Review

Providing care to young people with emerging risk of psychosis: balancing potential risks and benefits

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Practice points

- Increasing experimental evidence indicates that the course of psychotic illnesses is not fixed and that early therapeutic intervention has the potential to modify the course of illness and ameliorate outcome.
- Early detection of those with a clinical need for care and enhanced risk of progressing to fully fledged psychotic illness provides an opportunity to reduce the impact of illness and maximize psychosocial recovery.
- The therapeutic interventions offered should be sequential, closely linked to the stage of illness and designed to relieve symptoms and distress with minimal adverse effects, as well as reducing or preventing secondary morbidity and progression of illness.
- Careful and regular monitoring, as well as psychosocial interventions, such as supportive therapy and cognitive behavior therapy, should be the first-line interventions, with other benign interventions, such as omega-3 supplementation, being of potential benefit.
- Antipsychotic treatment should typically be reserved for those whose symptoms, distress and functional impairment have clearly worsened significantly, despite psychosocial intervention, to the point where sustained, full-threshold psychosis has developed. Antipsychotics should only be prescribed within a specialist mental health setting.
- In the event that antipsychotics are prescribed when the condition worsens as described, those with the most favorable metabolic and adverse event profiles should be prioritized and generally prescribed at the minimum effective dose for a trial period only.

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SUMMARY Early detection and treatment of those demonstrating emerging risk of developing a psychotic disorder has the potential to considerably ameliorate the negative psychological and social consequences of these serious mental illnesses or, possibly, even prevent their development. Psychosis does not usually suddenly appear in people who have been perfectly well, although conversely it is now known that isolated psychotic-like symptoms are relatively common in nonhelp-seeking people, particularly children and adolescents. Over the last two decades, clinical and epidemiological studies have enabled the characterization of a persistent subthreshold or prepsychotic clinical stage of illness in which help-seeking often occurs, driven by distress and functional decline and which manifests a greatly increased risk for worsening of the psychotic dimension of symptoms, such that the threshold for diagnosis of the first-episode psychosis is reached. This advance and careful clinical research has allowed the development of evidence-based interventions designed to minimize the impact of the illness, which have now been tested in a series of clinical trials. It appears that there are real benefits in engaging people in care prior to the onset of frank psychosis; however, the type and sequence of interventions must be carefully followed so that the benefits always outweigh the risks. Specifically, antipsychotic medications should not be offered as a first-line therapy for such patients, since cognitive behavioral therapy and supportive needs-based case management, perhaps combined with omega-3 fatty acids, represents a much safer initial approach.

Careful epidemiological studies have shown that psychotic illnesses typically emerge during late adolescence and early adulthood [1]. The onset of a potentially serious and significantly disabling illness at this time of life is potentially disastrous, since it is during this developmentally sensitive transitional phase that a young person must establish his or her individual psychological, social and vocational pathways leading to independent adulthood [2]. Ample evidence exists to show that mental illness in young people is associated with high rates of enduring disability, including educational failure, unstable employment and poor social and family functioning, which may lead to a spiral of disability and disadvantage that becomes difficult to reverse.

Over the last two decades, the systematic efforts of clinicians and researchers dedicated to improving the outcome for young people affected by a first episode of psychosis have succeeded in changing the historically pessimistic view of these psychotic illnesses. Evidence from large international studies has shown that the course of these disorders is not fixed, with an inevitable deterioration in social and occupational functioning and poor prognosis, but rather, is fluid and malleable [3–7]. Examination of the risk factors known to influence outcome has revealed that certain of these risk factors may be malleable, and that attention to these as part of treatment has the potential to alter the trajectory of illness. Hence the explosion of interest in phase-specific treatment and early intervention, with an additional aim being that of indicated prevention, that is, preventing the transition from the early (prodromal) stages of illness to full-threshold psychosis or, less ambitiously, the reduction or prevention of the secondary morbidity associated with a serious mental illness. As evidence supporting the validity of the early intervention paradigm mounts, the current view of serious mental illnesses has become more optimistic, and is driving a significant shift in today's psychiatry towards a more pre-emptive focus [8].

The prodromal stage: definition & assessment

Much of the initial research effort into early psychosis was focused on the timely recognition and phase-specific treatment of first-episode psychosis and the subsequent critical period. An

important consequence of this was the identification of the duration of untreated psychosis as one of the most important risk factors of outcome, with longer duration of untreated psychosis being both a marker and malleable risk factor of poor outcome [9,10]. Since it had long been recognized that most patients experienced a prolonged period of attenuated symptoms and impaired functioning well before their first psychotic episode [11,12], the next step was to seek to intervene during the prepsychotic phase as a means of minimizing the duration of not only untreated psychosis, but also untreated illness as a whole [13]. It was hoped that this would delay or even prevent the onset of a fully-fledged psychotic disorder, while also reducing the psychosocial damage to the individual's life, much of which develops during the prepsychotic period [13]. However, this presented a major challenge: the prospective identification of the psychosis prodrome, a difficult task, complicated by the nonspecific nature of prodromal symptoms [14–16].

Longitudinal studies have shown that, in general, negative symptoms such as decreased concentration, reduced drive, lack of energy and social withdrawal predominate early in this phase, accompanied by general symptoms such as sleep disturbance, anxiety and irritability. Affective symptoms, particularly anxiety and depression, as well as relationship difficulties are also common. These symptoms tend to accumulate and increase in severity until relatively late in the prodrome, when subthreshold psychotic symptoms emerge. Ultimately, these positive symptoms intensify and may culminate in a transition to frank psychosis. Typically, increasing levels of social and vocational disability accompany the increase in symptomatology and this phase is also characterized by high levels of self-harm and suicidal behavior [17]. Much of the disability associated with the psychotic disorders, particularly schizophrenia, develops well before the onset of frank psychosis and is difficult to reverse, even if the first psychotic episode is successfully treated [18].

As these symptoms, including subthreshold psychotic-like experiences, are common in the general population, particularly in adolescents and young adults, as well as in other nonpsychotic disorders [19], prospective identification was complicated, as they cannot be considered as diagnostic of a prepsychotic state in their own right [20,21]. Additional risk factors and specific criteria are necessary to exclude false positive cases to avoid unnecessary treatment and the stigma associated with the diagnosis of a mental illness. In the mid 1990s, the present authors' research group operationalized criteria for the prospective identification of individuals at increased risk of progressing to a first episode of psychosis, that is, being in the prodromal phase of illness. These 'ultra-high risk' (UHR) criteria (termed as such to distinguish them from the earlier genetic high-risk research strategy) are based on a combination of epidemiological evidence and known trait and state risk factors of psychosis **(Box 1)** [22,23]. These are:

- Being aged between 14 and 30 years of age, since young people in this age range are at greatest risk of developing a psychotic illness;
- Seeking clinical care, since young people who are not distressed by their symptoms and who have not experienced a decline in functioning are much less likely to become seriously unwell in the near future;
- Having attenuated positive psychotic symptoms;
- Having experienced brief self-limited psychotic symptoms;
- Having a family history of psychotic disorder or a schizotypal personality disorder, combined with chronic low functioning or a recent decline in functioning.

These criteria have subsequently been validated in a series of international studies [24–27] and a range of assessment tools for prodromal symptoms have now been developed, including the Comprehensive Assessment of the At-Risk Mental State [28], the Structured Interview for Prodromal Symptoms, the Scale of Prodromal Symptoms [29], the Bonn Scale for the Assessment of Basic Symptoms [30] and the Schizophrenia Proneness Instrument [31].

In the present authors' original 1-year study of 49 UHR patients, 41% went on to develop full-threshold psychosis [23]. Subsequently, the North American Prodrome Longitudinal Study followed 291 patients over 2 years and found a transition rate of 35%, corresponding to a relative risk of transition to full-threshold psychosis of 405 [24], while the European Prediction of Psychosis study followed 245 help-seeking

Box 1. The ultra-high risk criteria.

Patients must be aged between 14 and 30 years, must have been referred to a specialized center for help and meet the criteria for one or more of the following three groups:

- Attenuated psychotic symptoms
  - Presence of at least one of the following symptoms: ideas of reference, odd beliefs or magical thinking, perceptual disturbance, paranoid ideation, odd thinking and speech, odd behavior and appearance
  - Symptoms occur at least several times per week
  - Symptoms have been present within the last year
  - Symptoms have been present for at least 1 week and no longer than 5 years
- Brief, limited intermittent psychotic symptoms
  - Transient psychotic symptoms: ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, odd thinking or speech
  - Episodes last less than a week
  - Symptoms occur at least several times per week
  - Symptoms resolve spontaneously
  - Symptoms must have occurred within the last year
- Trait and state risk factors
  - Schizotypal personality disorder in the patient, or a relative with a psychotic disorder
  - Significant decline in mental state or functioning, maintained for at least one month and not longer than 5 years
  - The decline in functioning must have occurred within the last year

prodromal patients over 18 months and found a cumulative transition rate of 19%, as well as a relative risk of 364 [27]. However, other recent studies have shown transition rates as low as 8% [32]. The reasons for this reduction in the rate of transition are unclear. It may be a result of earlier detection and more effective intervention or, alternatively, due to the referral of more 'false positive' patients to UHR clinics (a dilution of risk and true positives) or lead-time bias where early referral leads to a longer follow-up time before transition occurs [33]. The problem almost certainly does not derive from issues with the criteria themselves, but rather the degree of enrichment of true risk in the sample in which they are being applied [34]. However, notwithstanding these somewhat variable transition rates, a very recent meta-analysis of 27 studies of UHR patients has provided strong evidence for the predictive validity of the UHR criteria regardless of setting, and has revealed a cumulative transition rate of 36% over a period of 3 years [35]. Interestingly, and supporting the influence of a lead-time bias effect, the transition rate increased with increasing length of follow-up; a rate of 18% was found after 6 months of follow-up, increasing to 22% after 12 months, 29% at 2 years and 36% after 3 years.

Regardless of the transition rate, another common outcome for UHR patients is not psychosis *per se*, but persistence or emergence of a non-psychotic illness, typically a blend of anxiety and depression [36–39] or of the UHR phenotype itself. All in all, only a small minority of these patients remit completely in terms of all symptoms and regain normal functional trajectories. Although recent studies have shown that up to 50% of UHR patients experience a remission of their subthreshold psychotic symptoms within a year of seeking help, they continue to report clinically relevant symptoms and difficulties in social, occupational and general functioning, indicative of a need for a broad range of clinical care [36–39]. This carries obvious implications for the treatment of these patients, who should be more broadly considered as being at risk of persistent and often enduring mental illness (see below). Furthermore, longer-term follow-up studies indicate that the longer-term risk for transition remains, with a subset of patients continuing to meet UHR criteria for at least 3 years after their initial presentation, with some of these ultimately transitioning to psychosis [35].

The successful identification of the UHR population has made two major advances possible: first, detailed research into the psychopathological, neurocognitive and neurobiological processes associated with the onset of psychosis and second, the implementation of a number of intervention trials designed to alleviate existing symptoms and minimize functional impairment in the UHR population, as well as the determination of whether specific interventions are able to ameliorate, delay or even prevent the onset of fully fledged psychotic disorder in this population [40–53].

Treatment during the subthreshold stage

The intervention studies carried out in UHR groups to date are summarized briefly below and in **Table 1**. The first such study was a randomized controlled trial (RCT) conducted by the present authors' group in Melbourne (Australia), comparing combined cognitive behavioral therapy (CBT) and low-dose (1–2 mg/day) atypical antipsychotic medication (risperidone; n = 31) with usual case management (n = 28) [40]. The rate of onset of psychosis was significantly lower in the treatment group than in the control group at the end of the 6-month treatment phase (9.7 vs 35%; p = 0.026). However, this finding was

Table 1. Clinical trials of therapeutic interventions in young people at ultra-high risk of psychosis.

Study (year)	Intervention	Time frame of study	Outcome (intervention vs control groups)	Ref.
Medication plus psychosocial intervention				
McGorry *et al.* (2002); Phillips *et al.* (2007)	RCT (n = 59) CBT + 1–2 mg/day risperidone vs needs-based psychosocial support	6-month treatment phase + 6-month follow-up phase Medium-term follow-up at 3–4 years postbaseline	Transition to psychosis: 9.7 vs 35%; p = 0.026	[40] [37]
McGlashan *et al.* (2006)	RCT (n = 60) 5–15 mg/day olanzapine vs placebo	12-month treatment phase + 12-month follow-up phase	Transition to psychosis: 16.1 vs 37.9%; p = 0.09	[41]
Ruhrmann *et al.* (2007)	RCT (n = 124) 50–800 mg/day amisulpride + needs-focused intervention vs needs-focused intervention	12 weeks	Improvement in both groups, with a significantly greater improvement seen in the aripiprazole group for positive (F[1.98] = 7.83; p < 0.01), negative (F[1.98] = 4.85; p < 0.05) and general symptoms (F[1.98] = 4.63; p < 0.05)	[43]
Woods *et al.* (2007)	Open-label pilot study (n = 15) 5–30 mg/day aripiprazole	8 weeks	Significant reductions in positive, negative and general symptoms (F = 9.2; p < 0.001), with 11 out of 15 participants responding to treatment	[42]
Cornblatt *et al.* (2007)	Naturalistic study (n = 48) Antidepressants or atypical antipsychotics	2 years	Transition to psychosis; 43% of those in the antipsychotic group vs 0 in the antidepressant group	[44]
Psychosocial interventions				
Morrison *et al.* (2004) Morrison *et al.* (2007)	RCT (n = 58) CBT vs monitoring of mental state	6-month treatment phase + 6-month follow-up Medium-term follow-up 3 years postbaseline	Transition to psychosis: 6 vs 26%; p = 0.019	[47] [48]
Bechdolf *et al.* (2012)	Multicenter RCT (n = 128) CBT, social skills training, cognitive remediation and psychoeducation vs supportive counseling	12-month treatment phase + 12-month follow-up	Onset of subthreshold psychotic symptoms: 3.2 vs 16.9%; p = 0.008	[49]
Addington *et al.* (2011)	RCT (n = 51) CBT vs supportive therapy	6-month treatment phase + 12-month follow-up phase	Both groups showed clinical improvement in positive symptoms, depression and anxiety, although there was no statistically significant difference between the groups	[50]
Morrison *et al.* (2012)	Multicenter RCT (n = 288) CBT vs monitoring	6-month treatment phase + 18-month follow-up	Transition to psychosis: 6.9 vs 9.0%; p = 0.45	[32]
Dietary supplementation				
Amminger *et al.* (2010)	RCT (n = 81) 1.2 g/day omega-3 fatty acids vs placebo	12-week treatment phase + 40-week follow-up phase	Rate of conversion to psychosis: 4.9 vs 27.5%; p = 0.007	[53]

CBT: Cognitive behavior therapy; RCT: Randomized controlled trial.

no longer statistically significant by the end of the 6-month follow-up period due to participants who were not fully adherent to risperidone during the treatment phase transitioning to full-threshold psychosis during the follow-up period. Those who were fully adherent during the treatment phase all remained nonpsychotic over the follow-up period, even though they had ceased drug treatment, demonstrating that the onset of psychosis can at least be delayed by specific intervention. However, since medication and CBT were combined in this trial, the active component of the treatment regime could not be identified. Longer-term follow-up of the study cohort over 3–4 years failed to show any persisting benefit in the experimental group, suggesting that a longer treatment time may be necessary [37].

A second, more sophisticated, randomized double-blind placebo-controlled trial was then conducted by researchers from Yale University (CT, USA). Low-dose olanzapine (5–15 mg/day; n = 31) was compared with placebo (n = 29) for 12 months, followed by a 12-month monitoring period [41]. Although there was a trend toward a reduced rate of transition to psychosis in the olanzapine-treated group, this finding was not statistically significant. There was, however, a statistically and clinically significant improvement in the levels of psychotic symptoms reported in the olanzapine group compared with the placebo group. However, the adverse effects associated with olanzapine treatment, primarily weight gain, led to a more conservative interpretation of the results of this trial.

Open-label trials of aripiprazole [42] and amisulpride [43] have also been conducted in UHR cohorts. In the aripiprazole trial, 15 UHR patients were treated with a flexible dose regime of 5–30 mg/day for 8 weeks [42]. Improvements in clinical measures were evident by the first week, adverse events were minimal and no participants transitioned to psychosis. Similar findings were seen in the amisulpride trial; a RCT involving a cohort of 124 UHR patients considered to be in the late initial prodromal stage received either amisulpride (50–800 mg/day) together with a needs-focused intervention or the needs-focused intervention alone for 12 weeks [43]. At the end of the study period, the amisulpride group showed significantly greater improvements in positive ($F[1.98] = 7.83$; $p < 0.01$), negative ($F[1.98] = 4.85$; $p < 0.05$) and general symptoms ($F[1.98] = 4.63$; $p < 0.05$), as well as in overall functioning ($F[1.98] = 5.70$; $p < 0.05$) than the control group. Adverse events were minor, with prolactinemia and a small weight gain being the most important. Together, these findings indicate a relatively promising efficacy and safety profile for these agents in UHR patients, yet they should still only be considered as second- or third-line treatments (and only then after further RCT research) given the effectiveness of CBT and other safer approaches (see below).

Antidepressants have also been proposed to reduce the risk of psychosis in UHR patients. Cornblatt and colleagues reported a naturalistic study of 48 young people with prodromal symptoms who were treated with either antidepressants or antipsychotics [44]. Twelve of the 28 patients (43%) who were prescribed antipsychotics progressed to full-threshold psychosis in the following 2 years, while none of the 20 patients prescribed antidepressants subsequently developed psychosis. Similar results were reported by Fusar-Poli *et al.* from a file-audit study [45]. However, these results need to be interpreted with caution due to the uncontrolled nature of these studies. First, there may have been differences in baseline symptoms, functioning or other variables between the treatment groups and second, nonadherence to treatment was far more prominent in those patients who had been prescribed antipsychotics than in those prescribed antidepressants. In this regard, the present authors' initial trial found that antidepressants, again prescribed according to clinical need, had no influence on the transition rate [40].

In a recent, more sophisticated double-blind placebo-controlled intervention trial, the present authors have compared the combinations of risperidone or CBT with placebo, and CBT or placebo with supportive therapy, in a group of 115 UHR patients [17]. The 6-month transition rates were low in all three groups [46], suggesting that antipsychotics may not be necessary for UHR patients who are detected early, or alternatively, that recent UHR cohorts are derived from less 'enriched' samples in terms of the true positive rate [33]. The reduced power of this study, caused by a lower than expected transition rate in all groups, makes definitive conclusions difficult, as it has done in the EDIE-2 study reported below [46].

The first treatment trial of a psychological intervention alone in UHR patients was conducted in Manchester (UK) [47]. Participants (n = 58) were randomized to receive either cognitive therapy or monitoring of mental state for only 6 months. The cognitive therapy group showed a statistically significantly lower rate of transition to full-threshold psychosis (6 vs 26%; $p < 0.05$), as well as a significantly greater reduction in symptoms ($p < 0.02$) at 12 months. Moreover, at the 3-year follow-up, cognitive therapy was associated with a significantly lower rate of transition to psychosis and a reduced likelihood of being prescribed antipsychotic medication [48].

Consistent with this, in a large RCT of an integrated psychological intervention consisting of CBT, modified social-skills training, cognitive remediation and family psychoeducation, Bechdolf *et al.* reported that CBT was superior to supportive counseling in reducing progression to subthreshold psychotic symptoms and to full-threshold psychosis over 24 months [49]. This study cohort was carefully selected as being in the putative early initial stage of the prodrome, with participants reporting basic symptoms but as yet no subthreshold psychotic symptoms. The primary outcome measure for the study was the onset of subthreshold psychotic symptoms, with all participants being followed for the full 24-month duration of the study. At the end of the 12-month treatment phase of the trial, 3.2% of the patients who had received CBT had made a transition to subthreshold psychosis, while 16.9% of those who had received supportive therapy now reported subthreshold psychotic symptoms, a statistically significant difference ($p = 0.008$). At the 24-month follow-up, the transition rates were 6.3% for the intervention group and 20% for the supportive therapy group, which is again a significant difference ($p = 0.019$). Interestingly, at the 24-month follow-up, significantly fewer patients from the intervention group had developed psychosis (3.2 vs 15.4%; $p = 0.018$) or schizophrenia/schizophreniform disorder in particular (1.6 vs 12.3%; $p = 0.033$) compared with those in the supportive therapy group. This is a particularly significant result given the small numbers of patients who converted to psychosis after the end of the intervention phase of the trial, which suggests that early treatment with such a safe and well-accepted intervention is able to reduce the overall rate of transition in a sustained fashion and, thus, considerably improve the prognosis for these vulnerable patients without introducing the risk of negative side effects [49].

By contrast, another recent trial of psychological therapies in a group of 51 UHR young people did not find any statistically significant difference in the rate of conversion to psychosis between the group randomized to treatment with CBT and the one that received supportive therapy alone [50]. While the group randomized to CBT showed a more rapid improvement in their levels of positive symptoms over the first 6 months of the study (the treatment phase), both groups showed similar improvements in overall positive symptoms and their levels of depression and anxiety, while neither treatment showed an effect on negative symptoms or social functioning. However, the investigators acknowledge that their study was underpowered, with the sample being too small to detect treatment differences, further complicated by an unexpectedly low transition rate, with only three patients in the supportive therapy group (n = 24) making a transition to psychosis, while none in the CBT group transitioned during the 18 months of the trial. The CBT group was also considered to have received an inadequate 'dose' of therapy, with a detailed analysis of this group revealing that many of these young people received interventions focusing primarily on engagement rather than more core strategies. Interestingly, the investigators proposed that simple interventions concentrating on support and problem-solving skills may be most useful for UHR clients when they first seek help, with more directed interventions, such as CBT, targeting positive symptoms or strategies for managing social-skill deficits possibly being reserved for the management of more severe attenuated symptoms.

Furthermore, another very recent, large-scale RCT of CBT versus supportive monitoring in 288 UHR patients (the EDIE-2 trial) reported no significant difference in the rate of transition to psychosis between the two groups by the final follow-up point of 24 months, with 6.9% of those in the CBT group making a transition to full-threshold psychosis, compared with 9.0% of those in the monitoring group [32]. Other outcomes assessed in this trial included the severity of participants' psychotic symptoms and the distress associated with these symptoms, as well as the degree of emotional dysfunction experienced

and the participants' quality of life. While the distress associated with the participants' psychotic symptoms did not differ between the two groups at the end of the treatment phase of the trial, the severity of these symptoms was significantly reduced in the group who had received CBT ($p = 0.018$) and most participants in both groups improved over time. The sampling approach used by these investigators has been called into question, as the unexpectedly low transition rates in both groups means that the study proved to be underpowered to detect any significant difference between the two groups and, hence, the study proved inconclusive [51,52].

Finally, in an extremely promising trial of a benign biological and potentially neuroprotective intervention, Amminger *et al.* ran a 12-week, placebo-controlled randomized trial of omega-3 fatty acids in a group of 80 UHR young people [53]. At the end of the 12-week treatment phase, eight out of 38 (21.1%) individuals in the placebo group and one out of 38 (2.6%) in the omega-3 group had transitioned to first-episode psychosis, a statistically significant difference ($p = 0.028$). No adverse effects were reported and omega-3 treatment was well accepted in this patient group. Most notably, the treatment effect was maintained at 12-month follow-up [53]. A large-scale international replication led by the present authors' research team and funded by the Stanley Foundation is now underway and will be completed during 2013. Significantly, previous treatment studies of omega-3 supplementation in different samples of psychotic patients indicate that the effect of omega-3 supplementation is dependent on the stage of illness. Omega-3 fatty acids have been found to be partially effective in samples with recent-onset psychosis [54,55], but have no effect in chronic schizophrenia [56]. There is also a considerable body of evidence showing that omega-3 supplementation may have more general positive effects on a range of mental health conditions [57]. This more general beneficial effect is particularly appropriate for the UHR group, with their wide range of psychiatric symptoms that are treatment targets in their own right.

The meta-analysis of Preti and Cella [58] and the more recent trials [40–50,53] show that a range of interventions are equally effective in delaying transition to psychosis. Given the risks associated with the use of antipsychotic medication, current analysis suggests that the more benign interventions, such as supportive therapy, CBT and supplementation with omega-3 fatty acids should certainly be offered first, in line with the present authors' clinical staging framework. It is only when symptoms and impairment persist or worsen, typically to the point of transition to sustained full-threshold psychosis, that antipsychotic treatment should be considered. The high rate of psychotic-like experiences in community cohorts [20,59] is consistent with the notion that a staged approach to treatment is indicated, with only individuals with distress, functional decline and a desire to seek and obtain help entering treatment at all. While antipsychotics are not indicated as first-line treatment for this subset of patients, they should not be ruled out in future research trials on ideological grounds alone, but rather, their use should be guided by ethical considerations, risk–benefit concerns and proportionality. Indeed, broad-spectrum antipsychotics may still be considered for use in future research trials as second- or third-line treatments. This should be performed purely to establish the balance between efficacy and risk, which only careful research can discern. This proposition is quite different from suggesting that antipsychotics have a place in routine treatment; some commentators have implied that because several clinical trials to date have involved minimally effective doses of antipsychotics alongside other interventions, those involved in such research support their use more widely. This is not the case as the guidelines for routine care by these same research groups explicitly state [60]. The extent of first-line, off-label use of antipsychotics, and by no means only in UHR patients, is a genuine problem. In fact, specialized youth mental health cultures, where evidence-based care can be better assured, is one way of preventing such off-label use, as seen in Melbourne.

Symptom type and other clinical phenomena, including comorbid substance use, triggers and stressors, genetic and other biomarkers, for example, will also influence the optimal treatment for a given patient. When antipsychotics are prescribed, the best candidates are those with a more favorable metabolic and neurological safety profile [61]. To date, the results of the intervention trials in UHR patients are promising, but remain in clinical equipoise; further research exploring treatment options and

sequences via sophisticated clinical trials is necessary to build a solid evidence base to inform future therapeutic strategies. In the meantime, treatment guidelines must remain conservative.

Risk syndromes in psychiatry

The concept of risk and the risk syndrome, although widely accepted in physical medicine, is relatively new in psychiatry. Since as yet we have a relatively poor knowledge of the causal and/or malleable risk factors for the onset of mental illness, subthreshold syndromes have been proposed to be risk factors of full-threshold disorders and it has been suggested that these subthreshold syndromes could be targeted by specific interventions as a step toward indicated prevention for serious mental illness [62–64].

The validation of the UHR criteria and the demonstration that the risk that they confer for transition to psychosis can be reduced, at least in the short term [58], supports this contention. This, together with similar evidence in depression (see for example [65]), provides proof-of-concept of the feasibility of early intervention for the psychoses. This has largely opened the way to a new era of 'pre-emptive psychiatry' [8] where the prediction of risk can be used to facilitate the early detection and strategic targeting of appropriate preventive interventions, not only for the psychoses, but for all serious mental illnesses. These advances in the field of early psychosis have also led to the proposal that a 'psychosis risk syndrome' be included as a new diagnostic category in the DSM-V [66,67]. While this proposal has now been rejected as the majority of UHR patients do not go on to develop full-threshold psychosis, it was felt that a condition describing their clinical needs – the 'attenuated psychosis syndrome' [68] – should be included as a research diagnosis in section III of the DSM-V. As a range of interventions, including monitoring and support, appear to be effective in reducing the rate of conversion to psychosis, the field remains in clinical equipoise and further research is needed to tease out the risk factors that will enable a more accurate identification of those UHR patients who are at greatest risk of developing full-threshold psychosis, while recognizing this population's need for appropriate clinical care and avoiding the risk of overtreatment or stigmatization (see below) [69].

Although it is widely accepted that the need for care substantially precedes the point at which a formal diagnosis can be assigned, the current diagnostic infrastructure fails to acknowledge the complex evolution of the onset of serious mental illness. Over recent years, there has been a growing awareness that mental disorders are not static, sharply defined illnesses with separate etiologies and courses, but rather, disorders that overlap and develop in stages [14,70–72]. However, until relatively recently, how symptoms are acquired and how they ebb and flow has not been widely considered and so there is a lack of clear definitions for distinguishing between benign, self-limiting states and symptoms that represent the early stages of what may become persistent and disabling conditions, despite the evidence showing that subthreshold symptoms strongly predict a future disorder [16,63,73–75].

The evolution of mental disorders is perhaps more usefully described within the context of a clinical staging model [76,77]. Clinical staging differs from conventional diagnostic practice in that it defines the extent of progression of a disorder at a particular point in time and where a person lies along the course of their illness. The differentiation of early, milder clinical phenomena from those that accompany illness extension, progression and chronicity lies at the heart of the concept. Staging frameworks are central to pre-emptive medicine, since they enable clinicians to select treatments relevant to the earlier stages of an illness and generally assume that such interventions will be both more effective and less harmful than treatments delivered at later stages. They also offer the possibility that early, successful intervention may change the expected course of a disorder by preventing progression to subsequent stages and result in remission and cure or, at the very least, delayed progression and minimization of secondary disability. The key advantage of clinical staging is that it encourages the balancing of the risks and benefits of treatment within a stepped-care approach. Such a framework has much to offer in terms of guiding treatment selection in the early stages of mental illness, where evolving mixes of symptoms and comorbidity are the norm rather than the exception and current diagnostic tools are of little use.

As discussed earlier, although the predictive validity of the UHR criteria is reasonable, a very common outcome of the UHR state is not psychosis *per se*, but persistence or emergence of nonpsychotic illness, most often a blend of

anxiety and depression [36–39]. This lends weight to the idea of a 'pluripotential risk syndrome' that precedes the more specific outcomes that may take shape if symptoms persist, progress or intensify [78]. Risk syndromes with greater specificity for schizophrenia on the one hand, or severe mood disorders on the other (if the condition does not resolve or remit) may evolve from this pluripotential risk syndrome, before ultimately intensifying to become the full-threshold target syndrome. Identification of the genetic, cognitive and neurobiological markers that provide an accurate assessment of risk is of crucial importance not only for the design of better therapeutic approaches, but also for a better understanding of the biological mechanisms that underlie the onset and early stages of illness. A clinical staging model not only offers a more useful therapeutic framework during these critical early stages, but also the possibility of integrating this basic biological data into a comprehensive and relevant diagnostic infrastructure. The use of clinical staging in psychiatry is a new concept and its implementation is currently in its very early stages and, hence, has yet to be validated. Formal clinical guidelines have yet to be established, although the present authors and others are currently actively conducting research in this area.

Ethical issues in the treatment of UHR patients

It is important to be aware of the pitfalls and potential for harm arising from the clinical use of risk syndromes. The term syndrome denotes the presence of a clinical condition that needs care; hence, it is not asymptomatic. However, the assumption that treatment needs of these patients are the same as for the fully fledged disorders is notable here. A pertinent example from physical medicine is the case of chest pain. This is a clinical picture that warrants urgent and expert assessment, even though many or most cases will prove benign and self-limiting. There is one very serious underlying disease – myocardial infarction (for which a more specific risk syndrome of angina pectoris exists that features chest pain) – and several other equally serious conditions, for example pneumonia, pulmonary embolism or pneumothorax that cause chest pain. Another slightly different example is that of prediabetes. Patients with prediabetes have higher-than-normal fasting blood glucose levels, but these do not reach the threshold that defines diabetes. Without intervention, every year up to 10% of individuals with prediabetes will meet the clinical criteria for a diagnosis of diabetes and up to 70% of those will ultimately develop diabetes. Prediabetes not only increases the risk of developing diabetes, but also that of the vascular and neurological complications associated with diabetes and is associated with significant morbidity. Significantly (as expected with a staging approach), clinical management strategies for prediabetes are very different to those for diabetes, with lifestyle interventions, primarily weight loss and increasing exercise levels – the first line of treatment – and individuals who manage to return their blood glucose levels to normal, even transiently, reduce their risk of going on to develop diabetes by up to 70% [79]. If these do not result in remission then drug therapies, such as metformin, can be offered. This is very similar to what is being explored in the staged approach to emerging mental ill health; indeed, stress management, reduction of substance use, as well as a comprehensive series of psychosocial interventions encouraging participation in meaningful activity, a healthy diet and physical exercise, as well as individual psychological therapy, form key components of the present authors' treatment approach for UHR young people.

In psychiatry, the clinical management of patients with subthreshold syndromes, such as the UHR population, has been particularly controversial due to the confusion between the issue of defining the boundary of the need for care on the one hand and the timing of commencement of medication on the other. The latter is likely to be, in the great majority of cases (except those with a very acute onset and rapid rise to peak severity), well after the former, although there is a genuine fear in some countries, particularly in the USA due to their limited models of care and health financing, that the two will be conflated and considered identical. Clearly, overmedicalization is a real danger in such settings and while manifest symptoms should be treated on their merits, treatment choices should be made with the maxim 'first, do no harm' firmly in mind. Thus, benign therapies, such as eicosapentenoic acid or psychosocial interventions, including CBT or supportive therapy, are most appropriate as a first-line treatment in UHR patients, with

the prescription of antipsychotic medication being reserved for those who respond poorly, or not at all, to the gentler therapies. Stigma is all too often another important consequence of a psychiatric diagnosis, particularly a diagnosis that implies psychosis and especially schizophrenia. The question of stigmatization by labeling young people with an 'at risk for psychosis' diagnosis is valid, and must be addressed. One answer is to broaden the risk syndrome concept discussed above to a pluripotential risk syndrome that simply indicates a need for care and that has remission, as well as multiple diagnostic outcomes rather than naming one specific outcome that may or may not eventuate. Another crucial factor in the reduction of stigma is the provision of an appropriate culture and context of care [80]. Given the demographics of this patient group, the best service models promote collaborative care within a respectful, youth-friendly setting that emphasizes engagement, optimism and hope for the future, even if early remission and recovery are somewhat elusive in the short term. In this world, even progression to first-episode psychosis or schizophrenia is not catastrophized as in traditional mental healthcare.

Conclusion

While there is now a substantial body of evidence backing the value of early intervention for the psychotic disorders in terms of the human, social and economic outcomes produced [81–85], many important issues remain to be addressed. Although the intervention studies that have been conducted to date are promising and have provided proof-of-concept, they remain in clinical equipoise. When the results of these studies are considered in the context of the balance of risks and benefits, the available evidence indicates that, at this point, psychosocial interventions should be offered as a first-line therapeutic approach, with antipsychotic medications being reserved for a second- or third-line approach in those that do not respond to these more benign therapies. A culture of care that values a respectful and collaborative approach to treatment, with a strong emphasis on optimism and hope for the future, is vital to promoting engagement in this patient group.

Future perspective

With the costs associated with mental ill health estimated to more than double worldwide over the next two decades [86], a greater emphasis on prevention and early intervention is imperative if we are to reduce the burden of disease associated with the mental disorders. The last two decades of research and clinical practice, largely in the area of early psychosis, have led to a paradigm shift in psychiatry and an explosion of interest in phase-specific treatment and early intervention, with the ultimate aim of indicated prevention. Over the next decade, advances in our understanding of the basic biological mechanisms underlying the onset and progression of the psychotic illnesses should allow the design of more rational therapeutic approaches, with an emphasis on personalized, more benign treatments and the ability to predict each patient's likely response to treatment. Here, the areas that show particular promise are genetics, neurobiology and neuroimmunology, all of which are likely to yield significant insights.

While the clinical staging approach has much to offer, particularly in the context of the early stages of mental illness, to definitively resolve the question of the optimal types and sequences of interventions – biological and/or psychosocial – that are most appropriate at each stage of illness, sophisticated, large-scale clinical trials, informed by this ongoing biological research, will be necessary. We believe that this combination of basic and clinical research will validate the staging model and contribute to the design of more appropriate therapies, particularly for those young people at risk of developing a serious mental illness. Ultimately, this should provide further impetus for the rapidly growing shift towards more pre-emptive psychiatry.

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