Is clinical intervention in the ultra high risk phase effective?

A intervenção clínica na fase de ultra alto risco é eficaz?

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Abstract

Recent research suggests that early intervention in psychosis might improve the chances of recovery and may even be able to prevent the onset of psychotic disorders. Clinical intervention in subjects at ultra high risk (UHR) of psychosis can have three different objectives. The first aim is to improve the 'prodromal' symptoms and problems that subjects usually present with. The second is to reduce the risk of the subsequent onset of frank psychosis. The third objective is to minimize the delay before the initiation of antipsychotic treatment in the subgroup of UHR subjects that go on to develop a first episode of psychosis. Both pharmacological and psychological interventions appear to be effective in reducing the severity of presenting symptoms in UHR subjects. Clinical trials of the impact of these interventions on the risk of subsequent transition to psychosis have been positive, but have involved small samples, and thus the issue of whether the effects persist in the long term remains to be determined. The monitoring of UHR subjects for the first signs of frank psychosis is an effective means of reducing the delay between the onset of the first episode and the start of antipsychotic treatment. Follow-up studies are required to test whether the reduction in this delay leads to an improved long term outcome. To date, the majority of the interventions that have been used in UHR subjects, such as case management, antipsychotic medication, and cognitive behavior therapy have previously been employed in patients with established psychosis. However, it is possible that treatments that are not normally used in patients with psychotic disorders may prove effective when applied at this stage.

Descriptors: Psychotic disorders; Antipsychotic agents; Symptoms; Cognitive Therapy; Treatment outcome

Resumo

Estudos recentes sugerem que a intervenção precoce na psicose poderia melhorar as chances de recuperação e inclusive evitar o início de transtornos psicóticos. A intervenção clínica para indivíduos em ultra alto risco (UAR) de psicose pode ter três objetivos diferentes. O primeiro é o de melhorar os sintomas e problemas "prodrômicos" que os indivíduos normalmente apresentam. O segundo é o de reduzir o risco de psicose franca subsequente. O terceiro objetivo é o de minimizar a demora antes do início do tratamento antipsicótico no subgrupo de indivíduos em UAR que evoluem para um primeiro episódio psicótico. Tanto as intervenções farmacológicas como as psicológicas parecem ser eficazes para reduzir a gravidade dos sintomas apresentados pelos indivíduos em UAR. Ensaios clínicos sobre o impacto dessas intervenções no risco de transição subsequente para psicose foram positivos, mas envolveram amostras pequenas e, dessa forma, a questão de se os efeitos persistem ou não no longo prazo ainda precisa ser resolvida. O monitoramento dos indivíduos em UAR para os primeiros sinais de psicose franca é uma forma eficaz de reduzir a demora entre o início do primeiro episódio e o começo do tratamento antipsicótico. Estudos de acompanhamento são necessários para testar se a redução desse tempo leva a um desfecho melhor no longo prazo. Até hoje, a maioria das intervenções para indivíduos em UAR, como manejo de caso, medicação antipsicótica e terapia cognitivo-comportamental, foram empregadas anteriormente em pacientes com psicose estabelecida. No entanto, é possível que tratamentos que não são normalmente utilizados para pacientes com transtornos psicóticos possam ser eficazes ao serem aplicados nesse estágio.

Descritores: *Transtornos psicóticos; Agentes antipsicóticos; Sintomas; Terapia cognitiva; Resultado de tratamento*

Introduction

The first episode of a psychotic disorder is often preceded by a syndrome of attenuated psychotic symptoms and a decline in social and occupational function[1]. People who present with these 'prodromal' features are described as being at ultra high risk (UHR) of psychosis, as they are associated with an approximately 30% risk of developing psychosis in the following two years[2], a risk that is about 400 times greater than normal[3,4]. While the presence of this phase has been known for a long time[1], it is only in the last decade or so that clinicians have tried to clinically intervene at this stage[5]. Conventionally, treatment for psychotic disorders is withheld until the first episode of frank illness.

This recent interest in early clinical intervention has occurred in the context of new research on the neurobiology of the UHR phase. Magnetic resonance imaging (MRI) studies have shown

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that reductions in grey matter volume in the frontal and temporal cortices, the limbic system and cerebellum are evident in UHR subjects, well before the first episode of psychosis[6,7,8]. Similarly, both dopaminergic and glutamatergic function, as measured using F-DOPA PET and MR spectroscopy, respectively, are altered before the first episode of psychosis[9,10,11], and functional MRI studies have shown that UHR subjects display abnormalities that are qualitatively similar to those seen in patients with schizophrenia[12,13,14]. Furthermore, longitudinal neuroimaging studies in UHR subjects indicate that some of these structural and neurochemical abnormalities progress as subjects make the transition from the prodromal to the psychotic state[6,15,16]. Such progressive changes suggest that there is an active neuropathological process underlying the onset of illness at this stage, which might therefore be arrested through clinical intervention.

The aim of this article is to provide a state-of-the-art review of studies that have sought to examine the effectiveness of clinical intervention in UHR subjects.

Subjects at ultra high risk of psychosis

People who are at UHR of psychosis are usually identified on the basis of a combination of trait and state risk factors. The PACE criteria[17] require that subjects have one or more of the following: (1) attenuated psychotic symptoms, (2) brief limited intermittent psychotic symptoms within the last year, and (3) a significant decrease in functioning, maintained for at least a month, plus either a schizotypal personality disorder or a first-degree relative with a psychotic disorder. The criteria of the Structured Interview for Prodromal Syndromes (SIPS[18]), developed in North America, are similar to the PACE criteria. UHR subjects can also be identified on the basis of subjective changes in thinking, language and attention, termed 'basic symptoms'[19]. Subjects meeting either of these criteria have a risk of transition to psychosis of 15-54% in the next 24 months[4,20]. Many centers now use both sets of inclusion criteria, as they are based on complementary types of clinical features. A recent meta-analysis of 27 follow-up studies estimated the mean risk of transition to psychosis to be 31% in 24 months[14], and found that the risk was similar for studies using either set of inclusion criteria.

Treatment of presenting symptoms

The first aim of clinical intervention in UHR subjects is to relieve their presenting problems and symptoms. These are often the patient's main concern, as they are usually what led to their referral. UHR subjects typically present with distressing symptoms (attenuated psychotic symptoms, anxiety, and depression) that occur in the context of social and vocational problems[21]. The presenting subject will often want some form of treatment or assistance for these problems, and they are thus described as 'help-seeking' individuals (as distinct from subjects who may experience psychotic symptoms but do not seek clinical help).

Woods et al.[22] studied the acute symptomatic effects of olanzapine versus placebo in UHR subjects (n=31 and n=29 in each arm) in a double-blind randomized controlled trial. They found that at an average dose of 10.2 mg/day, olanzapine had significantly improved symptom levels at eight weeks, but was also associated with significant weight gain. In an open-label trial, Ruhrmann et al., randomly assigned UHR subjects to a needs-focused intervention, with (n=65) or without (n=59) amisulpride[23]. They found that amisulpride significantly reduced attenuated and full-blown psychotic symptoms, basic, depressive and negative symptoms, and improved global functioning at 12 weeks. Similarly, Woods et al.[24], in another open-label study, found that aripiprazole reduced positive and negative symptoms scores at eight weeks, although this was associated with mild akathisia.

A trial of cognitive behavioral therapy (CBT) in UHR subjects reported that this improved attenuated positive symptoms, with some benefits sustained at three years of follow-up[25]. Bechdolf et al. recruited young people (n=113) meeting criteria for the early initial prodromal states and provided both individual and group CBT, comparing this to supportive counseling[26]. The CBT targeted self-experienced cognitive thought and perception deficits, negative symptoms, anxiety, depressive symptoms, family and occupational problems. CBT was not superior to supportive counseling, with both treatments leading to significant improvements in social adjustment measures. Addington et al. compared CBT and supportive therapy[27]. They reported no group differences, but both therapy groups made significant improvements in attenuated positive symptoms, anxiety and depression relative to baseline.

Reducing the risk of psychosis

A longer-term objective of treatment is to reduce the risk that the UHR subject will go on to develop a full-blown psychotic disorder. If an UHR subject is going to develop psychosis, in most (but not all) cases this will occur within two years of presentation[3,4,14]. Over the last 10 years, a number of clinical trials have examined the impact of intervention on the risk of transition to psychosis in this group.

Pharmacological trials

Antipsychotic medication

To date, two randomized clinical trials using antipsychotic medication have been conducted. In the first study, UHR subjects received a needs-based intervention plus either risperidone (1-2 mg/day) and CBT, or needs-based intervention alone for six months. After 6 months, 3 of 31 subjects in the actively treated group had developed a psychotic disorder, compared to 10 of 28 in the control arm[28]. A further 3 subjects in the active treatment group had become psychotic at 12 months of follow-up. However, the study groups were not blinded to the treatment, and the effects of treatment did not persist at either 12 months or 3 years of follow-up[28]. Because the active treatment arm involved both risperidone and CBT, it is unclear if the beneficial effect was due to the pharmacological or the psychological treatment, or both. McGlashan et al. compared the effects of olanzapine (n=31) *vs* placebo (n=29) for 12 months in a double-blind randomized

trial[29]. There was a high dropout rate, with only 33 subjects completing the trial, and only 17 completing the 12-month follow-up period. There was a strong trend for a reduced rate of conversion to psychosis at 12 months with olanzapine. However, the olanzapine group gained a mean 8 kg over a period of 12 months, and were more likely to have dropped out than the placebo group[29].

Antidepressants

Up to 50% of UHR subjects present with low mood and anxiety, in addition to attenuated psychotic symptoms[30]. Antidepressants are commonly used to treat these symptoms in UHR subjects, and until recently there was no expectation that this would influence the risk of transition to psychosis. However, in a naturalistic study (n=48), Cornblatt et al. followed up young adolescents with at-risk symptoms who had been prescribed either an antidepressant (n=20) or an atypical antipsychotic (n=28) by their treating clinician[31]. They observed that while both groups improved symptomatically, there had been no transitions to psychosis in the group who had been prescribed antidepressants. However, 11 of the 12 UHR subjects in the antipsychotic group who had converted to psychosis were non-compliant with antipsychotic medication. It is also possible that the treating clinicians chose to prescribe antidepressants to the UHR subjects in whom they were less concerned about the risk of later psychosis, and used antipsychotics in those that they thought were most at risk. Nevertheless, Fusar-Poli and colleagues found similar results in a retrospective naturalistic study of an independent UHR sample, with a much lower transition rate in the subjects who had been treated with antidepressants than in tho se who had been given either antipsychotics or CBT[32].

Although unexpected, these findings are consistent with cognitive models of psychosis[33] that propose that isolated psychotic experiences are more likely to develop into frank psychosis if they occur in the context of depression. Moreover, it is possible that the putative effect of CBT on the risk of transition (below) reflects an impact on depressive, as opposed to psychotic, symptoms. In addition, subjects in the community who report psychotic experiences in the presence of depressed mood have a higher risk of developing a psychotic disorder than those who do not[34]. Treatment with antidepressants may influence the response to environmental stress and therefore alter the risk of psychosis[35]. However, because these findings are based on retrospective naturalistic studies, they require replication in a randomized trial.

CBT

CBT is widely used in UHR subjects. For example, in the OASIS service, when offered the choice of treatment, 70% of UHR subjects were willing to have CBT, but only 25% accepted antipsychotic medication[36]. This willingness to try CBT may reflect the fact that many UHR subjects are open to the possibility that their symptoms may be related to an underlying disorder[37]. Data from two randomized clinical trials of CBT in UHR subjects have been published to date[25,27,38]. Morrison et al. reported that CBT was superior to clinical monitoring in reducing the progression to psychosis over 12 months (2/35 developed psychosis in the CBT arm, *vs* 5/23 in the monitoring arm)[38]. However, this effect was no longer significant at three years of follow-up[25]. Addington et al. compared CBT with supportive therapy[27]. Although more subjects in the supportive therapy group developed psychosis than in the CBT group, the difference was not statistically significant[27].

Eicosapentaenoic acid (EPA)

Amminger et al. conducted a 12-week trial comparing eicosapentaenoic acid (EPA) with placebo in UHR subjects[39]. At 12 months of follow-up, 2 of 41 individuals in the EPA group had developed psychosis, compared to 11 of 40 in the placebo group. There were also improvements in the levels of attenuated positive and negative symptoms in the active EPA treatment group. These findings are of particular interest, as EPA is an example of what early intervention clinicians would regard as an ideal intervention for UHR subjects[5]. It is an inexpensive nutritional supplement, with minimal side effects, and which may have beneficial effects on physical health, which is particularly poor in patients with psychosis. Moreover, in contrast to antipsychotic medication, treatment with EPA is non-stigmatizing. However, the promising initial results require replication in a larger sample, and a large multi-center study of EPA in UHR subjects is currently ongoing[5].

Because only a minority (about 30%) of UHR subjects will subsequently become frankly psychotic[14], there are concerns about the ethics of clinical intervention to reduce the risk of psychosis in this group[5,40]. Thus, the potential benefit of reducing the risk of psychosis has to be balanced against the risk that subjects who might never have developed psychosis will receive treatments that may be associated with adverse effects and stigmatization. However, these concerns relate specifically to treatment that is designed to prevent the onset of psychosis: they are less relevant to the treatment of the presenting symptoms, which occur in all UHR subjects and which the subjects usually want to have treated.

Reducing the duration of untreated psychosis (DUP)

A potential benefit of intervention at the UHR stage that is often overlooked stems from the engagement of subjects with mental health services before the first episode of psychotic illness. If a clinician is already seeing the patient, has established a clinical rapport with him/her, and the patient is already aware of the early signs of psychotic illness and what happens should psychosis develop, it should be easier to detect the first onset of psychosis and reduce the delay before the initiation of its treatment. In addition, the patient is more likely to understand the rationale for treatment and to accept that it is worthwhile. As a short DUP is associated with a better prognosis (above), reducing the DUP through engagement in the UHR phase may therefore improve the subsequent clinical outcome. To date, only one study has examined this issue. In subjects engaged by the OASIS service in London, and who subsequently developed psychosis, the average DUP was

10 days. This compared with a DUP of 12 months in patients from the same geographical area who did not present until they were experiencing their first episode of psychosis[36]. The patients who developed psychosis after engagement in the UHR phase were also less likely to require admission, compulsory treatment or police involvement. This probably reflects the initiation of treatment at the start of the first episode (as opposed to several months later), when the illness is less severe, and patients are more willing to cooperate with the clinical team. Further work is required to assess whether this approach has beneficial effects on long-term clinical and functional outcome.

Limitations of trials to date

The results of the above studies suggest that both pharmacological and psychological intervention at the UHR stage can reduce the severity of the presenting symptoms. However, whether intervention can delay or prevent the onset of a psychotic disorder remains unclear, mainly because most trials in this area to date have been underpowered, due to small sample sizes. A further caveat is that, in the trials conducted so far, both the duration of the interventions and the follow-up periods have been relatively short. It thus remains unclear how long treatment in the UHR stage should be given for. Given that the majority of transitions to psychosis occur within the first two years after presentation, a reasonable approach would be to provide treatment for this period, thereby covering the 'window of highest risk'. However, in practice, some UHR subjects are unwilling to continue with active treatment for this length of time, particularly if their presenting symptoms have resolved.

Outstanding issues

Duration of specialized intervention

It remains unclear how long specialized treatment should be delivered for. At present, a popular approach is to provide care for two years, as this period is when the risk of transition to psychosis is maximal.

Multisite clinical trials

A key limitation of all trials to date in UHR subjects has been limited sample size, and a resultant lack of power to test the effectiveness of interventions. It is unlikely that any single site can recruit sufficiently large numbers of this population for a definitive clinical trial, as UHR subjects are relatively difficult to identify and engage. This problem can be overcome by conducting multi-center trials, and these are now ongoing[5,41,42].

Clinical staging

Clinical staging has been proposed as a model for a future intervention strategy in UHR subjects[5]. This suggests that the nature of the intervention should depend on the stage of illness, progressing in a step-wise fashion from benign, low-risk treatments towards more intensive interventions for those who do not show a response, and who may be more at risk. McGorry et al. suggest that through clinical staging, it is possible to provide acceptable and less stigmatizing interventions to patients[5].

Targeted intervention

Because only a minority of UHR subjects will later develop psychosis, there is great interest in determining factors that could identify the subgroup of subjects that are destined to become psychotic, so that preventative treatment could be given to those who need it most. This would permit a more efficient use of clinical resources and would be more acceptable from an ethical perspective. A number of clinical measures have been identified that are associated with the later onset of psychosis within UHR samples. The multi-center NAPLS study reported that the combination of a family history of schizophrenia, recent functional deterioration, unusual thought content and suspiciousness/paranoia, and social functioning deficits provided a positive predictive power for later psychosis of up to 80%[4]. The EPOS multi-center study found that SIPS positive score, bizarre thinking, sleep disturbances, schizotypal personality disorder, global functioning score in the past year, and years of education were the best predictor variables[43]. Neuropsychological studies of UHR subjects at clinical presentation have suggested that certain deficits, particularly impairments in episodic memory, are more marked in subjects who later develop psychosis[44,45,46].

Neuroimaging studies of UHR subjects at presentation have found that the subsequent onset of psychosis is associated with smaller prefrontal and medial temporal volumes[6,7,8], increased prefrontal, medial temporal, lateral temporal and midbrain activation[47,48], increased subcortical dopamine function[10], and an alteration in the relationship between subcortical dopamine function and medial temporal glutamate levels[49]. Longitudinal neuroimaging studies have also linked transition to psychosis with progressive changes in some of these measures subsequent to presentation[6,15,16,50].

While there have thus been a number of clinical, neuropsychological and neuroimaging findings linked to the onset of psychosis in UHR subjects, these have generally been identified at a group level. However, in clinical practice, the psychiatrist needs to be able to use such measures from an individual patient to make a reliable prediction about the likelihood of later transition in that person. One method which has the potential to permit predictions at an individual subject level is machine learning[51], which allows a comparison of a given patient's data with existing datasets that are representative of subjects who have or have not subsequently developed psychosis[52]. To date, this approach has been applied to neuroimaging data form UHR subjects, but it can be applied to any form of data, and can incorporate clinical, cognitive, and neuroimaging data in the same analysis.

Conclusions

Both pharmacological and psychological treatments in UHR subjects appear to improve presenting symptoms. Trials of their ability to reduce the risk of later psychosis have been positive, but have involved small samples. It is also unclear if the reported beneficial effects persist in the long term, and

it remains to be established how long intervention in UHR subjects should be given for. The clinical monitoring of UHR subjects for early signs of frank psychosis is a very effective means of reducing the DUP, and appears to reduce the severity of the first episode. Follow-up studies are required to test whether this reduction in DUP leads to improved clinical outcomes.

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