Editorial
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Psychosis risk syndrome: Pharmacological interventions

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The potential benefits of providing effective treatment for young people at psychosis risk syndrome (PRS) –known variably as ultra high risk (UHR)– of developing a psychotic disorder has been recognized only the last decade. Interventions on this phase, which can be divided to psychosocial and pharmacological, aim to reduce symptom severity, as well as to delay or even to fully prevent the onset of psychosis.

There are few published studies to date that have studied the use of medications in PRS. As antipsychotics are helpful in the treatment and relapse prevention for psychosis, these drugs have been tried for the PRS individuals. According to the first published study, a randomized controlled trial (RCT), UHR subjects receiving Cognitive Behavior Therapy (CBT) and a low dose of risperidone for 6 months, manifested significantly lower rate of transition to psychosis (9.7%) compared to UHR subjects receiving supportive psychotherapy (36%). However, in subsequent follow ups (f.u.), 6 months and 3–4 years later, this significant difference had been disappeared.[1] Another RCT double blind study, comparing olanzapine to placebo, reached similar results[2] while two open label studies found significant improvement on both several symptom dimensions and functioning at the end of 8 and 12 weeks of treatment with aripiprazole and amisulpride correspondingly.[3] Furthermore, a naturalistic multisite study reported that antipsychotics improve positive attenuated symptoms and disorganized behavior in PRS subjects but did not influence negative and general symptoms, while antidepressants did not decline symptom severity.[4] Finally, according to the latest published RCT double blind study,[5] UHR individuals who received cognitive therapy plus a low dose of risperidone or cognitive therapy plus placebo or supportive psychotherapy plus placebo for 6 months, did not manifest any difference both in symptom improvement and conversion rate to psychosis.

In summary, from all the above studies, one can assume that intervention with antipsychotic medication in PRS subjects may delay conversion to psychosis and improve symptoms, especially positive symptoms, during the active phase of treatment, but there is no evidence of long lasting effects after therapy termination.

There are a number of reasons against the use of antipsychotics in PRS individuals. First of all there are potentially serious side effects associated with all antipsychotic drugs such as extrapyramidal symptoms, metabolic syndrome, sexual dysfunction etc. In addition, many UHR subjects, as they have strange experiences, are concerned that they are going "mad". The prescription of drugs with indications for schizophrenia and other psychotic disorders increases the distress and make them feel stigmatized, especially if it occurs without information about potential benefits. Finally, of concern is recent evidence that long term use of antipsychotics,

even in low doses, can cause sensitization of dopamine receptors, leading to rapid-onset psychosis following treatment termination.

Apart from the previously mentioned naturalistic study,[4] two other open label studies examined the effect of antidepressants on PRS subjects and found a significantly lower rate of conversion to psychosis compared to antipsychotics.[6] It has been suggested that depression increases the likelihood that prodrome anomalous experiences develop into a psychotic disorder. Thus, antidepressants may have a protective effect by improving mood and reducing the individual's faulty appraisal of prodromal symptoms.[3] In addition, antidepressants may modulate the person's response to environmental stressors. Stress has been linked with both the onset and relapse of psychosis by an overactivity of the hypothalamus-pituitary-adrenal (HPA) axis. According to the one and only RCT double blind study, ω-3 had a significantly superior beneficial effect both on conversion rate to psychosis and improvement of symptomatology and functioning compared to placebo.[7] The most important finding of that study is that group differences were sustained after cessation of interventions. Trials with antipsychotics have not found this. Furthermore, the researchers reported high consent rate, low drop-out rate and non group differences regarding side effects, indicating that this treatment is well tolerated. Omega-3 fatty acids have neuroprotective properties by inducing antiapoptotic and antioxidative factors.[7] It was found that eicosapentaenoic acid (EPA) increases glutathione, the brain's principal antioxidant defense. There are findings supporting that acute psychosis is related with glutathione deficiency.[6] There is also evidence that ω-3 have a generalized positive effect on mental health. Controlled trials reported beneficial effects in depression, bipolar disorder, borderline personality disorder, antisocial behavior/aggression, attention deficit/hyperactivity disorder (ADHD) and autism, suggesting that ω-3 modulate mood, impulsivity and aggression.[6]

There is a continuing research interest on the field of pharmacological intervention in PRS subjects. There are several ongoing studies, most of them double-blind, placebo-controlled trials. Three of them intend to compare antipsychotic drugs i.e. ziprasidone, quetiapine, aripiprazole to placebo and another one tests the effect of ω-3. Finally, two other studies investigate the influence of D –serine and sarcosine-substances involved in the glutamate pathways– compared to placebo.

In conclusion, research on early intervention for UHR individuals is still in its infancy. Current scientific data suggest that the "clinical staging model"[6] of care should be followed. Intervention should begin with the more benign treatments such as psychosocial and/or omega-3 fatty acids as a first step, by progressing to more intensive interventions for patients who do not improve. Depression and anxiety are highly prevalent in UHR subjects and represent a key treatment target in their own right. In these cases prescription of antidepressants should be considered. On the contrary, antipsychotic medication should not be considered as a first treatment option. However, a rapid worsening of psychotic symptoms together with significant decrease in functioning are indices suggesting prescription of a 2nd generation antipsychotic at low dose.

Future research is needed. A main research effort should be focused to indentify those within the UHR population who are at greatest risk to develop a frank psychosis. The achievement of this aim includes among others: (1) Improvements in diagnostic tools. (2) To find out if there is a relationship between the presence/absence of individual symptoms or clusters of symptoms and remission or progression of PRS. (3) Use of laboratory findings such as neuroimaging findings. For instance, it is suggested that PRS subjects who later developed psychosis had less gray matter volume in specific brain areas than those who did not. In addition, there are some questions which should be answered[6] such as for how long should treatment continue? Or can interventions during PRS modify the outcome if the full blown psychosis develops? etc.

It is evident that UHR population is a heterogenous clinical population at risk not only for schizophrenia but also other mental health problems[6] such as depression, anxiety, substance abuse etc. In addition, they have

cognitive, social and vocational difficulties. Although most of them will not develop psychosis, they are not well and they need help, especially as adolescence and early adulthood are crucial periods regarding personal growth and development of academic, social and occupational skills. Developing effective intervention strategies will provide therapy of existing distress and disability in addition to introducing the possibility of delaying or preventing the onset of a psychotic disorder.[6]

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