Original Article

A Systematic Review of pharmacological efficacy and alternative treatments for the prevention of ultra-high risk for psychosis

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Objective: To present and evaluate the latest findings of studies pertaining to the pharmacological and alternative treatment of individuals at ultra-high risk (UHR) for psychosis.

Methodology: A title or abstract appeared to describe a study eligible for inclusion; the full article was obtained and examined to assess its relevance. The PUBMED search terms in the title used were "psychosis," "schizophrenia," "ultra-high risk," "clinical high risk," "at risk mental state," "intervention," "efficacy," "effectiveness," "management," "treatment," and "prevention." The combined search strategies yielded over 100 abstracts but, after an analysis of the abstracts, 97 full-text articles were reviewed. Finally, 35 articles were included.

Results: Antipsychotics that have been tried to date are amisulpride, aripiprazole, olanzapine, perospirone, risperidone, and ziprasidone. Although most studies included small groups, the baseline symptoms improved after pharmacological treatment. However, the antipsychotic effect of treatment with antipsychotics in UHR groups was insufficient to confirm positive results. In the long-term follow-up of UHR groups, more than 30% of studied individuals remained in the high-risk group and had clinically significant symptoms and difficulties.

Conclusion: If antipsychotics are to be used, atypical antipsychotics should be selected; starting with a low dose, and the treatment response and side effects should be periodically evaluated, while administration should last for an appropriately limited period of time. In addition to antipsychotics, use of antidepressants, nutrients/supplements including omega-3, and alternative drugs should be considered. (Rawal Med J 202;46:240-244).

Keywords: Psychosis, psychiatric symptoms, alternative treatments.

INTRODUCTION

Early diagnosis and intervention for psychosis including schizophrenia are important goals of psychiatric treatment in that they may positively change the natural course of psychotic disorder. The concept of ultra-high risk (UHR) for psychosis, also known as at-risk mental state, prodromal schizophrenia, and clinical high risk for psychosis, was defined to capture the pre-psychotic phase, describing high and imminent risk of developing first-episode psychosis.[1] Individuals at UHR for psychosis have a risk of developing first-episode psychosis of 15–30% within 1 year, and of over 36% after 3 years.[2] In Germany, strategies for predicting the imminent outbreak of schizophrenia have been developed based on subjective, subtle, and unobservable abnormal experiences in thinking, perception, and language under the clinical threshold; a study found that psychotic disorders developed at approximately 35% in a 2-year period.[3] In UHR groups, psychosis incidence is hundreds of times that in the general population.[4] Longer duration of untreated psychosis could lead to poorer outcomes including functional deficits and severe psychotic symptoms.[5,6] Therefore, to date, several countries have attempted to reduce the risk by creating intervention guidelines.[7-11] Two main purposes of treatment of individuals at UHR for psychosis have been the management of current symptoms and reducing the risk of developing a psychotic disorder.[4] However, as UHR for psychosis does not constitute manifest psychotic disorder, considering the negative aspects of antipsychotic treatment such as stigma and drug side effects, guidelines and studies to date have indicated that cognitive behavioral therapy (CBT) can be mainly used instead to improve symptoms and reduce the risk of transition to psychosis.[12-15] Various attempts

have been made for the treatment of individuals at UHR for psychosis according to the biological basis of the disease. Therefore, this review covers the research results and potential of various pharmacological and alternative treatment methods that have been tried in UHR for psychosis groups.

METHODOLOGY

To provide an appropriate review of treatment for individuals at UHR for psychosis, I performed a careful PUBMED search to identify all relevant papers and book chapters in English during the period 1996–2019 and included studies reporting on individuals at UHR for psychosis. I only included studies reporting on the treatment or management of symptoms or means used to prevent transition to psychosis.

Where a title or abstract appeared to describe a study eligible for inclusion, the full article was obtained and examined to assess its relevance. The PUBMED search terms in the title used were "psychosis," "schizophrenia," "ultra-high risk," "clinical high risk," "at risk mental state," "intervention," "efficacy," "effectiveness," "management," "treatment," and "prevention." The combined search strategies yielded over 100 abstracts but, after an analysis of the abstracts, 97 full-text articles were reviewed. Finally, 35 articles were included.

RESULTS

The degree of evidence for treatment of ultra high risk for psychosis is shown in the table.

Table. Assessment of the degree of evidence for the effectiveness of treatment in ultra-high risk for psychosis.

	Psych pharmacotherapy			Nutritive supplements and alternative medication					
	Antipsychotics	Antidepressants	Mood stabilizers	Omega-3 PUFA	D-serine and glycine	Vitamin supplements	Oxytocin	Minocycline	Cannabidiol
Preventing psychosis	Very Low *	Very Low	(-)	Low	(-)	(-)	(-)	(-)	Very Low
Improving symptoms	Very Low †	Very Low	Very Low	Low	Very Low	Very Low	Very Low	Very Low	Very Low

* Olanzapine, risperidone case control study † Olanzapine case control study (-) No study

The degree of evidence for the effectiveness of treatment: based on randomized controlled trials (RCTs): **High:** More than two RCTs with effectiveness exceeding 50%. **Intermediate**: More than two RCTs with effectiveness lower than 50% **Low**: One RCT **Very Low**: No RCTs

DISCUSSION

Psych pharmacotherapy treatment

Antipsychotics: The use of antipsychotics for the treatment of UHR groups requires caution. The use of antipsychotics is likely to cause several unnecessary side effects and stigma. Therefore, antipsychotics have been seldom used for the treatment of UHR groups in very complex situations given the lack of clear evidence.[7,8,9] Therefore, their use is mainly recommended when there is rapid status deterioration and the risk of self-injury, aggression, or hostility increases.[7] When the use of antipsychotics is indicated, atypical antipsychotics have been recommended for the management of such individuals.[10,11] Antipsychotics that have been tried to date include amisulpride, aripiprazole, olanzapine, perospirone, risperidone, and ziprasidone.[16] Although most studies included small groups, the baseline symptoms improved after pharmacological treatment.[16,17] However, the antipsychotic effect of treatment with antipsychotics in UHR groups was insufficient to confirm positive results.[16] In the long-term follow-up of UHR groups, more than 30% of studied individuals remained in the high-risk group and had clinically significant symptoms and difficulties; hence, although the use of antipsychotics has shown no protective effect against the development of psychotic disorder.[18]

Antidepressants: It is generally not recommended to prescribe antidepressants to individuals with acute psychosis because antidepressants may worsen psychotic symptoms.[16] However, mood

symptoms comprise a distinct psychopathology, and their amelioration constitutes an important goal of treatment, distinct from psychosis symptoms in UHR groups.[19] The use of antidepressants is considered effective in improving some psychosis symptoms and in decreasing the feelings of depression and anxiety that individuals at UHR for psychosis may usually experience.[20] Studies have shown that antidepressants did not have a pronounced effect on improving symptoms in high-risk groups.[16,19] Additionally, there have been reports that treating depression in high-risk groups may delay the appearance of psychosis, but there is still insufficient evidence to accept these findings.[21]

Mood stabilizers: It is speculated that very complicated biological processes may be involved in the progression from UHR for psychosis to psychotic disorder, but they have not been clarified. It is considered that the removal of synapses that apexes in adolescence is a natural developmental process, but excessive synaptic pruning may cause disease manifestation.[16] Accordingly, neuronal protection has emerged as an alternative strategy to control the psychotic process. Lithium at low doses as a mood stabilizer acts to protect synapses from various attacks, such as glutamatergic toxicity, lack of nerve growth factor, glucocorticoids, ionizing radiation, ischemia, and oxidative stress.[22]

Nutritive/supplements and alternative medication

Omega-3 polyunsaturated fatty acid (PUFA): Omega-3 PUFA is a long-chain PUFA (LC-PUFA) composed of eicosatetraenoic and docosahexaenoic acids. LC-PUFAs are major components of cell membrane phospholipids and are involved in various receptor binding, neuronal signaling and inflammation, oxidative stress, and defense processes.[23] LC-PUFA cannot be synthesized in the human body, and lack of intake leads to deficiency, increasing the risk of transition from UHR for psychosis to psychosis.[23,24] The neuroprotective effect of omega-3 PUFA delays the initial psychotic morbidity of UHR groups because of its neuroprotective effect and has emerged as an alternative for the treatment of UHR groups with relatively weak and fewer side effects than those of psychoactive agents including antipsychotics.[24]

D-serine and glycine: D-serine is an amino acid mainly synthesized from glycine in astrocytes. It has been reported that serine decreases in the synapses of patients with psychosis.[26] Glycine is an excitatory neurotransmitter acting as a potent agonist to the glycine binding site of the N-methyl-D-aspartic acid (NMDA) receptor, the site of glutamate action, and D-serine also acts on the binding site of glycine.[26] Hypofunction of NMDA receptors is involved in several symptoms of psychosis, including cognitive impairment in the early stages of psychosis.[26,27]

Vitamin supplement therapy: Cobalamin and folate also facilitate the conversion of homocysteine to methionine, promoting the production of S-adenosylmethionine.[23] Homocysteine is an amino acid, an intermediate metabolite in the process of synthesizing cysteine from methionine, and is involved in oxidative stress by interacting with the NMDA receptor, causing apoptosis, dysfunction of the mitochondria at the cellular level, and vascular damage.[24-28] High blood levels of homocysteine are associated with decreased cognitive function in healthy individuals, and some patients with schizophrenia show elevated levels of homocysteine in the blood.[29]

Oxytocin: Oxytocin is a nonapeptide hormone composed of amino acids synthesized in neurons located in the paraventricular and supraoptic nuclei in the hypothalamus and stored in the posterior lobe of the pituitary gland.[30] Oxytocin regulates reproductive function and acts as a neurotransmitter in the central nervous system.[30] The oxytocin receptor in the brain is located in the basal ganglia, in the limbic system, an anatomical structure associated with schizophrenia.[30] The action of the oxytocin receptor, located in the nucleus accumbens, the septal prosthesis of the ventral striatum, is considered helpful in attachment and socialization in children.[31]

Minocycline: Minocycline is a tetracycline-based broad-spectrum antibiotic. It is lipophilic and has excellent permeability of the blood-brain barrier and was found to be effective in the treatment of psychosis because of its neuroprotective action, which reduces gray-matter loss and helps improve the overall function and speech symptoms of

individuals with psychosis and the neural changes caused by the action of microglia and cytokines given its anti-inflammatory action.[32] The effect on the NMDA glutamate receptor is also considered to have a protective effect against neurotoxicity by stabilizing glutamate release, and minocycline is expected to help improve symptoms in UHR groups.[33]

Cannabidiol (CBD): The main psychoactive component of *Cannabis sativa* is Δ9-tetrahydrocannabinol (Δ9-THC) and induces psychotic symptoms. CBD could antagonize the effects of Δ9-THC in healthy volunteers.[34] This observation has triggered a series of studies in both animals and humans, which have established a link between CBD and antipsychotic effects.[35]

CONCLUSION

If antipsychotics are to be used, atypical antipsychotics should be selected; starting with a low dose, and the treatment response and side effects should be periodically evaluated, while administration should last for an appropriately limited period of time. In addition to antipsychotics, use of antidepressants, nutrients/supplements including omega-3, and alternative drugs should be considered.

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