Intervention in Individuals at Ultra-High Risk for Psychosis: A Review and Future Directions

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Objective: Over the last 15 years, a focus on early intervention in psychotic disorders has emerged. Initially, the early psychosis movement focused on timely recognition and phase-specific treatment of first-episode psychosis. However, early psychosis researchers suspected that pushing the point of intervention even further back to the prodromal phase of psychotic disorders may result in even better outcomes. This article reviews intervention research in the ultra–high-risk phase of psychotic disorders.

Data sources: A literature search of intervention trials with ultra–high-risk cohorts published after 1980 was conducted on PubMed with the search terms *prodrome* and *intervention*.

Study selection: All published intervention trials with ultra–high-risk cohorts.

Data synthesis: The first generation of intervention trials indicated that both pharmacologic and psychological intervention strategies may be of value in terms of symptom reduction and delay or prevention of onset of threshold psychotic disorder.

Conclusions: Further controlled intervention trials with larger sample sizes are required in order to confirm and extend these findings. We argue that the clinical staging model provides a framework for the rationale and design of such studies, with simpler, safer, and more benign interventions being better candidates for first-line treatment, while more complex and potentially harmful treatments should be reserved for those cases in which response has failed to occur. Recent evidence indicates that neuroprotective agents, such as essential fatty acids, may be a suitable form of intervention for the ultra–high-risk phase of psychotic disorders, with a positive risk-benefit balance. Ethical aspects have become more salient given the recently observed declining transition rate in ultra–high-risk samples. We outline the key questions for the next generation of ultra–high-risk intervention trials.

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For over a century, a shroud of pessimism, stigma, and neglect confined therapeutic efforts for schizophrenia and other psychotic disorders to delayed and patchy palliative care. However, during the past 15 years, a systematic international collaborative movement of clinicians and researchers has sought to modify and apply the principles and practice of early diagnosis and staged treatment that are well established in other areas of clinical medicine, such as cancer and cardiovascular disease, to the field of psychotic disorders.[1–4] A key rationale for early intervention has been the relationship between prolonged illness duration and poor outcome in psychotic disorders.[5,6] In a recent meta-analysis[7] and a systematic review,[6] longer duration of untreated psychosis was associated with poorer response to antipsychotic treatment as measured by severity of global psychopathology, positive and negative symptoms, demoralization, depression, and functional outcomes. Neuroimaging studies have also indicated that prolonged untreated illness is associated with more pronounced structural brain abnormalities, while this is less prominent earlier in the course of the disorder.[8] Treatment delay may be reduced by early detection and intervention, resulting in improved short-term and longer-term outcome. Randomized trials have also suggested that initiation of atypical antipsychotic therapy at the first episode can prevent progression of the structural changes seen in the disorder.[9]

Initially, the early psychosis movement focused on timely recognition and phase-specific treatment of first-episode psychosis. However, it was also recognized that, for most patients, a prolonged period of attenuated symptoms and impaired functioning precedes the first psychotic episode.[10,11] Much of the disability associated with psychotic disorders, particularly schizophrenia, develops long before

the onset of frank psychosis and is difficult to reverse, even if the first psychotic episode is successfully treated.[12] This preonset period of illness has been termed the *prodromal phase*.[13,14] Within the context of the early intervention paradigm, researchers suspected that pushing the point of intervention even further back from the first episode of psychosis to the prodromal phase may result in even better outcomes.[15–17] Intervening during this phase may ameliorate, delay, or even prevent onset of fully fledged disorder,[18] thereby reducing the burden of disability, prevalence, and possibly even the incidence of psychotic disorders.

However, this goal presented the major challenge of prospectively identifying the prodromal phase, a task that is complicated by the nonspecific nature of prodromal symptoms.[19] Criteria were introduced for the prospective identification of individuals at heightened risk for developing first-episode psychosis within a brief time period—that is, as possibly being in the prodromal phase of illness. These criteria are based on a combination of known trait and state risk factors for psychosis, including attenuated positive psychotic symptoms, brief self-limited psychotic symptoms, and family history of psychotic disorder. They have been termed the *ultra–high-risk* (UHR) criteria.[20] The first published study using the UHR criteria found a transition rate of 40% to threshold psychotic disorder within 1 year,[20] despite the provision of needs-based psychosocial intervention and antidepressant treatment when indicated. This finding has subsequently been replicated by several groups internationally.[21–23] Using a combination of studies, Ruhrmann et al[24] reported an average 1-year transition rate of 36.7% in UHR subjects who did not receive antipsychotic treatment. These results indicated that the UHR criteria are valid and reliable criteria for predicting psychosis onset in this population.

The recent North American Prodrome Longitudinal Study (NAPLS) further contributes to the evidence for the validity of the UHR criteria. The NAPLS consisted of a blend of cohorts from 8 North American centers involved in prodromal research since the late 1990s.[25,26] With a sample of 291 subjects, it is the largest longitudinal UHR study to date. The key findings were that the UHR criteria do indeed predict a UHR group for early transition to psychosis (with a large RR of 405) and that the predictive power can probably be enhanced by the use of variables such as genetic risk, functional impairment, and substance use. However, a limitation of the study was that treatment was uncontrolled and varied within and across sites.

A similar early detection strategy complementary to the UHR strategy was developed in Germany. This approach found that *basic symptoms*, which refers to subtle, self-experienced disturbances in a range of domains, predicted onset of schizophrenia with reasonable accuracy within a nonspecific clinical sample from even earlier in the course of the illness than was possible with the UHR criteria.[27] This led to a distinction between a late and early initial prodromal state in the German early detection approach.[28] However, further examination of the accuracy of predicting onset of psychosis within 12 months after baseline assessment revealed that presenting with at least 2 of 9 symptoms of the cognitive disturbances cluster of basic symptoms resulted in a transition rate to psychosis of 23.9% within 12 months, an additional 22.4% within the second year, and a further 14.9% within the third year. Thus, the 12-month transition rate of the cognitive disturbances cluster of basic symptoms was comparable with individuals at risk with attenuated positive symptoms (APS) from the UHR criteria (ie, 12-month transition rate of 26.5% for APS alone[29]).

THE FIRST GENERATION OF ULTRA–HIGH-RISK INTERVENTION STUDIES

The successful identification of the at-risk population facilitated 2 important advances in the early psychosis field: (1) research into processes associated with psychosis onset, including psychopathological, neurocognitive, and neurobiologic variables, and (2) the implementation of intervention trials aimed at treating existing symptomatic and functional impairment in the UHR population and determining whether specific interventions are able to ameliorate, delay, or prevent onset of fully fledged psychotic disorder in this population. The challenge has been to define the clinical frontier for earliest intervention and need for care and the most effective and acceptable type of intervention.

The first such intervention trial, conducted in Melbourne, Australia, compared combined cognitive-behavioral therapy (CBT) and low-dose atypical antipsychotic medication (risperidone) (n = 31) with usual case management (n = 28).[30] Subjects were randomly assigned, but neither patients nor investigators were blind to the intervention received. The rate of psychosis onset in the treatment group was significantly lower than in the control group after the 6-month treatment phase (9.7% vs 35%, $P = .026$). However, this finding was nonsignificant after a further 6 months of follow-up, which was due to patients who were not fully adherent to the antipsychotic medication and who developed psychotic disorder in the second 6-month period. This study demonstrated that psychosis onset can at least be delayed by specific intervention, if not prevented. However, the active component of the treatment regimen could not be identified, as medication and cognitive psychotherapy were combined. The results also suggested that a longer treatment period is required.

A more sophisticated randomized, double-blind, placebo-controlled trial was then conducted in the UHR population by a second group of researchers from Yale University.[31] Low-dose olanzapine (n = 31) was compared to placebo (n = 29) for 12 months, followed by a 12-month monitoring period. Of the total sample of 60 participants, 16 (26.6%) developed psychotic disorder during the treatment period. Five of those who developed psychosis were

in the olanzapine group and 11 were in the placebo group. Over the second 12-month period, an additional 3 from the olanzapine group and 2 from the placebo group developed psychosis. These results are similar to the first trial indicating that provision of a specific antipsychotic medication could delay the onset of psychosis. However, this trial narrowly missed significance, and the adverse effects were more serious, which led to a more conservative interpretation of the findings.[32]

A third treatment trial in the UHR group was conducted in Manchester, United Kingdom.[33] Subjects (n = 58) were randomly assigned to receive cognitive therapy for 6 months or monitoring of mental state only. The group that received cognitive therapy had a significantly lower rate of transition to full threshold disorder (6% vs 26%, $P < .05$) and a significantly greater reduction in psychiatric symptoms ($P < .02$) at 12 months. At 3-year follow-up, cognitive therapy was associated with a significantly lower rate of transition to psychosis when baseline cognitive factors were controlled for and a significantly reduced likelihood of being prescribed antipsychotic medication. Bechdolf et al[34] reported that cognitive therapy for patients in the early initial prodromal state, as identified by the presence of basic symptoms, was superior to supportive counseling in reducing progression to subthreshold psychotic symptoms and to full-threshold psychosis over 24 months. Cognitive-behavioral therapy was found to be well accepted and tolerated by high-risk patients in all 3 intervention studies. The OPUS trial[35] also indicated that transition rates could be reduced in a group of patients with schizotypal disorder by intervening with the OPUS package, which consisted of intensive clinical case management, family involvement, and psychoeducational approach within a cognitive-behavioral framework.

Recently, there has been interest in the possibility of using antidepressants to reduce risk of psychosis in high-risk samples.[36,37] Cornblatt et al[37] reported a naturalistic study of young people with prodromal symptoms treated with either antidepressants or antipsychotics. Twelve of 28 patients (43%) who had been prescribed antipsychotics went on to develop psychosis in the following 2 years, whereas none of the 20 patients treated with antidepressants subsequently developed psychosis. Similar results are reported by Fusar-Poli et al[36] on the basis of a file audit. It is possible that antidepressants reduce the risk of psychosis onset by improving mood and thereby reducing the faulty appraisal of anomalous experiences (see Fusar-Poli et al[36] and Yung et al[38]). Antidepressants may also modulate the individual's response to environmental stressors, which may indirectly reduce the risk of subsequent psychosis.[36,39] However, the results to date need to be interpreted with caution due to the uncontrolled nature of the studies: there may have been differences in baseline symptom, functioning, or other variables between treatment groups, and nonadherence was far more prominent among patients prescribed antipsychotics than patients prescribed antidepressants.

Another critical finding in the UHR group is that the transition rate has been dropping in recent cohorts.[40] At the Personal Assessment and Crisis Evaluation Clinic (PACE) Clinic in Melbourne, Australia, the transition rate has dropped from about 50% in 1995 to about 12% in 2000, with each successive year showing a transition rate of 0.80 times that of the preceding year.[40] A similarly reducing transition rate has been observed at other UHR clinics. The reasons for this are unclear, but it may be due to earlier detection and treatment of UHR samples, different referral patterns and sampling from referral sources, or more effective psychosocial interventions or a combination of these factors.[40] Longer-term follow-up of UHR samples is critical in order to clarify these possibilities.

THE CLINICAL STAGING MODEL AS A WAY FORWARD

The lower transition rates and consequently higher false-positive rates (at least in short-term follow-up) mean that safer interventions must be offered as the first line of treatment for people who nevertheless have a clear-cut need for care of some kind. Conceptually, this is supported by the clinical staging model,[41–43] which proposes that the earlier in the course of illness that treatment is offered the safer it should be and the more effective it may be in terms of remission and recovery rates. This approach is consistent with the early results of a recently completed study in Melbourne, Australia. Subjects (N = 115) were recruited to a 3-cell, double-blind, placebo-controlled trial comparing combinations of risperidone, placebo, CBT, and supportive therapy (ST) (ie, risperidone + CBT vs placebo + CBT vs placebo + supportive therapy).[44] The findings indicate that 6-month transition rates were low in all 3 treatment groups, which suggests that UHR cases who are detected early are probably derived from less "enriched" samples in terms of true-positive rate or that, at this stage, antipsychotics are not necessary (A.R.Y.; L. J. Phillips, PhD; B.N.; et al, manuscript submitted). The high rates of psychotic-like experiences in community cohorts[38,45] lends additional support to the notion that a staged approach may reduce the necessity to treat all individuals with antipsychotic agents.

Finally, another important study that lends support for this staged approach to intervention was a randomized, double-blind, placebo-controlled trial of omega-3 fatty acids in the UHR group.[46] This Vienna-based study found that 1.2 g/d of omega-3 fatty acids (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]) ("fish oil"), provided for 12 weeks, were effective in reducing the transition rate to first-episode psychosis in UHR adolescents. Seventy-six (93.8%) of 81 participants completed the intervention. By study end (12 months), 4.9% (2/41) individuals in the omega-3 group and 27.5% (11/40) in the placebo group made a transition to psychosis ($P = .004$). The difference between the groups in the cumulative risk of progression

to psychosis was 22.6% (95% CI = 4.8 to 40.4). Omega-3 also significantly reduced positive symptoms, negative symptoms, and global symptoms and improved functioning compared to placebo. Consistent with a preventative effect, group differences were sustained after cessation of interventions. The study also found that clinical improvement was significantly associated with an increase of omega-3 fatty acids in red blood cells, and individuals in the placebo group who transitioned to psychosis were characterized by significantly lower arachidonic acid levels at baseline. These results suggest that fatty acid deficits may predate onset of fully fledged psychotic disorder and that disturbed membrane fatty acid metabolism may contribute to the onset of sustained psychotic illness.

Eicosapentaenoic acid increases glutathione, the brain's principal antioxidant defense.[47] There is evidence that acute psychosis is associated with glutathione deficiency[48] and, hence, oxidative stress, and that this may be a part of the neurotoxic pathway. Oxidative stress leads to lipid peroxidation, which is a documented finding in psychosis.[49] The differential efficacy of agents such as EPA and/or DHA in early stages of the disorder supports differential pathophysiologic pathways in early onset illness that may be amenable to intervention. Treatment studies of omega-3 fatty acid supplementation in different samples of psychotic patients indicate that treatment efficacy is dependent on the stage of illness. Omega-3 fatty acids have been found to be partially effective in recent onset psychosis[50,51] but showed no effect in chronic schizophrenia.[52] This stage-of-illness finding supports the clinical staging model[41–43] in that the effect of the intervention is dependent on the stage of illness progression. There is also good evidence that omega-3 fatty acids have a generalized positive effect on mental health. Controlled clinical trials in major depression,[53,54] bipolar affective disorder,[55] borderline personality disorder,[56] incarcerated young males,[57] children with developmental coordination disorders,[58] and preliminary findings in autism[59] suggest that omega-3 fatty acids may modulate mood, impulsivity, and aggression, while potential neuroprotective effects were found in Huntington's disease.[60]

In all EPA and/or DHA treatment studies, no clinically relevant side effects or adverse biochemical or hematologic effects have been observed. Across all randomized controlled trials (RCTs), individuals with schizophrenia or other psychoses found omega-3 fatty acids highly tolerable. For instance, in Puri and colleagues' study,[60] the proportion of patients who completed 12 weeks of omega-3 supplements (89%) compares favorably with mean withdrawal rates of 54% in the novel antipsychotics groups and 67% in the placebo groups in trials in the US Food and Drug Administration database. In the Vienna RCT in UHR individuals, 94% of participants completed the 12-week intervention period.[46] Omega-3 fatty acids proved safe to administer as an alternative therapy and did not cause side effects other than mild gastrointestinal symptoms. In fact, omega-3 as an adjunctive medication has been found to be associated with significantly fewer side effects resulting from existing drugs.[47] Also of note is the relatively high rate of acceptance among UHR patients to participate in an RCT involving substances that are normally found in the human body (76% consent rate for omega-3) compared to RCTs involving antipsychotics (35% in the most recent PACE cohort[44]).

Applying the clinical staging model to treatment of the UHR population, the use of psychological therapies presents a number of advantages over antipsychotic medication as a first-line treatment. These include (1) being more acceptable, tolerable and less stigmatizing to patients[61,62]; (2) having no risk of exposing false-positive subjects to pharmacologic side effects; and (3) providing effective treatment of false-positives, who, although they do not go on to develop psychosis, generally suffer from other disorders, such as mood and anxiety disorders. Indeed, CBT has proven to be a safe and effective treatment of UHR patients.[30,33,34] As discussed above, recent UHR cohorts seem to consist of less "enriched" samples in terms of true-positive rate. In these cohorts, simple, supportive psychosocial interventions may be sufficient to reduce risk of transition, at least in the short term. However, this poses the problem of not providing specific psychological intervention for nonpsychotic conditions, which are highly prevalent in the UHR population.[44]

The clinical staging model does not mean eschewing the study of the role of antipsychotic medication in the UHR population. Broad-spectrum antipsychotics with minimal side effects, especially in those who fail to respond to initial intervention with gentler therapies (such as EPA, CBT, or supportive therapy), may still have a place in delaying or preventing psychosis onset and should be further studied. Broad-spectrum psychotropic agents that are effective in treating positive psychotic symptoms, depression, and anxiety may be appropriate. Depression and anxiety are highly prevalent in the prodromal phase of psychotic disorders and represent a key treatment target in their own right. The best candidates are those with a more favorable metabolic and neurologic safety profile.

THE WAY FORWARD: THE NEXT GENERATION OF UHR INTERVENTION TRIALS

The research reviewed above indicates that intervention, both psychological and pharmacologic, is likely to benefit UHR patients in terms of both symptom reduction and delay or in prevention of onset of threshold disorder. However, this notion still has to be confirmed because of nonsignificant findings of the trial with the highest scientific rigor so far[32] and further nonsignificant findings of other trials, especially at longer follow-up.[30,63,64] Duration of intervention is another focus that requires further study.

The falling transition rate in recent studies, the high rates of psychotic-like experiences in community studies, and the effectiveness of more benign treatments mean that a staged

approach to treating UHR patients is appropriate, both clinically and ethically. This does not mean rejecting the study of the role of antipsychotic medication, but it does mean that the timing of such treatment must be studied, and that safer alternatives are to be preferred if they are efficacious in the early stages of illness. For example, the Prevention Through Risk Identification Management and Education study[31] showed that the risk-benefit ratio for olanzapine was unfavorable. Newer antipsychotics may turn out to be more benign and yet equally or more effective, especially if reserved for nonresponders to initial and less-specific interventions. Drawing on acceptability, tolerability, and further risk-benefit considerations, it is important to investigate the differential efficacy of antipsychotics and more benign treatments like CBT or EPA and to explore whether antipsychotics should be used only in patients who do not respond to more benign treatments in the first instance.

Some of the negative findings mentioned above may be primarily due to low power from small sample sizes. Following the initial series of single-site studies with relatively low numbers, research needs to progress to studies with substantially larger samples. The most effective way of achieving this is through multicenter RCTs. These will be able to provide a clearer evidence base to guide clinical care of UHR patients and minimize the risk that young people will be provided with potentially ineffective and harmful treatments. Well-designed RCTs will not only address the critical question of the most effective treatment for UHR patients but also enable rigorous naturalistic data to be collected through the use of placebo and by including a minimal intervention arm of nonconsenters to randomization. The follow-up of the natural history of UHR groups remains an important research focus given the complexity of the UHR clinical population. To this end, the next set of questions in UHR intervention research is as follows:

- Are specific treatments superior to nonspecific treatments in this phase of illness?
- How acceptable are the different treatment options to the patients themselves, their families and caregivers, health professionals, and the wider community?
- What is the optimal sequence of treatments based on risk-benefit considerations?
- For how long should treatment continue?
- Is there a hierarchy of treatment needs depending on mental state, other risk factors, and flux in symptoms?
- What factors in which phase of illness predict treatment response or nonresponse?

CONCLUSION

Initially, the early psychosis movement focused on timely recognition and phase-specific treatment of first-episode psychosis, which was all too frequently diagnosed very late and treated poorly.[65] However, as in cancer and cardiovascular disease, an earlier clinical stage was known to exist, one in which much of the collateral psychosocial damage was known to occur.[66,67] This meant that even timely diagnosis and treatment of first-episode psychosis was in fact already late for many patients. The UHR identification strategy provided a valid and reliable means of identifying patients in this phase. It opened the door to the first generation of intervention trials in this population, which indicated that both psychosocial and pharmacologic intervention may be of benefit in delaying or preventing the onset of psychosis. However, a number of critical questions remain in clinical equipoise.

A second generation of single-site clinical trials has been completed that shows interesting results for a range of psychosocial and biologic therapies, including cognitive therapy, lithium, essential fatty acids, and atypical antipsychotics.[46] A large, international, multicenter clinical trial is now required to draw and build on these findings. It is clear that the UHR population is a heterogeneous clinical population, at risk for not only schizophrenia but also other adverse mental health outcomes. Consequently, we have broadened our own clinical and research focus cross-sectionally with the development of a low-stigma youth mental health model[68–71] and, longitudinally, with the creation of a clinical staging model for psychotic and mood disorders.[41–43] The clinical staging model addresses the declining transition rate in UHR samples by suggesting safer, more benign interventions as a first step and by progressing to more intensive interventions for patients who do not improve. This ensures an enriched sample in terms of risk of psychosis with which to test more specific intervention strategies in the context of a clinical trial. These conceptual and strategic advances help us to move beyond some of the obstacles that critics of early diagnosis and intervention have pointed out,[72] namely, the false-positive issue, potential stigma, and lack of predictive specificity, and set the stage for future large-scale, controlled, intervention trials. The UHR population has significant symptomatic and functional impairment. Developing effective intervention strategies will provide treatment of this existing distress and disability in addition to introducing the possibility of delaying, ameliorating, or preventing onset of psychotic disorder.

Drug names: lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), risperidone (Risperdal and others).

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