

REVIEW ARTICLE

Indicated Prevention of Schizophrenia

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SUMMARY

Introduction: Despite recent advances in their treatment, schizophrenic disorders are still among the diseases that most severely impair patients' quality of life. For this reason, centers for the early recognition of schizophrenic disorders have come into existence worldwide. In these centers, much effort is devoted to the development and testing of suitable preventive strategies.

Methods: In this article, we selectively review the literature on the currently available means of assessing the individual risk of becoming ill with schizophrenia and of preventing the imminent onset of the disease.

Results: The currently recognized neurobiological and psychosocial risk factors are not predictive enough to enable the development and application of selective prevention measures for asymptomatic persons at risk. The imminent onset of schizophrenia can be predicted with high accuracy, however, in cases where an initially non-psychotic patient develops early cognitive symptoms that imply a risk of schizophrenia and then, later on in the prodrome of the disease (which typically lasts about five years), goes on to develop high-risk symptoms with mild psychosis. At this point, a differential strategy of indicated prevention can be put into action, including cognitive behavioral therapy, atypical antipsychotics in low doses, and neuroprotective agents.

Discussion: The current state of knowledge in this innovative field of research leads us to expect that it will soon be possible to offer individually tailored preventive measures to persons seeking medical help and advice because of the early warning signs of schizophrenia.

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Key words: schizophrenia, risk factor, early course, risk symptom, indicated prevention

In the mid 1990s, the Medical Institute in Washington – as commissioned by the Congress of the United States of America – began to develop recommendations to prevent psychiatric diseases. Three different approaches to reduce the incidence of new cases were then distinguished (1). The universal approach is applied to the total population (2); the selective approach applies to healthy persons at increased risk of disease; the indicated approach applies to persons who already exhibit risk symptoms requiring treatment (at risk mental states, ARMS) (3) (*figure 1*). Every doctor is familiar with examples of these approaches from physical medicine: for example, series of vaccinations (universal), preventive medicine for persons at increased risk of infarction (selective) or surgery for precancerous symptoms (indicated). In accordance with this, the psychiatrist may employ multimodal training programs (universal approach), psychotherapeutic intervention after psychic traumatization (selective approach) or medication to prevent dementia in persons with "mild cognitive disorders" (indicated approach). The present article is an extension of the first WHO report on the prevention of mental disorders (4) and presents a selective literature review on the current status of work to reduce the incidence of schizophrenic disorders.

Epidemiology

The annual incidence of schizophrenic disorders is 15 to 20 new cases per 100 000 inhabitants per year (0.01% to 0.02%), with a life time prevalence of 400 000 to 800 000 German citizens (0.5% to 1%). It follows that these are not very frequent conditions. On the other hand, schizophrenic disorders are among the most burdensome illnesses for the life of the patient and caregivers and cause a comparable "global burden of disease" to the major endemic diseases, such as stroke or diabetes mellitus (5). This is linked to the early age at first diagnosis – 18 to 35 years – and the long-term course, which is often unfavorable, even today. Delusional phenomena, thought disorders (e.g., thought broadcasting, thought withdrawal, thought insertion), and acoustic hallucinations are primarily employed in diagnosis. Although these so-called positive symptoms are often highly dramatic, frightening and dangerous, they normally regress during the clinical

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course, which is mostly episodic. On the other hand, the "negative symptoms" of impoverishment of thought, feeling, and action and ability to make social contacts frequently become permanent features, leading to psychosocial handicap and inability to work at an early age. If the resulting economic losses are added to the direct costs of medical and psychosocial care, the financial costs of schizophrenic disorders to the community are about 10 billion euros for Germany per year (6).

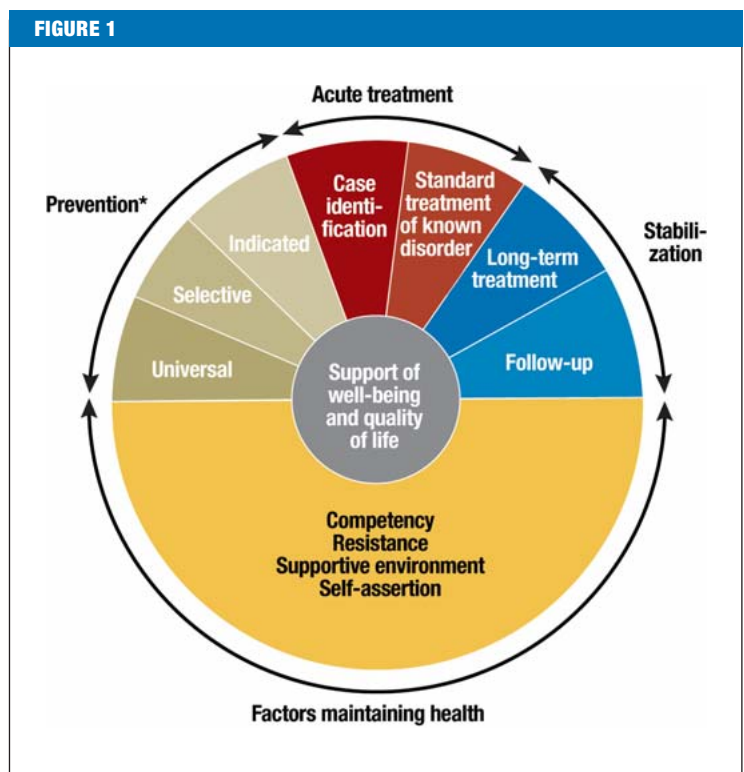
Etiopathogenesis

As a result of etiological research, it is becoming increasingly clear that schizophrenia is a complex disorder with polygenic heredity and that its pathogenesis is greatly influenced by interactions between different genes and interactions between genes and the environment. Genetic associations to various variants of the genes for *dysbindin* and *neuregulin-1*, the genetic locus G72 and the *DAOA* gene with which it interacts (D-amino acid oxidase activator) have now been confirmed several times (figure 2). However, these initial genetic findings are not thought to play a causal role in this complex disorder. They play a role in the disposition to the disease, by modulating the risk of its occurrence. Moreover these findings are only preliminary. Once genuinely pathogenic gene variants have been identified, they may turn out to be only a very small section of the dispositional foundation, which might include numerous genes that are currently unknown. On the other hand, these initial molecular neurogenetic insights are highly informative, as the identified candidate genes code for proteins with functions ranging from brain development to maintenance of the glutaminergic synapse in the mature brain, and thus regulate neuronal proliferation, migration, terminal differentiation, and synaptic functions. This functional relevance fits well with other findings obtained with neuropathological testing methods, lesion animal models, and functional and structural brain imaging, which, taken together, are most likely to indicate a disorder in the plastic processes of brain development, resulting in disconnections in a network of cortical and subcortical centers (7).

Risk factors and early course

Figure 2 also lists the environmental risk factors which have been established, which may occur immediately, soon after birth or later during development in childhood or adolescence. However, each of these appears to increase the lifetime risk of the disease by not more than 4%. Thus the currently known risk factors, either alone or taken all together, cannot be used for early detection and prevention without knowledge of the complete dispositional foundation and the gene-gene and gene-environment interactions, which are probably numerous.

A more promising approach is to consider the early course, in which the pathophysiologically active disturbance in brain development at the age of about

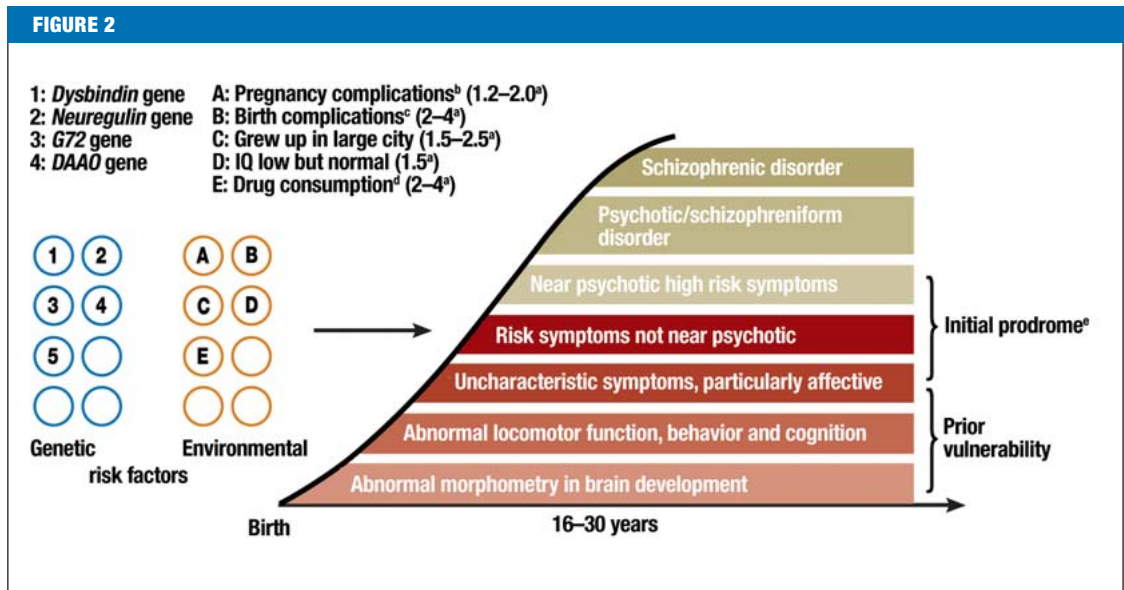


Support of psychological health (from Mrazek & Haggerty 1994); Universal prevention: targeting population – for example, pregnancy and birth care or multimodal training programs. Selective prevention: targeting persons with risk factors – for example interventions after psychological trauma, early support programs, programs for children of psychiatric patients. Indicated prevention: targeting persons with risk symptoms – for example interventions for subclinical anxiety or depression symptoms, drugs to prevent dementia with "mild cognitive disorder"

16 extends beyond early abnormalities in behavior into definable risk or high risk symptoms, depending on the individual constellation of stressors and protective factors. First episode research has shown that the outbreak of the disease is preceded in about three quarters of all cases by an initial prodrome, which lasts for an average of five years. Even in highly developed health care systems, an average of one year then elapses from the first manifestation of psychotic positive symptoms relevant to the diagnosis and the initiation of adequate treatment. The period over which the first psychotic episode remains untreated (duration of untreated psychosis, DUP) correlates with

- delayed and incomplete remission of the symptoms,
- necessity of more protracted treatment and greater risk of relapse,
- lower compliance, greater burden to the family, and a higher level of "expressed emotion,"
- increased risk of depression and suicide,
- greater burden on the work or training situation,
- increased drug abuse and delinquent behavior, and
- markedly increased costs of treatment (8).

Indicators for increased risk of schizophrenia



Program for prevention

These correlations have now been confirmed by a reliable meta-analysis (9), with correlation coefficients from 0.285 to 0.434 (95% confidence interval [CI]). This not only provides strong arguments for treating the first psychotic episode as soon as possible, but has also led to the foundation of specialized centers for early diagnosis and treatment. The first of these were in Melbourne, Australia, and in Cologne, Germany, followed by numerous other sites, both within Germany and elsewhere. There has been increasing evidence that even the initial prodromal symptoms are a great burden to the patients and their caregivers and encourage them to seek help. There can also be a massive collapse in the psychosocial performance in the initial prodrome and pathophysiological cerebral changes may proceed in parallel, extending to the full outbreak of the disease. With this background, all centers have been carrying out public information campaigns and offer individual risk assessment, as a contribution towards the goal of indicated prevention as required. The following three objectives have been specified:

- improvement in the current burden of prodromal symptoms,
- avoidance or perhaps delay in the developing psychosocial handicap, and above all
- prevention of, or at least delay or attenuation in the threatened first psychotic disease (10).

Prediction of first disease using early risk criteria

The two most important studies on the early course of the first psychotic manifestation have been a retrospective study with optimized methods (11) and a longer term prospective study of just under 10 years (12). These have shown that the earliest and most common symptoms, which generally dominate during the pro-

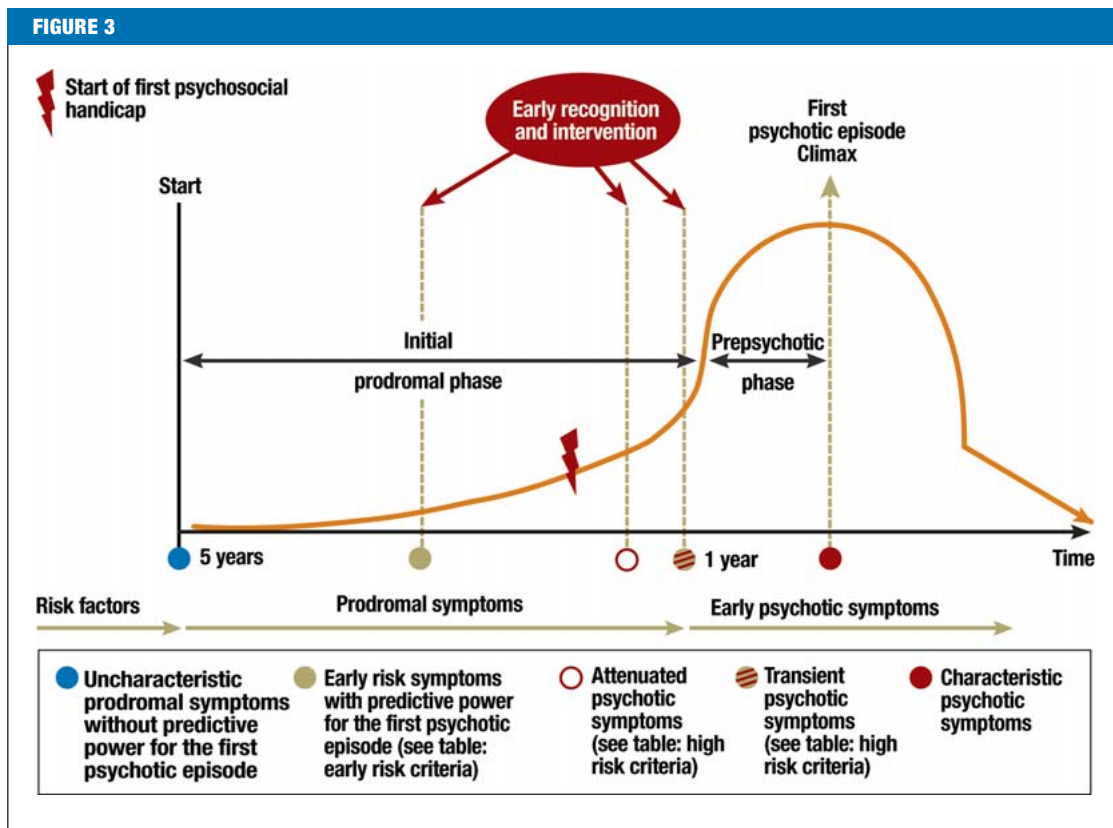
drome, are uncharacteristic and cannot be distinguished from the impairment in mood, drive, contact, and concentration in depressive episodes. Nevertheless, there were also striking cognitive impairments in the form of subjective disorders in thought, speech, and perception. These were found in more than a quarter of patients, with specificities of 0.85 and high positive predictive power of at least 0.70, accompanied by a low rate of false positives (7.4%). These basic symptoms can now be reliably detected with standardized test instruments. An initial study was performed with 160 persons with these symptoms who sought help. After 12 months, 20% had developed a schizophrenic disorder. An additional 17% of patients followed after 24 months, with an additional 13% after 36 months. Finally, 70% of the patients had developed a schizophrenic disorder after an average of 4.5 years. An additional study was performed on 146 persons at risk, each with at least one of the predictive basic symptoms given in the *box*. After only 12 months of observation, 29.5% of this group had developed a psychosis (13). As a result of these findings, several modifications of predictive basic symptoms have been established as a set of criteria for risk assessment in national and international research on the early recognition of psychosis. In particular, the German Research Network on Schizophrenia (GRNS) has used these symptoms – together with the loss in function shown in the *box* – for the definition of the early initial prodromal state (EIPS), in the sense of clinical staging (*figure 3*).

Prediction of disease with high risk criteria

It is also interesting that the positive symptoms typical of schizophrenia – such as delusions, hallucinations or formal thought disorders – appear already towards the end of the initial prodrome. These are often in an

FIGURE 3

Approaches for indicated prevention



BOX

Early risk criteria and high risk criteria

Early risk criteria*1 – early initial prodromal state (EIPS):

1.) Predictive basic symptoms (at least one several times weekly during the last three months)

- Thought interference, perseveration, pressure or blockages
- Disturbance of receptive speech (either heard or read)
- Decreased ability to discriminate between ideas and perception, fantasy and true memories

- Unstable ideas of reference
- Derealization
- Visual perception disturbances
- Acoustic perception disturbances

or

2.) Clear loss of level of performance and function with prior risk

- Reduction in the Global Assessment of Functioning Scores (as in DSM IV) by at least 30 points for at least a month and
- At least one of the following risk factors: psychosis of the schizophrenic type in a first degree blood relative or complications at birth

High risk criteria*1 – late initial prodromal state (LIPS):

1.) Attenuated psychotic symptoms (APS) (presence of at least one of the following symptoms with repeated occurrence over a period of at least a week)

- Idea of reference
- Odd ideas or magic thinking
- Unusual experiences of perception
- Odd manner of thinking or speaking
- Paranoid ideas

or

2.) Transient psychotic symptoms (brief limited intermittent psychotic symptoms, BLIPS) (duration of BLIPS less than seven days and not more frequent than twice per week in one month, spontaneous remission, at least one of the following symptoms)

- Hallucinations (PANSS*2 P3 ≥ 4)
- Delusion (PANSS*2 P1, P5 or P6 ≥ 4)
- Formal thought disorders (PANSS*2 P2 ≥ 4)

*1 Recorded with reliable and valid early recognition instruments

*2 PANSS, Positive and Negative Syndrome Scale

attenuated form, but can then become full-blown, but only transient. As it was expected that these symptoms would provide a comparatively reliable prediction of a transition to the first psychotic manifestation, particularly in the short term, advance warnings of this sort have been exploited as ultra-high risk (UHR) criteria (*figure 3*). There have now been 11 relevant and reliable early recognition studies by national and international

groups. According to their results, the outbreak of the first psychotic episode can be expected within the next 12 months in 40% of affected patients (4, 8, 14) if these UHR criteria are fulfilled. As the annual incidence for all forms of psychosis in the general population is only about 0.034%, this is indeed a highly dramatic increase in the relative risk of illness. As a consequence, the UHR have been introduced in a slightly modified form by the GRNS and have been used for the definition of the late initial prodromal state (LIPS) in the project unit "Early Recognition and Early Intervention" (*box*).

The large scale research projects on psychosis prevention include the EPOS (European Prediction of Psychosis) study (15). This was promoted by the 5th support program of the European Commission and has just been completed. In addition, the seven center parallel group study PREVENT in the special program "clinical studies" of the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) is now being started. The third major project is the prodrome intervention study NEURAPRO (16), which is planned for North American, European, and Australian centers. All these projects use an integrative set of criteria for risk assessment, covering the characteristics shown in the *box*.

Differentiated prevention strategy

Five international intervention studies have attempted to find out whether or to what extent the three objectives for indicated prevention given above can be reached (17–22) (*table*). The preventive measures used were either cognitive behavioral therapy (CBT) adapted to the requirements of the persons at risk (twice) or atypical antipsychotics – risperidone, olanzapine, and amisulpride – at the lowest possible dosage (three times). As these are all randomized controlled studies, level of evidence 1b (randomized intervention study) can be claimed for the effects demonstrated for these measures. However, there were problems with the condition of blinding in the two CBT interventions and the test group with risperidone was also given CBT, so that no unambiguous differentiation can be made between pharmacological and psychotherapeutic effects. These and other methodological shortcomings restrict the reliability of the conclusions for the moment and have encouraged the research groups working in this areas to plan new optimized intervention studies. For example, the current large scale project PREVENT contains careful comparative analyses and superiority and inferiority tests of the psychological and pharmacological treatments. Staging between different grades of risk and also probably the nearness to the first psychotic manifestation (*figure 3*) were mainly considered in the two German GRNS intervention studies. One of these covered EIPS and only offered CBT as a preventive measure (20, 21). The other was designed for LIPS and used preventive treatment with the antipsychotic amisulpride for only this highly advanced degree of risk (20, 22). This differential

TABLE

Prospective, randomized, controlled prevention studies in persons with increased risk of psychosis

Study	Inclusion criteria: early risk and high risk criteria	Transition criterion	Sample (n)	Design	Experimental condition	Control condition	Catamnesis (since inclusion)	Results
McGorry et al. (17)	APS and/or BLIPS and/or reduction in the level of social function and first degree relatives with schizophrenia or index person has diagnosis of schizotypal personality disorder	More than one week of consistent positive symptoms	59	Randomized controlled unblinded study	6 months individual CBT and risperidone (average dosage 1.3 mg/day)	6 months supportive psychosocial intervention	12 months	Improvement in the symptoms and social adjustment under both conditions; significant reduction in transition rate in experimental group after 6 months by intention-to-treat analysis (6 months: exp. 10% vs. ctl. 36% p = 0.026; 12 months: exp. 20% vs. ctl. 36%, p = 0.24) and after 12 months by per-protocol analysis (exp. 7%, vs. ctl. 36%; p = 0.017) (NNT = 4)
Morrison et al. (18)	APS and/or BLIPS and/or reduction in the level of social function and first degree relatives with schizophrenia or index person has diagnosis of schizotypal personality disorder	More than one week of consistent positive symptoms	58	Randomized controlled study	6 months individual CBT	6 months monitoring	12 months	Significant improvement in the positive symptoms with CBT; condition compared with monitoring; improvement in social adjustment in both conditions; significant reduction in the transition rate after 12 months (exp. 6% vs. ctl. 22%; p = 0.028)
McGlashan et al. (19)	APS (modified) and/or BLIPS (modified) and/or reduction in the level of social function and first degree relatives with schizophrenia or index person has diagnosis of schizotypal personality disorder	4 weeks consistent positive symptoms, behavior disorganized or a danger to self or others	60	Randomized placebo-controlled double-blind study	12 months olanzapine (5–15 mg daily), supportive psychoeducative individual and family intervention	12 months placebo, supportive psycho-educative individual and family intervention	24 months	12 months improvement in the positive, negative, and general psychopathology significantly greater in the olanzapine group than in the placebo group; statistical trend towards reduction in the transition rate after 12 months (exp. 16% vs. ctl. 38%; p = 0.08) Adverse effects: weight increase, tachycardia
Häfner et al. (20); Bechdolf et al. (21)	Basic symptoms predictive of psychosis and/or reduction in the level of social function with genetic and/or obstetric risk factors	APS*1 and/or BLIPS*2 and/or more than one week of consistent positive symptoms	128	Randomized controlled study	12 months individual CBT, group CBT, cognitive training, psychoeducation of relatives	12 months supportive individual treatment	24 months	Interim evaluation: significant improvement in prodromal symptoms and level of social function in the pre vs. post comparison; large strength of effects (d = 1.85–3.80) in pilot-exp. sample (n = 12); after 12 months: transition rates: exp. 5%, ctl. 15% (p = 0.008) in subsample with heterogeneous observation period (NNT = 8)
Häfner et al. (20); Ruhrmann et al. (22)	APS and/or BLIPS	More than one week of consistent positive symptoms	124	Randomized controlled study	24 months amisulpride (50–800 mg daily), supportive psychoeducative individual and family education	24 months supportive psycho-educative individual and family psycho-education	24 months	Interim evaluation: significant improvement in prodromal symptoms and level of social function in pre vs. post comparison after 6 and 12 months; after 6 months, transition rates: exp. 5%, ctl. 21% (p = 0.019) in subsample (n = 102)

APS, attenuated positive symptoms; BLIPS, brief limited intermittent psychotic symptoms; CBT, cognitive behavioral therapy; p, level of significance; d, strength of effect; NNT, number needed to treat; exp. experimental group; ctl., control group

prevention strategy is now pursued in all German early recognition centers and is winning increasing numbers of adherents in other countries. For example, in the NEURAPRO study, an antipsychotic – quetiapine – is only to be used if effective intervention strategies for milder risk symptoms – here neuroprotective fish oil (14, 23) – have had no preventive effect.

Ethical questions

In the new early recognition centers throughout the world, ethical and legal questions are taken very seriously. An attempt is made to provide an individual answer for the specific circumstances of the patient and the caregivers, by using regulated procedures for advice and decision. There is a problem that the result of the risk assessment can cause additional psychological stress. This is met by totally avoiding the term "schizophrenia," unless the patient has direct experience of the disease, in which case it is explained in an objective and calming manner. The discussion is always based on the symptoms of the person seeking advice and help and it is explained that an "early psychosis" may develop if the risk criteria are fulfilled, which might be prevented by the possible therapies. As part of the differential strategy, the preventive measures are primarily selected for their ability to improve the risk symptoms and to counteract psychosocial handicap. Hence, the costs and benefits are always weighted against the perceived need for treatment. This is clearly present even in those who do not convert, as has been demonstrated in a large number of studies on at-risk samples. Furthermore, the early detection and intervention programme will also pass the most critical ethical evaluation if the following principles are adhered to: (i) In EIPS, primarily use psychotherapeutic strategies that pose little stress on the patient, are generally well accepted and provide enough time to choose a well-tolerated antipsychotic, should attenuated or transient psychotic symptoms develop regardless. (ii) In early detection, aim at a percentage of false-positive predictions of less than 10% and, consequently, at a further reduction of the number needed to treat (NNT; see *table*).

Conclusion

On the basis of the available studies, the indicated prevention of schizophrenic disease must certainly be regarded as being at the stage of scientific testing. However, if the developments in this innovative area continue to be so rapid, it will be possible in the coming years to implement the evidence-based results in the practice of clinical care and, if at all possible, to provide every person with early warning signs seeking advice with individualized possible preventive strategies. This might already be too late to cause a major reduction in incidence, given the complexity of this condition, the long duration of the prodromal phase and the importance of the dispositional basis. The present approach is not restricted to risk symptoms, but already includes risk factors in making the indica-

tion (*box*). Depending on developments in basic research, there would have to be developments in the direction of selective prevention in asymptomatic predisposed persons. However, given the current state of knowledge, the relationship to risk symptoms offers major scientific, ethical, and legal advantages in implementation. This is indeed a promising step on the way to preventive psychiatry (4, 10, 14, 24).

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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