Randomized Controlled Trial of Interventions Designed to Reduce the Risk of Progression to First-Episode Psychosis in a Clinical Sample With Subthreshold Symptoms

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Background: Most disability produced by psychotic illnesses, especially schizophrenia, develops during the prepsychotic period, creating a case for intervention during this period. However, only recently has it been possible to engage people in treatment during this phase.

Methods: A randomized controlled trial compared 2 interventions in 59 patients at incipient risk of progression to first-episode psychosis. We termed this group ultra-high risk to emphasize the enhanced risk vs conventional genetic high-risk studies. Needs-based intervention was compared with specific preventive intervention comprising low-dose risperidone therapy (mean dosage, 1.3 mg/d) and cognitive behavior therapy. Treatment was provided for 6 months, after which all patients were offered ongoing needs-based intervention. Assessments were performed at baseline, 6 months, and 12 months.

Results: By the end of treatment, 10 of 28 people who received needs-based intervention progressed to first-episode psychosis vs 3 of 31 from the specific preventive intervention group (P = 0.03). After 6-month follow-up, another 3 people in the specific preventive intervention group became psychotic, and with intention-to-treat analysis, the difference was no longer significant (P = 0.24). However, for risperidone therapy–adherent patients in the specific preventive intervention group, protection against progression extended for 6 months after cessation of risperidone use.

Conclusions: More specific pharmacotherapy and psychotherapy reduces the risk of early transition to psychosis in young people at ultra-high risk, although their relative contributions could not be determined. This represents at least delay in onset (prevalence reduction), and possibly some reduction in incidence.

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The notion of intervention in the prepsychotic phase of schizophrenia and related psychoses is not new. However, the dramatic recent growth of research and clinical programs in early psychosis has made it possible to systematically explore preventive interventions in this symptomatic but prepsychotic phase of disorder for the first time.

Prepsychotic intervention is based on the concept of prodrome. Until recently, the entire period before clearcut diagnosis in schizophrenia has been referred to as the premorbid phase. Studies of childhood antecedents have demonstrated statistically significant but clinically trivial differences between control subjects and those who later develop schizophrenia. These studies were originally interpreted as providing support for the neurodevelopmental hypothesis of schizophrenia, but they paradoxically highlight the quiescence of the illness during this phase of life, showing it to be a true premorbid or latent phase. In fact, as Häfner and colleagues revealed, these illnesses really begin to have clinical and social consequences after puberty, typically during adolescence and early adult life. Most patients with broadly defined schizophrenia experience a lengthy prodromal period of nonspecific symptoms and growing functional impairment before the full emergence of the more diagnostically specific positive psychotic symptoms. The development of disability during the prodromal period creates a ceiling for eventual recovery and is the key rationale for prepsychotic intervention.
However, the prodrome concept is retrospective, and clinical definitions compatible with a prospective approach are needed. From 1994, we conducted a series of naturalistic prospective studies to define operational criteria for a clinical sample at ultra-high risk (UHR) for progression to psychotic disorder.

This approach differs not only from the retrospective one but also from the conventional genetic high-risk paradigm. Cornblatt et al have since termed it the “clinical high-risk” approach. The rate of progression within 12 months for a sample meeting UHR criteria approaches 40%, much higher than the conventional genetic high-risk rate and several thousand times higher than the annual population risk. A full account of the development of this clinical research strategy and associated ethical issues is available elsewhere. Other centers have subsequently adopted and adapted these UHR criteria.

Progression to psychosis in these first-generation studies seemed neither inevitable nor predetermined, although it was high. Progression occurred despite supportive psychosocial treatment that included active treatment of depression and anxiety. Without such intervention, the rate could have been even higher. Nevertheless, we concluded that research examining more specific interventions was justified. We did not assume that the psychobiologic characteristics of the preschizophrenic phase are the same as those in later phases of illness, and we believe that a range of potentially neuroprotective interventions may ultimately be useful. However, our strategy for this initial study was to include “best bet” specific therapies in a single enhanced intervention package to determine whether it was possible to delay the onset of psychosis. We hypothesized that low-dose atypical antipsychotic medication combined with cognitive behavior therapy (CBT), effective interventions in manifest psychotic illness, would reduce the risk of early progression to psychosis when added to needs-based intervention (NBI) in contrast to the latter provided alone.

PATIENTS AND METHODS

PATIENTS

The study was performed in a specially designed setting, the PACE (Personal Assessment and Crisis Evaluation) Clinic, an extension of the Early Psychosis Prevention and Intervention Centre (EPPIC). The clinic is located within a generic youth health service, the Centre for Adolescent Health. The venue and the name were chosen to avoid stigma and to promote help seeking among young people; this has been a successful strategy.

A fuller description is provided elsewhere. Referrals between October 1, 1996, and January 31, 1999, were considered and were derived from educational settings, primary care settings, mental health professionals, and other youth services; however, many came via EPPIC.

Patients were eligible for the study if they (1) were aged 14 to 30 years; (2) lived in the Melbourne metropolitan area; and (3) met criteria for 1 or more of 3 operationally defined UHR groups. The rationale and validation of these criteria are fully described elsewhere, and the precise criteria are available from the authors. The first group comprised patients with a family history of psychotic disorder in a first-degree relative plus nonspecific symptoms and impaired functioning resulting in a decrease of 30 points on the Global Assessment of Functioning scale within the previous 12 months. The second group included those with attenuated positive psychotic symptoms that, although sustained for at least a week, remained below the threshold for frank psychosis. The third group was characterized by brief episodes of psychotic symptoms above the threshold but not sustained beyond a week.

The key outcome of interest was the development of suprathreshold levels of psychosis. The severity threshold was operationally defined using the Brief Psychiatric Rating Scale and the Comprehensive Assessment of Symptoms and History as follows: a score of 3 or more on the hallucinations subscale, a score of 4 or more on the unusual thought content subscale (plus a score ≥3 for delusional conviction on the Comprehensive Assessment of Symptoms and History), or a score of 4 or more on the conceptual disorganization subscale of the Brief Psychiatric Rating Scale. These levels had to be sustained for at least 1 week. The preventive outcome target was therefore not the onset of a schizophrenia diagnosis, which if it occurred was usually a later development. Although somewhat arbitrary, these exit criteria marked the threshold (linked to positive symptoms) at which we believed that antipsychotic medication should usually be commenced. All patients defined by these criteria as having progressed met the criteria for a DSM-IV psychotic disorder. Patients were also withdrawn from the study if they developed a full manic syndrome. The many diagnostic complexities in early psychosis beyond the scope of this article are addressed elsewhere.

Patients were excluded from the study if they had (1) a previous psychotic or manic episode, (2) previous treatment with an antipsychotic or mood stabilizing agent, (3) a substance-induced psychotic disorder, (4) an IQ lower than 70, or (5) an inadequate command of the English language.

STUDY DESIGN AND INTERVENTIONS

The study was designed as a single-blind, randomized controlled trial, with research interviewers intended to be blind to the interventions received. However, this was difficult to achieve because the 2 intervention groups were treated by different clinicians, a feature that was difficult to conceal from raters. Clinicians and patients were not blinded. Patients who met intake criteria and gave written informed consent for randomization were assigned by the study coordinator to one of the treatment groups using simple randomization without replacement.

The study was approved by the research and ethics committees of North-West Health (Melbourne, Australia). All participants received detailed information about the study, including a plain-language statement. The distinction between treatment of manifest conditions (treatment as usual) and intervention aimed at risk reduction of psychosis (the research focus) was clearly explained. For participants younger than 18 years, informed consent was obtained from a parent or guardian as well as the patient when possible. Only patients of the clinic who were judged to be fully competent to give informed consent for participation and who did so were included. Participation could be withdrawn at any time, and nonparticipation in the research in no way affected access to clinical care.

The 2 interventions were offered for 6 months. Following this, NBI continued to be offered.

Needs-Based Intervention

Needs-based intervention focused on the presenting symptoms and problems already manifest. Patients assigned to this group received needs-based supportive psychotherapy primary
illy focusing on pertinent issues such as social relationships and vocational and family issues. Therapists also performed a case management role, providing assistance with accommodation, education or employment, and family education and support. Although patients in this group did not receive antipsychotic medication, they could receive antidepressants (sertraline hydrochloride) if moderate to severe depression was present or benzodiazepines for insomnia (usually temazepam).

**Specific Preventive Intervention**

Specific preventive intervention (SPI) involved all elements of NBI and 2 additional treatment components hypothesized to have greater specificity for the reduction of risk of progression to psychosis. Hence, SPI, in common with NBI, aimed to treat features already manifest and, in addition, to reduce the risk of progression. The first additional component was administration of 1 to 2 mg of risperidone daily for 6 months, and the second was modified CBT. Risperidone therapy was commenced at 1 mg/d and increased to 2 mg/d provided that no adverse effects were experienced. If adverse effects occurred, the dosage was reduced to 1 mg/d. Antidepressants or benzodiazepines were again used when appropriate.

Cognitive behavior therapy was conducted according to a manual developed by us. The overall aims were to develop an understanding of the symptoms experienced, to learn strategies to enhance control of these symptoms, and to reduce associated distress. These strategies were drawn from mainstream CBT for nonpsychotic disorders and, where appropriate, by adapting psychological techniques that are useful in more established psychotic disorders. The following modules were offered flexibly: Stress Management, Depression/Negative Symptoms, Positive Symptoms, and Other Comorbidity (including substance abuse, obsessive-compulsive features, and social anxiety).

Several psychiatrists (P.D.M., A.R.Y., A.B., and S.A.) managed the drug therapy for both groups. Adherence was assessed via verbal report from patients and relatives of the percentage of doses taken as prescribed. This was believed to be sufficiently accurate given the voluntary basis and cooperative atmosphere of the study. The psychological therapists (L.J.P., S.F., E.M.C., D.G., and J.B.) were all experienced therapists. In contrast to the pharmacotherapy, the psychological treatments were delivered by separate teams of therapists (CBT, L.J.P., E.M.G., and D.G.; and supportive therapy, S.F. and J.B.). Varying the frequency and duration of sessions accommodated the differing needs and tolerance of the individual patients. All therapists were supervised weekly by senior clinical psychologists experienced in psychotherapy research methods (S.F. and H.J.) to enhance adherence to the treatment paradigm. However, no formal measures of treatment fidelity were used.

**ASSESSMENTS**

The principal outcome of interest was the rate of progression to psychosis, using a categorical model, to the predetermined threshold of positive psychotic symptoms. Independent assessments were carried out by a research psychiatrist (T.M.) at 3 points: baseline; after the intervention, approximately 6 months after study entry (mean [SD] 6.6 [0.9] months); and approximately 6 months later, or 12 months after study entry (mean [SD] 13.0 [1.4] months). Dimensional measures used were the Brief Psychiatric Rating Scale, the Scale for the Assessment of Negative Symptoms, the Hamilton Rating Scales for Depression and Anxiety, the Young Mania Scale, the drug and alcohol component of the Schedules for Clinical Assessment in Neuropsychiatry, and the Comprehensive Assessment of At-Risk Mental States, a semistructured interview specifically designed for monitoring prepsychotic symptoms. The Quality of Life Scale and the Global Assessment of Functioning scale represent measures of psychosocial functioning.

Clinicians assessed patients approximately every 2 weeks and carefully monitored them in relation to the psychosis threshold. When patients were judged to have progressed to psychosis, they were independently reassessed by the research psychologist (T.M.) using the operationally defined criteria for the threshold. Most patients were then treated within the EPPIC program. All patients were independently confirmed by nonproject psychiatrists as meeting criteria for a psychotic illness requiring antipsychotic medication. Updated study diagnoses were assigned for all patients using data collected at 12-month follow-up supplemented by multiple data sources, including medical record review and informant interview when possible. A consensus method of best-estimate diagnosis was applied. The clinical presentation of each patient was also meticulously reviewed in relation to the inclusion criteria and the criteria for progression to first-episode psychosis where this occurred, ensuring minimal risk of misclassification. In particular, we are convinced that no patient was covertly psychotic at study entry and, hence, that all progressions were genuine transitions to psychosis. The reliability of these procedures has been assessed in a separate reliability study (n=21), and pairwise χ² values for entry criteria (x²=0.81-1.0) and exit criteria (x²=0.77-1.0) were excellent. All medications and adverse effects were closely monitored and recorded by psychiatrists using a brief semistructured interview.

**STATISTICAL ANALYSIS**

Statistical software programs (SPSS for Windows 8.0; SPSS Inc, Chicago, Ill, and S-PLUS for Windows 4.0; MathSoft Inc, Seattle, Wash) were used for all statistical analyses. Comparison of the 2 interventions was principally by intention to treat, although the relationship of outcomes to adherence to treatment was also examined via an efficacy subset analysis. The Fisher exact test and survival analysis were used to carry out the comparison in terms of transition to psychosis. Use of analysis of covariance enabled the effect of potential confounders (age, sex, antidepressant drug use, time to presentation, and accommodation) for other dimensional outcome measures to be considered. All tests were 2-tailed, and significance was set at P= .05. Using the statistic number needed to treat (NNT) is a clinically appealing way of summarizing the effect of treatment in terms of the number of patients a clinician needs to treat with a particular therapy to prevent an adverse event and is calculated as the reciprocal of the absolute risk reduction. Herein, NNT is defined as the number of patients who need to be treated with risperidone and CBT in addition to NBI to prevent 1 from progressing to psychosis.

**RESULTS**

A total of 59 patients were randomized, 28 to the NBI group and 31 to the SPI group (Figure 1). Twenty-five patients were female (42%), and mean (SD) age at entry was 20 (3.6) years (range, 14-28 years). The baseline characteristics of the 2 intervention groups and of those refusing randomization are presented in Table 1. The data confirm that these young people are highly symptomatic and moderately disabled by their symptoms, although none are as yet frankly psychotic. Most patients manifested attenuated psychotic symptoms. Although there were no signifi-
cificant differences between the randomized SPI and NBI groups, when the total group of trial participants (n = 59) was compared with refusers (n = 33), the latter manifested significantly lower levels of symptoms and disability at baseline. Therefore, perhaps not surprisingly, the refusers showed a lower rate of transition to psychosis (12.1% at first follow-up and 18.2% at second follow-up) than the randomized NBI group. Tragically however, 2 members of those refusing randomization committed suicide during follow-up despite remaining engaged in NBI and apparently progressing well.

Figure 1. Randomization of 59 patients at incipient risk of progression to first-episode psychosis. PACE indicates Personal Assessment and Crisis Evaluation.

Table 1. Baseline Characteristics of 59 Patients Randomized to the Study and 33 Patients Who Refused Randomization

<table>
<thead>
<tr>
<th></th>
<th>NBI (n = 28)</th>
<th>SPI (n = 31)</th>
<th>P Value</th>
<th>NBI + SPI (N = 59)</th>
<th>Refusers (N = 33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, No. (%)</td>
<td>14 (50)</td>
<td>20 (65)</td>
<td>.26†</td>
<td>34 (56)</td>
<td>14 (42)</td>
<td>.16†</td>
</tr>
<tr>
<td>Australian born, No. (%)</td>
<td>25 (89)</td>
<td>28 (90)</td>
<td>.90‡</td>
<td>53 (90)</td>
<td>31 (94)</td>
<td>.50‡</td>
</tr>
<tr>
<td>Live with family, No. (%)</td>
<td>17 (61)</td>
<td>12 (39)</td>
<td>.09†</td>
<td>29 (49)</td>
<td>16 (49)</td>
<td>.95†</td>
</tr>
<tr>
<td>Age, y</td>
<td>20 (3)</td>
<td>20 (4)</td>
<td>.76‡</td>
<td>20 (4)</td>
<td>20 (4)</td>
<td>.54‡</td>
</tr>
<tr>
<td>Time-contact, d</td>
<td>320 (359)</td>
<td>523 (1086)</td>
<td>.33‡</td>
<td>344 (490)</td>
<td>296 (382)</td>
<td>.61‡</td>
</tr>
<tr>
<td>Time-PACE, d</td>
<td>369 (373)</td>
<td>572 (1110)</td>
<td>.34‡</td>
<td>398 (533)</td>
<td>385 (453)</td>
<td>.91‡</td>
</tr>
<tr>
<td>HRSA score</td>
<td>16.8 (9.0)</td>
<td>16.1 (7.0)</td>
<td>.76‡</td>
<td>16.5 (7.9)</td>
<td>11.6 (6.8)</td>
<td>.004‡</td>
</tr>
<tr>
<td>BPRS score</td>
<td>20.9 (9.3)</td>
<td>20.1 (7.2)</td>
<td>.73‡</td>
<td>20.5 (8.2)</td>
<td>16.1 (7.8)</td>
<td>.02‡</td>
</tr>
<tr>
<td>BPRSP score</td>
<td>4.6 (2.6)</td>
<td>4.7 (2.7)</td>
<td>.92‡</td>
<td>4.6 (2.6)</td>
<td>3.3 (2.8)</td>
<td>.03‡</td>
</tr>
<tr>
<td>HRSDD score</td>
<td>20.4 (10.2)</td>
<td>19.4 (7.0)</td>
<td>.67‡</td>
<td>19.9 (8.7)</td>
<td>12.3 (7.4)</td>
<td>&lt;.001‡</td>
</tr>
<tr>
<td>YMS score</td>
<td>3.4 (3.6)</td>
<td>4.2 (4.9)</td>
<td>.45‡</td>
<td>3.7 (4.2)</td>
<td>4.3 (4.8)</td>
<td>.59‡</td>
</tr>
<tr>
<td>QLS score</td>
<td>66.1 (23.5)</td>
<td>69.2 (19.2)</td>
<td>.58‡</td>
<td>68.3 (21.2)</td>
<td>84.2 (19.2)</td>
<td>.001‡</td>
</tr>
<tr>
<td>SANS score</td>
<td>21.2 (14.3)</td>
<td>18.0 (11.2)</td>
<td>.35‡</td>
<td>19.5 (12.8)</td>
<td>10.9 (10.5)</td>
<td>.001‡</td>
</tr>
<tr>
<td>GAF score scale</td>
<td>59 (14)</td>
<td>63 (12)</td>
<td>.24‡</td>
<td>61 (13)</td>
<td>69 (13)</td>
<td>.01‡</td>
</tr>
</tbody>
</table>

*TREATMENT EXPOSURE

Although there were no dropouts from the SPI group and adherence was high for CBT, adherence to risperidone therapy was more variable, which is also a characteristic of even well-engaged young people. Hence, in addition to intention-to-treat analysis, the data were analyzed by adherence to risperidone therapy, divided into full (almost 100% of doses taken) or partial (>50% of doses taken) adherence and poor adherence (<50% of doses taken). Of the 31 patients in the SPI group, 13 were classified as nonadherent, 4 as partially adherent, and 14 as fully adherent. The mean (SD) dosage of risperidone for the SPI group was 1.3 (0.901) mg/d. The use of sertraline was +1.9% (SPI) and 60.7% (NBI). Although the frequency of medical review was similar in the 2 groups, there was a significant difference in the number of psychological sessions attended by NBI (mean [SD], 5.9 [4.3]) and SPI (mean [SD], 11.3 [8.4]) patients (t = −3.06; P = .003), which reflected the greater structure and better engagement inherent in the CBT model. The supervision process seemed to support differentiation of the interventions and fidelity.

OUTCOME MEASURES

When analyzed by intention to treat, there was a significant difference between the groups at first follow-up that was lost by second follow-up because of the progression to psychosis of another 3 patients from the original SPI group (Table 2). Final diagnoses of psychotic and non-psychotic patients are given in Table 3. Survival analysis (intention to treat) (Figure 2) depicts this pattern, and although the curves were significantly different at the end of treatment, this significance was lost during subsequent follow-up. However, when the survival analysis is extended, taking into account levels of antipsychotic...
drug adherence, a significant difference is maintained between the fully adherent SPI group and the NBI group throughout follow-up.

Some psychiatrists believe that antidepressants can trigger psychotic episodes in vulnerable patients. Because the use of serotonin was 50% higher in the NBI group than in the SPI group, this could have been a possible explanation for the increased rate of transition. However, the transition rate within the NBI group was not significantly different whether or not sertraline was prescribed.

From data in Table 2, the NNT for end of treatment is computed as $1/(0.37-0.10)$, which is 4 (95% confidence interval, 3-19). This means that 4 patients would need to be treated to prevent 1 from progressing to psychosis over a 6-month period.

The NBI and SPI groups were also compared at the end of the treatment phase and at the end of follow-up on a range of symptomatic and functional measures (Table 4). No differences were observed between the groups on any of these measures, which were performed at relatively fixed times, and for those making the transition to psychosis, usually when they had already received treatment for psychosis. Levels of all symptoms improved in both groups, whereas functional levels were more stable, perhaps indicating the need for more extensive reparative psychosocial strategies. These measures were also compared for patients who remained nonpsychotic (Table 5). Irrespective of treatment group, and despite having manifested at some point a diagnosable psychiatric disorder, these patients were in much better shape symptomatically and functionally after treatment than at study entry. This is also true for SPI patients who received risperidone and did not become psychotic. Thus, although it is unclear which of these people were headed for but avoided transition, it seems clear that the group improved and was not harmed by the interventions. Furthermore, no other types of harm were detectable through stigmatization (assessed by routine clinician inquiry), anxiety due to being informed of the risk of progression to psychosis (all patients were well aware that something potentially serious was happening to them even before they presented to the clinic), or neuroleptic adverse effects (minor rigidity in 1 patient and mild sedation in 3 patients, relieved in all 4 cases by dose reduction). Patients and relatives benefited from

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Psychotic Cases, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At End of Treatment Phase</td>
</tr>
<tr>
<td>NBI (n = 28)</td>
<td>10 (36)</td>
</tr>
<tr>
<td>SPI (n = 31)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>SPI-NP (n = 17)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>SPI-F (n = 14)</td>
<td>1 (7)</td>
</tr>
</tbody>
</table>

*NBI indicates needs-based intervention; SPI, specific preventive intervention; SPI-NP, SPI with no or partial drug adherence; and SPI-F, SPI with full drug adherence. At end of treatment phase: NBI vs SPI, $P = .03$; NBI vs SPI-NP vs SPI-F, $P = .07$ (by Fisher exact test for both). At follow-up: NBI vs SPI, $P = .24$; NBI vs SPI-NP vs SPI-F, $P = .14$ (by Fisher exact test for both).

Table 3. Final Diagnoses of the Psychotic and Nonpsychotic Subgroups at 12-Month Follow-up

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotic Patients (n = 16)</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia/schizophreniform</td>
<td>7</td>
</tr>
<tr>
<td>Major depressive disorder with psychotic features</td>
<td>3</td>
</tr>
<tr>
<td>Bipolar disorder (with psychotic features)</td>
<td>3</td>
</tr>
<tr>
<td>Brief psychotic disorder</td>
<td>1</td>
</tr>
<tr>
<td>Psychotic disorder not otherwise specified</td>
<td>1</td>
</tr>
<tr>
<td>Substance-induced psychotic disorder</td>
<td>1</td>
</tr>
<tr>
<td>Nonpsychotic Patients (n = 43)</td>
<td></td>
</tr>
<tr>
<td>Nil disorder</td>
<td>26</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>4</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>1</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>2</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>2</td>
</tr>
<tr>
<td>Social phobia</td>
<td>3</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>4</td>
</tr>
<tr>
<td>Eating disorder</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 2. Survival analysis (intention to treat) showing the proportion of nonpsychotic patients throughout the study. SPI indicates specific preventive intervention; SPI-NP, SPI with no or partial drug adherence; SPI-F, SPI with full drug adherence; and NBI, needs-based intervention. $P = .09$, SPI vs NBI; $P = .03$, SPI-F vs NBI, both by log-rank test.

This is the first study, to our knowledge, to suggest it may be possible to at least delay, and in some cases perhaps even avert, progression to full diagnostic threshold for psychotic disorder in individuals at UHR of schizophrenia and related psychotic disorders. The study builds on a foundation of naturalistic research and careful definition of the UHR clinical state. However, it is an initial step, and the findings should be investigated further using more rigorous designs. Our “close-in” research strategy contrasts with the traditional high-risk strategy in that genetic risk markers are only part of the definition of risk, and early symptomatic and functional changes are required, ensuring that cases are close to onset. It also differs from the revived focus on nonpsychotic variants of schizophrenia, which represents a
broadening of the therapeutic focus in schizophrenia, not a true early intervention approach. In contrast, we identified progressive positive symptoms as a preventive therapeutic target in their own right, thus including a broader range of psychotic disorders, not only schizophrenia.

The NNT of 4 for this study indicates that the intervention is relatively potent and contrasts with an NNT of 13 for drug treatment of moderate hypertension in the prevention of stroke.19,20 Furthermore, if SPI had been compared with monitoring alone, it may have been even more potent because the transition rate in such a control group may well have been higher. Several patients in the NBI group recovered even though they had strong genetic risk and seemed highly “incipient.” There were no significant symptomatic and functional differences between groups at follow-up because although those avoiding progression had improved, so too had those who had developed psychotic disorders as a result of timely and effective treatment. Indeed, the latter were performing much better than at entry. The data initially suggested that the advantage in risk reduction is especially present during the treatment phase and may erode when treatment is withdrawn. However, when drug adherence is taken into account, a more sustained effect emerges. Even a well-timed 6-month course of antipsychotic medication plus CBT may conceivably inhibit progression to psychosis for a more prolonged period. Larger sample sizes and longer follow-up are essential.

An obvious limitation of this study is the lack of blindness. However, this is unlikely to account for the robust difference seen in transition rates, particularly because independent psychiatrists confirmed the diagnosis of psychosis and all entry and exit decisions in the study were reviewed by expert consensus. A second limitation is that we could not assess the relative contributions of risperidone treatment and CBT. A critical question for future research is whether use of antipsychotic medications is always required to reduce the risk. Per-
therapy could be considered as a conservative second step for patients who did not improve or who worsened. In continuing research we are exploring this option using a multiple-cell design under double-blind conditions. We are also controlling for the amount of psychosocial contact, which, despite our efforts, was greater here in the SPI group. In future research, we need to examine other alternatives because neuroprotective agents may ultimately prove to be safer and more effective. The present results cannot be generalized beyond the help-seeking subset of UHR patients who accepted randomization. We know that most young people in the surrounding community who were eligible for PACE and participation in this study were not accessed. Those who entered the clinic but refused randomization were also a somewhat different clinical population.

All participants understood the study well and were capable of giving, refusing, or withdrawing informed consent. They were provided with clinical care that was in no way contingent on participation in the study. Participants in the clinical trial uniformly benefited, and no obvious harm was detectable. Moderate improvement across a broad range of psychosocial indicators was noted, although participants were significantly compromised on these measures at entry and in many cases could have been expected to deteriorate further in the absence of treatment. Even those who became psychotic were well engaged in treatment and thus were treated promptly without needing emergency or inpatient care. Administration of low-dose risperidone was well tolerated, with minimal adverse effects. Patients who wanted to discontinue therapy could do so freely. The most serious adverse outcomes were seen in nonparticipants.

The ethical dimension is complex.18,22 The concept of subthreshold intervention presents a dilemma. As the NNT parameter illustrates, there is a false-positive issue for all interventions, and an acceptable range needs to be defined. This is a decision that ultimately should be made by patients and families, informed by adequate data on the benefits and risks of interventions. Further ethically sound studies using a range of potentially preventive and neuroprotective interventions, biological and psychosocial, are needed so that robust NNT data can be amassed and shared. Such studies are presently in clinical equipoise and should be as strongly supported as they have been in nonpsychiatric fields. To censor this type of research for pseudoethical reasons would create a much less ethically acceptable scenario in which no evidence base is developed to guide clinical practice. However, until such data exist, our general stance is that off-label use of even novel antipsychotic medications in such patients should not be first-line treatment.

The potential benefits of prespsychotic intervention are as follows. First, patients are more easily engaged and can therefore receive treatment for manifest syndromes, whether or not the preventive treatment of the potential psychosis turns out to have been unnecessary or ineffective. Second, those who progress to psychosis have developed a level of trust that enables them to accept treatment, to have a minimal duration of untreated psychosis and reduced comorbidity, and to require inpatient care rarely. Third, the psychosocial impact of the disorder may also be minimized and the ceiling for recovery set at a higher level. Finally, some people may delay or avoid a first psychotic episode. For a subset of patients, prespsychotic prevention may prove to be highly cost-effective. It is an important frontier for further research.

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