, and impaired stress response without impaired mood, emotions, and increased emotional reactivity (5).

The Comprehensive Assessment of At-Risk Mental States (CAARMS) and Structured Interview of Prodromal Symptoms (SIPS) are scales that are often used for the assessment of high-risk individuals. The CAARMS and SIPS evaluate multiple risk factors for transition to psychosis and provide an understanding of whether the individual is in one of the four groups (6, 7).

These groups are Mild Psychosis, Brief Intermittent Psychotic Syndrome (BIPS), Genetic Risk and Deterioration Syndrome (GRDS), and Attenuated Positive Symptom Syndrome (APSS) (8). According to SIPS, the Mild Psychosis group includes individuals with at least one mild symptom that lasts several minutes and is experienced more than once a week in the last month with onset within the last year or with increasing severity in the last year. The BIPS group includes those with at least one symptom on the psychotic threshold that lasts at least several minutes and is experienced at least once a month with onset in the last three months. The GRDS group includes individuals who are diagnosed with schizotypal personality disorder and have a decrease of at least 30% in the Global Assessment of Functioning score in the last month compared to 12 months previously, or who have a first-degree relative with a history of psychotic disorder. The APSS group includes those with current psychotic symptoms or a history of psychotic symptoms lasting more than 1 hour a day on an average of 4 days a week (7).

Early Interventions for Groups at High Risk of Psychosis

Sub-threshold psychotic symptoms, social, emotional, and cognitive

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impairments, and help-seeking behavior for these are often seen in individuals at clinical high risk of psychosis (9–11). Early interventions for groups at high risk of psychosis are promising for alleviating symptoms such as sub-threshold psychotic symptoms, halting the progression of deterioration in the quality of life, and increasing the quality of life of these individuals. However, a 2018 meta-analysis investigating whether specific interventions are useful for the prevention of transition to psychosis did not show any evidence regarding the efficacy of any specific intervention in preventing transition to psychosis (12). The current treatment guidelines on clinical high-risk syndrome for psychosis recommend cognitive behavioral therapy, family-focused therapy, and psychotherapies such as integrated psychological interventions. In addition to these interventions, needs-based interventions and pharmacological interventions are other methods used to prevent transition to psychosis.

Non-Pharmacological Interventions

Cognitive Behavioral Therapy (CBT)

CBT is a therapy method often used for the treatment of several psychiatric disorders. CBT has a role in alleviating symptoms and preventing transition to psychosis, as in the treatment of schizophrenia. These methods are preferred as they are well tolerated and pose no risk of side effects compared to pharmacological interventions. A meta-analysis including 5 studies with 24- and 48-month follow-up periods and 10 studies with 12-month follow-up period on the effect of CBT on decreasing the risk of transition to psychosis found that CBT reduced the risk of transition to psychosis by 54% at 12-month follow-up, and by 37% at 24–48 month follow-ups (13). Another randomized, controlled study comparing the efficacy of CBT and supportive therapy found that CBT improved low-level positive symptoms more rapidly than supportive therapy (14).

The Van der Gaag protocol is a different CBT protocol among the commonly used treatment protocols. In behavioral experiments, it is added to the French and Morrison protocol due to the cognitive bias in the structure of paranoid thoughts and psychoeducation related to dopamine system hypersensitivity. A study using the Van der Gaag protocol showed that CBT could decrease subclinical psychotic symptoms and the rate of transition to psychosis (15, 16). Another study on 288 subjects between 14–35 years of age who were at high risk of psychosis showed that CBT decreased the severity of psychotic symptoms in this sample of young people though it did not significantly decrease the rates of transition to psychosis (17). The results of a recent meta-analysis were pleasing as CBT was reported to be associated with a significant decrease in transition to psychosis at 12- and 18-month follow-ups compared to control groups (18).

In conclusion, despite the ongoing debate on the extent of the efficacy of CBT, the effect size, applicability (the requirement for at least 6–8 sessions, a certain level of education), and the limitations in the methodology of studies (the skill of the practitioner, the lack of an objective measurement tool for the efficacy of psychotherapy) when effects/side-effects are compared, there is a stronger opinion that CBT should be first selected as an early preventative intervention for individuals at high risk of psychosis, considering its high tolerability and no side effects.

Family-focused Therapy

It is important that family members participate in early psychosocial interventions since individuals at high risk of psychosis are mostly adolescents and young adults living together with their families. Another reason is that strong emotional responses shown by parents may be a risk factor for psychosis. Family-focused therapy can develop the stress-coping strategies of family members, decrease negative symptoms, and increase problem-solving skills and interpersonal communication skills (19).

Family psychotherapy (extended care) and family-focused therapy provide an improvement in negative symptoms and low-level positive symptoms (19). A study comparing the efficacy of family-focused therapy and extended care in individuals at high risk of psychosis showed that family-focused therapy was a better intervention method for communication and problem-solving skills than extended care (20). However, family-focused therapy lasts approximately 6 months, requires at least 18 therapy sessions, and has a higher cost than those of other intervention options. Nevertheless, the future establishment of family-focused therapy methods with a relatively lower cost, ease of access, and applicability can eliminate these kinds of drawbacks to family-focused therapy (20).

Integrated Psychological Intervention (IPI)

The integrated psychological intervention method consists of several elements. These include personalized CBT applications and social skills training aiming at improving cognition, impaired thoughts, and perceptions. A study comparing needs-based intervention and IPI concluded that IPI was effective in delaying the onset of psychosis for 24 months (21). The results of a recent meta-analysis showed no superiority of IPI, CBT, supportive therapy, family therapy, and needs-based interventions over the use of omega-3, risperidone and CBT, olanzapine, and risperidone in terms of transition to psychosis (18).

Pharmacological Interventions

Pharmacological interventions to be administered to individuals at high risk of psychosis should address existing clinical symptoms. For example, needs-based pharmacological interventions such as mood regulators and anti-depressants can be used in cases of predominant symptoms associated with mood fluctuations or anxiety (22), whereas the short-term use of antipsychotics can be appropriate for sub-clinical psychotic symptoms. Pharmacological interventions also include new and experimental pharmacotherapies and food supplements.

Antipsychotics

There are several studies in the literature on the efficacy of pharmacotherapy interventions with antipsychotic content in individuals at high risk of psychosis. Pharmacotherapy can be used in combination with another intervention and the individuals are followed up in respect of side effects. To date, studies investigating the efficacy of antipsychotic use to prevent transition to psychosis in groups at high risk have investigated the efficacy of olanzapine, risperidone, aripiprazole, and ziprasidone (23–26).

A study evaluating the efficacy of olanzapine in delaying transition to psychosis and reducing symptoms in individuals with symptoms of prodromal schizophrenia found the rate of transition to psychosis approximately 2.5-fold higher in the placebo group compared to the group receiving olanzapine (23). Ziprasidone is another second-generation antipsychotic used for the treatment of schizophrenia and bipolar disorder. The results of a study examining the efficacy of ziprasidone in individuals at high risk of psychosis showed no difference between ziprasidone and placebo in terms of the prevention of transition to psychosis (25). A comparison of antipsychotics with non-pharmacological interventions, CBT, aripiprazole, and a placebo revealed no significant difference between the groups in respect of the risk of transition to psychosis (26). Similarly, another study found no difference between CBT, antipsychotics, and supportive treatment. Despite no difference between the groups, there was an improvement in general functionality and especially in negative symptoms in the group treated with all three intervention options (27). The lack of significant difference between the groups has been interpreted as that antipsychotic treatment should not be the first option for high-risk groups before other therapy methods (28).

New/Experimental Pharmacotherapies and Nutritional Supplements

In the prodromal period of this disorder, more reliable interventions such as omega-3 long-chain polyunsaturated fatty acids (PUFA) and CBT are accepted as the preferred options for first-line treatment (29). However, the efficacy of PUFAs can be speculated to represent more false-positive results in individuals at high risk of psychosis (30). The results of a study examining the efficacy and safety of long-chain omega-3 PUFAs showed that they decreased the risk of transition to psychosis and stated that they could be an alternative effective preventative strategy in young subjects with subclinical psychotic symptoms (31). However, this was not confirmed by a more recent study with a larger sample, which compared treatment with CBT case management and omega-3 PUFAs, and placebo and CBT case management, as omega-3 PUFAs were not found to be superior to the placebo (32). Another randomized, double-blind study comparing omega-3 fatty acids (FA) and placebo in a group at clinical high risk of psychosis for a period of 24 weeks showed no change in the group treated with omega-3 fatty acids compared to the placebo group in respect of transition to psychosis (33).

D-serine, an N-methyl-D-aspartate (NMDA) modulator, has been found to have a more positive effect on negative symptoms compared to placebo (34). Research should continue to investigate the potential improvements and preventative effects of D-serine on transition to psychosis in the treatment of negative symptoms, which is a challenging subject in the treatment of individuals with a psychotic disorder.

Needs-Based Intervention (NBI)

There is no proven treatment algorithm for the prevention of psychosis in individuals at high risk of psychosis, thus personalized interventions have come to the fore because of the heterogeneity of symptoms in individuals in the high-risk group. NBI encompasses supportive psychotherapy, case management, family psychoeducation, drugs other than antipsychotics, clinical follow-up, and crisis management (27). An example of drug use in an NBI approach is sertraline, a type of antidepressant, and benzodiazepine for insomnia (27).

The results of a study comparing CBT intervention and low-dose risperidone (mean 1.3 mg) with NBI showed that 10 of 28 subjects at high risk of psychosis who were treated with NBI developed a first episode of psychosis over time, whereas only 3 of 31 subjects in the other group developed a first episode of psychosis (27). Non-directive reflective listening, one of the NBI methods, in which people can discuss not only their mental state but also topics of their own choice, and the therapist presents empathetic thoughts, has been shown to significantly reduce the problems associated with psychotic symptoms compared to CBT (35).

Limitations of the Concept of High Risk of Psychosis

Psychotic experiences do not only indicate psychosis and the concept of high risk for psychosis has several limitations such as the presence of very few community-based epidemiological studies (the existing studies include individuals seeking help) among the studies conducted on the subject (30, 36). The major limitation of the high-risk concept is that psychotic experiences usually accompany several psychiatric conditions. Psychiatric experiences may accompany disorders such as anxiety, depression, substance abuse, and some personality disorders (especially schizotypal personality disorder), which have been associated with a poor course. The results of a large-scale epidemiological study showed that positive psychotic experiences were more common than assumed and were associated with not only psychosis but also help-seeking behavior, attempted suicide, and impairments in functionality and cognition (37–42).

A longitudinal, community-level study examining the concepts of "risk" and "transition" determined that the incidence of new psychosis cases in the community was related to precursor high-risk conditions (risk ratio: 7.86) (43). This study also calculated the population attributable fraction (PAF) to be able to determine the incidence of psychosis (43). PAF is an epidemiological measurement used to evaluate the effect of exposure and is defined as the proportion of all the cases of a certain disease in a population which can be attributed to a certain exposure (44). A high-risk state of psychosis has been determined to be a PAF of 36.9 for the incidence of psychosis. However, the PAF for psychosis incidence of a previously diagnosed mood disorder is higher (66.2). Substance abuse also has an insignificant PAF of 18.7 (43).

This result, which may initially seem to be surprising and confusing, is due to the very low prevalence of high-risk individuals in the general population. The frequency of diagnoses such as mood disorders and anxiety disorders is higher in the community. This can be explained by the phenomenon of the "prevention paradox", which is well known in epidemiology (30). The prevention paradox is defined as the conflicting situation in which the majority of cases of a disease in a population have a low or moderate risk of the relevant disease and those at high risk of the disease constitute only a small proportion of the cases (45). The prevention paradox emphasizes that while preventative efforts of individuals at high risk on a personal basis provide a high rate of benefit in the prevention of transition to psychosis, the effect is lower compared to a community-based strategy to reduce the incidence and disease-related burden (36).

In brief, only a small proportion of those who clinically progress to psychosis has been previously found to be individuals at high risk of psychosis, suggesting that the approach of focusing only on high-risk groups is more trouble than it is worth when the high cost of identifying these individuals in the community is considered.

In conclusion, the limitations of the high-risk concept can be interpreted as that the prevalence of individuals at high risk of psychosis is low in the general population, measurement tools primarily measure only positive symptoms, studies have been conducted on limited clinical samples, and there are few community-based studies. The development of measurement tools on those seeking help is also a limitation that prevents their general use in the community due to low accuracy.

High Risk and Beyond: Community-Based Approaches to the Prevention of Psychosis

The symptomatology of psychosis is heterogeneous and the etiology has not yet been fully understood, therefore trying to eliminate potential etiological factors is like looking for a needle in a haystack (46). Although the concept of "high risk of psychosis" prevents an indisputably important clinical framework for transition to psychosis, the results of a recently published study showing no measurement tool with high sensitivity and specificity which could be used for community screening have opened this concept up for discussion (30, 36).

Epidemiological studies have shown that psychotic experiences could be a good marker to be able to understand the general severity of multi-dimensional psychopathology; however, as there are fluctuations in the dimensions of psychosis, it is difficult to discount false positives. Positive symptoms as the primary marker for the concept of "transition" in the high-risk group are not only predictive of psychosis but also a measure of the level of positive psychotic symptoms of the individual in the presence of a categorical transition. Psychotic experiences are multi-dimensional, and considering that they may start with non-specific symptoms such as frequent sleep disorders, anxiety, depression, and cognitive difficulties, the high-risk group defined by positive symptoms can be at a very late stage for intervention, and outcomes may therefore not be pleasing. Accordingly, to be more inclusive, interventional methods have evolved to be directed at the community (47).

Speaking of a community-based approach to the prevention of psychosis, Headspace comes to mind, which is the National Youth Mental Health Foundation founded in Australia in 2006 (48). Headspace centers have a target of young people aged 12–25 years and have a national network, which consisted of 10 centers in 2007 and 110 centers in 2008 (49). Studies evaluating the effectiveness of Headspace centers have shown that these centers provide a significant improvement in symptoms and functionality of young people (48, 50). Youth mental health centers providing a service similar to the Headspace centers have been established not only in Australia but also in many other countries.

Providing easily accessible healthcare services, youth mental health centers aim to provide interventions and follow-up before a condition turns into a clinical syndrome. After their establishment in Australia, these centers, which aim to provide easy access to services for those seeking all kinds of psychiatric help, have become widespread in countries such as the Netherlands, Ireland, and Denmark.

Youth mental health centers provide access to the necessary care by identifying the actual needs of the young people and their families as well as culturally specific needs. Thus, they prevent the stigmatization of these young people. The services of these centers are not only in the field of mental health but also include improvements in physical health and services to reduce alcohol and drug abuse (47). Although a personalized and more easily accepted intervention and follow-up plan can be created in these centers, various factors make it difficult to gain more benefit from these centers, primarily the abandonment of treatment. A study investigating the risk factors for abandoning treatment before completion found a correlation between a high rate of abandonment of treatment and male gender, older age, living in a rural area, and heterosexual orientation (51).

CONCLUSION

To be able to accurately evaluate the effect of early intervention on rates of transition to psychosis in a group at high risk of psychosis, it is initially necessary to have a good understanding of the limitations of the high-risk concept and make a more inclusive definition. The high sensitivity and low specificity of tools measuring the risk of psychosis in individuals at high risk of transition to psychosis have led to a preference for therapy-focused and protective protocols in early protective interventions rather than an aggressive treatment protocol in which antipsychotics are considered the first choice.

It should be taken into consideration that individuals not exhibiting a transition to psychosis may develop other psychiatric disorders over time such as anxiety disorder and the continuation of low-level psychotic symptoms. The goal of early interventions should not only be to prevent transition to psychosis but also to improve the quality of life and provide early treatment for other psychiatric disorders. Therefore, the most effective interventions are not diagnosis-focused but community-based approaches. The expansion of community-based youth mental health services and increase in the number of studies on the efficacy of these services will provide greater guidance in the future.

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