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# SNLGI 14

Early intervention in schizophrenia

GUIDELINES

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## ***The Italian national guidelines system (SNLG)***

*In Italy, guidelines and other instruments aimed at enhancing the quality of healthcare are developed within the National Health Institute's National Guidelines System (SNLG).*

*Current legislation in Italy proposes the adoption of guidelines in healthcare, underscoring the need to make the most efficient and efficacious use of resources possible and to improve the appropriateness of this sector's diagnostic instruments.*

*These are the general aims of the SNLG, which has the specific aims:*

- to produce information to help guide clinical and non-clinical professionals in more effective and appropriate decision-making and a more efficient use of resources;*
- to render such information easily accessible;*
- to monitor the adoption of these guidelines by examining optimal conditions for their introduction into clinical practice;*
- to evaluate their organisational impact and outcomes.*

*The instruments used to pursue these aims are clinical-organisational guidelines such as the present document, orientation documents for implementation, and orientation documents for evaluating healthcare services.*

## **USER NOTES**

These Guidelines make it possible to rapidly transfer knowledge yielded by biomedical research into daily clinical practice. They are behavioural recommendations developed through a process of systematic review of expert opinion and the literature and can therefore serve as an instrument for doctors and healthcare administrators in their efforts to improve quality of care and to rationalise the use of resources.

Clinical decisions concerning individual patients require that these recommendations, founded on best scientific evidence, be applied in light of a physician's clinical experience and by considering all of a given context's circumstances. The guidelines represent a synthesis of the best knowledge available and can serve as an updating and training tool for doctors. Individual professionals must therefore base their decisions on their own expertise and experience in terms of the extent to which these guideline-recommended behaviours, which meet qualitative standards defined on the basis of the most up-to-date scientific evidence, are applicable to a specific clinical case.

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## **PRESENTATION**

*Awareness of mental illness and its actual healthcare system- and social impact is recent. Although schizophrenia is fortunately not the most widespread mental illness in the global population, it takes a heavy toll on its sufferers, on family members, on healthcare systems, and on the society at large. In fact, although recent World Health Organization estimates indicate that depressive syndromes are the most common mental health problems in Italy, schizophrenia is certainly not rare and is currently estimated to affect approximately 150.000 individuals in this country.*

*In addition to schizophrenia's unusual and incapacitating manifestations, afflicted individuals are subjected to the social stigma that inevitably accompanies psychosis—i.e., a climate of unjustified fear, suspicion, and prejudice. This bias accentuates the sense of isolation and suffering of these individuals and of their frequently overburdened family members.*

*The Italian Ministry of Health is therefore particularly committed to surmounting the discrimination that still characterizes mental illness, with awareness, moreover, that these disorders are always treatable and that proper treatment is based on accurate information and on targeted intervention.*

*The present guidelines focusing on early intervention in schizophrenia are therefore long overdue. In fact, many regions and local contexts have already begun experimentation and have set up early intervention programs. The present guidelines can serve as an important source of scientific and organizational specification for all efforts aimed at rendering these forms of intervention more attentive and effective.*

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**Associazione Unitaria Psicologi Italiani (United Italian Psychologists Association) (AUPI)**  
**Fondazione Italiana per lo studio della Schizofrenia (Italian Foundation for Schizophrenia Research)**  
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**Psichiatria Democratica (Democratic Psychiatry)**

## LEVELS OF EVIDENCE

### Evidence type

- I** High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
- II** Evidence from a single, well-conducted RCT
- III** Non-randomised or quasi-randomised cohort studies or meta-analyses of non-randomised or quasi-randomised cohort studies.
- IV** Case-control studies or meta-analysis of case-control studies
- V** Non-analytic studies, e.g., case reports, case series
- VI** Expert opinion

## GRADES OF RECOMMENDATION

- A** The procedure is strongly recommended.  
The grade indicates a particular type of recommendation that is supported by good quality scientific evidence, even if not necessarily evidence of Level I or II.
- B** There are doubts concerning recommendation of the procedure, but its application should be carefully considered.
- C** The body of evidence does not allow for recommendation, either for or against the procedure.
- D** The procedure is not recommended.
- E** The body of evidence strongly advises against the procedure.

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## SUMMARY

Schizophrenia can be considered the most severe and disabling of mental illnesses for several reasons: for its disabling effects, the stigma marking individuals affected by it, and for the frequently enormous burden it places on patients' families and on healthcare services.

Schizophrenia causes 1.1% of total years lost to disability and 2.8% of years lived in disability, and the disorder strikes the population with a prevalence of 4 per 1,000. It is estimated that 245,000 individuals in Italy alone are, or have been affected by schizophrenic-type disorders.

The theme of early intervention in schizophrenia is currently at the core of a widespread debate. Although there is a general consensus that early diagnosis of the illness helps improve its prognosis, there is a dearth of precise indications on how to comprehensively treat this disorder.

The present guidelines have been developed by a multidisciplinary Guidelines Development Group (GDG) based on evidence available in the literature. They are aimed at shedding light on the topic, considering the great personal and social consequences of the illness and the ambiguity one encounters when dealing with it actual clinical practice. The guidelines are also aimed at supporting all professionals dedicated to caring for patients suffering from schizophrenia.

During the development of these guidelines, a distinction was made between individuals at risk of schizophrenia and individuals with first episode psychosis.

For at-risk individuals, the efficacy of different types of intervention was examined by referring to the goal of modification of prognosis or prevention of onset. The literature on the topic, however, is quite limited. It therefore was not possible to delineate clear-cut and explicit recommendations in this regard.

Conversely, when considering individuals with first episode psychosis, the efficacy of the various forms of intervention was evaluated with the goal of modification of prognosis and/or improvement in prognosis. Research in this domain is undoubtedly more extensive and more structured--if not always conclusive. Many demonstrations of efficacy are indirect and exposed (for various reasons) to bias, although literature reports on the topic show a certain degree of coherence and several instruments are available to ensure a rapid and accurate diagnosis with a minimum of invasiveness. These forms of intervention are therefore recommended by citing the importance of creating specialised centres for treating schizophrenia and of ensuring the multiplicity and integration of various treatments.

Specifically:

- Identification and treatment of first episode psychosis patients through structured early intervention programs is recommended. (Their efficacy is presumably mediated by a reduction in the DUP and by the quality of delivered care that specialised centres are able to provide);
- The use of satisfactorily accurate assessment scales for diagnosing schizophrenia is recommended, to identify individuals with first-episode schizophrenia;
- The use of imaging techniques (MRI, CT) as a diagnostic support is recommended to identify individuals with first-episode schizophrenia;
- Given its efficacy in reducing relapse rates, pharmacological therapy is recommended for the period following the schizophrenic patient's psychotic onset;
- Family psychoeducational treatment for individual families and social skills training for patients are recommended for the period following the first psychotic episode;
- Cognitive behavioural therapy in synergy with other treatment strategies is recommended;
- An Assertive Community Treatment (ACT) regimen as well as the characteristics of multidisciplinary, home care, and flexibility are recommended as pre-requisites for the proper functioning of services specialised in the early identification and treatment of individuals with first-episode schizophrenia.

The indicator system developed by the *SIEP: Società italiana di epidemiologia psichiatrica* (Italian Psychiatric Epidemiology Society) is presented in Appendix 1 and renders the degree of application of these guidelines' recommendations measurable. The system is also aimed at promoting the evaluation of practices currently implemented in Italian mental health services and to stimulate reflection on each specific service's strong and weak points.

# INTRODUCTION

Schizophrenia can be a highly disabling disorder and can severely limit the autonomy of individuals suffering from it—both in their social relationships and in their capacity to carry out daily activities.

Moreover, patients' families can find themselves completely overwhelmed by the illness and having to cope with an onerous burden of anxiety and worry, due also to the social stigma this condition still involves.

Although there is currently a general consensus that the early diagnosis of schizophrenia helps improve its prognosis, precise indications for a comprehensive approach to the illness are lacking. Several investigations have shown that reduction of the duration of untreated psychosis (DUP) is correlated with a more benign prognosis, and mounting evidence points to a need to study the prodromes of the illness and to identify its risk factors.

Yet, the various studies that have been conducted to date have yielded partially contradictory findings, and knowledge on the natural history of the illness—particularly, of illness left untreated through long-term institutionalisation (as typically occurred in the past)—is still quite limited. Moreover, the extent to which the much-desired aim of prevention is actually achievable remains unclear, given that its efficacy has been verified through highly different outcomes (and frequently of doubtful significance).

The current body of knowledge available on early intervention in schizophrenia presents a great deal of uncertainty.

The present guidelines are aimed at contributing to a clarification process, rendered necessary by the great personal and social consequences of the illness and by the ambiguous situations one typically encounters in actual clinical practice. The guidelines have also been developed to serve as a support tool for all professional categories dedicated to caring for at-risk patients or for patients at their first episode of illness, by promoting a multiform therapeutic alliance that makes it possible to construct an efficient and effective care network.

## The epidemiology of schizophrenia

For many reasons, schizophrenia can legitimately be considered the most severe and disabling mental illness: for the disability associated with it, the stigma branding individuals affected by it, and for the frequently enormous burden it places on healthcare services and on patients' families. It therefore represents a serious public health problem and—indeed, from Kraepelin's day onward—it has represented the true paradigm of psychiatric theory and practice. A broad-based international project promoted by the World Health Organization (WHO) has determined that schizophrenia

causes 1.1% of the total of Disability Adjusted Life Years (DALY's) and 2.8% of years lived in disability.<sup>3</sup>

Starting with the WHO studies, most research conducted to date in various socio-cultural contexts has shown that schizophrenia is a universal disorder, which can be observed as frequently in industrialised countries as it can in developing countries and in predominantly rural areas. A large-scale systematic revision of incidence studies (N=55) (i.e., studies on the number of new cases per year, conducted in 33 countries and in different social-environmental contexts, found a median (10%-90% quantile) incidence rate of 15.2 (7.7-43.0) per 100,000 inhabitants.<sup>2</sup> The incidence rate was significantly higher for males than it was for females, showing a male/female (median) ratio of 1.40. The incidence was also significantly higher among immigrants than it was for native populations, with an immigrant/local (median) ratio as high as 4.6; it was also higher for individuals born in urban areas, with risk being higher in direct proportion to size of urban area of birth.

As to the disorder's prevalence, the authors of a recent systematic review (which included 20 studies estimating life span prevalence) calculated a median (10%-90% quantile) life span prevalence estimate of 4.0 (1.6-12.1) per 1,000.<sup>5</sup> This figure was highly similar to that observed by Warner & de Girolamo in a comprehensive analysis<sup>6</sup> of 106 schizophrenia prevalence studies conducted in 27 countries on a total of 132 different population samples. Hence, it can be estimated that in Italy, with its adult population (> 18 years) of 49 million individuals, approximately

245,000 people suffer or have suffered, at some point in their lives, from some form of schizophrenia.

The average onset age of the disorder is 15-35 years, although the three most important cohort studies conducted to date observed a median onset age of 22 or 23 years.<sup>1</sup> In females, illness onset usually occurs with an average delay of 3-4 years, with respect to males. Life prevalence rates, however, are quite similar for both genders, as they also are for urban, rural, and mixed areas. In addition to earlier onset age, affected males tend to present a more severe course, showing a greater number of and more severe negative symptoms, lower probability of recovery, and globally poorer outcomes.<sup>4</sup>

Schizophrenia is a multifactorial illness, the most important risk factor of which is family history of illness. Whereas the life span risk for the general population is just under 1%, this figure is as high as 6.5% for first-degree family members, and increases to over 40% in monozygotic twins. Most likely, many genetic risk factors are involved, each of which has a limited effect and is relatively common in the general population. Moreover, individuals affected with schizophrenia most probably inherit many genetic risk factors, which then interact among each other and with various environmental factors to produce the illness, once a critical threshold is reached.

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## METHODS

### Establishment of Guidelines Development Group (GDG) and identification of key questions

The multidisciplinary Guidelines Development Group (GDG) developing these guidelines included clinicians representing the main disciplines involved in the early diagnosis and treatment of schizophrenia, as well as experts in EBM (evidence-based medicine) and guideline-developing methodology.

The Panel met on numerous occasions between September 2004 and May 2007 to work on the guideline draft.

The national scientific societies involved were contacted during the drafting phase. The intermediate work documents--i.e., data-rating charts and summary charts, can be viewed at <http://www.snlq-iss.it>.

The GDG first identified the key questions and coherently with these, identified study inclusion and exclusion criteria and search words for constructing the search strategy used to consult the biomedical database established.

### Literature search

#### Databases consulted

PubMed	Embase
BIOSIS	British Nursing Index
Cinahl	Pascal
PsychInfo	Social Science Citation Index
Science Citation Index	

Time range: January 2000 - June 2006

The search strategies were diversified in terms of topic and were formulated in terms of each question. The comprehensive strategy for all the searches conducted is available at <http://www.snlq-iss.it>.

The following search terms comprised the main search filter:

1. (*Schizophrenia and Disorders with Psychotic Features OR psychotic disorder*)
2. (*schizophreniform disorder\* [tiab] OR psychotic disorder\* [tiab] OR psychotic symptom\* [tiab] OR schizotypal disorder\* [tiab] OR "pre schizotypy" [tiab] OR schizotypy [tiab]*)
3. (*"early prodrom\* state" [tiab] OR "prodrom\* phase" [tiab] OR "prior onset" [tiab] OR "early symptom\*" [tiab] OR "early stage\*" [tiab] OR "prodrom\* patient\*" [tiab] OR "early phase" [tiab] OR "early intervention\*" [tiab] OR "critical period" [tiab] OR "untreated psychosis" [tiab]*) OR
4. (*"early course" [tiab] OR "prodrom\* psychosis" [tiab] OR "early course" [tiab] OR "early schizophrenia like disorder\*" [tiab] OR prepsychotic [tiab] OR latent [tiab] OR "early detection" [tiab] OR "high risk" [tiab] OR "ultra risk" [tiab]*) OR
5. (*"prevent\* onset" [tiab] OR "delay\* onset" [tiab] OR "risk mental state" [tiab] OR "criteria prodromal symptom\*" [tiab] OR cops [tiab] OR "scale prodromal symptom\*" [tiab] OR sops [tiab] OR "european prediction psychosis study"[tiab]*)
6. (*prodrom\* [ti] OR early [ti] OR risk[ti] OR critical [ti] OR untreated [ti]*)

(1 AND 6) OR (2 AND (3 OR 4 OR 5))

## **Guidelines**

The main guideline sites were interrogated in March 2005 to verify whether any documents of interest were available. With the exception of the main filter, no particular filters were used, nor were time limits set on the search strategy. Three guidelines for the treatment of schizophrenia were identified thereby: *Psychosocial interventions in the management of schizophrenia*, Scottish Intercollegiate Guidelines Network (SIGN, 1998); *Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care*, National Institute for health and Clinical Excellence (NICE, 2002); and the *American Psychiatric Association practice guideline for the treatment of patients with schizophrenia* (APA, 1997, updated 2004). None of these documents, however, had the primary aim of the early diagnosis and treatment of schizophrenia.

### **Guidelines. Selection criteria**

Although not specifically addressing the investigative topic, the NICE and APA guidelines were selected because they had been published more recently and presented interesting ideas, especially concerning the treatment and management of the prodromal phase and first episode psychosis.

### **Guidelines. Methodological evaluation**

The complete texts of the selected guidelines were obtained and subjected to methodological quality verification and data-rating in terms of topic(s) considered to be appropriate to and useful for the present guidelines.

## **Systematic reviews and primary documents**

Diversified research strategies were executed for each Panel-established question at the beginning of October 2005. Upon realising the difficulty of obtaining systematic reviews and primary documents dealing specifically with the theme of early intervention in schizophrenia, the Panel chose not to limit the search to this type of study only. Hence, the outcome of these consultations yielded various types of materials, which were then selected and evaluated in terms of their methodology and pertinence.

## **Other searches**

Research groups and individual researchers were contacted in an effort to obtain information on studies or projects that happened to be underway at the time and on unpublished studies. Panel members also proposed material of interest that had not emerged in the bibliographies yielded by database consultation. Suggested bibliographies were included if judged to be pertinent and to have been published in the same time range adopted for the primary study.

## **Selection criteria and instruments for methodological evaluation**

The online search yielded 2,159 titles and abstracts; 374 of these were considered to be pertinent, and their complete texts were therefore requested. These titles were then subjected to further selection, and only 212 studies were actually used for data rating. Further articles were obtained based on Panel proposal. Only 144 documents were chosen for the final, methodological and adherence-to-guideline-topic evaluation.

Each study's evaluation and data-rating were conducted by using the National Institute for health and Clinical Excellence (NICE) methodological checklist.

## Data rating, evidence synthesis, and formulation of recommendations

Considering the relatively limited number of studies available on diagnosis and early intervention in schizophrenia and the difficulty in demarcating the boundaries of the established research questions, the Panel opted to orient the literature search in terms of the criterion of sensitivity (vs. specificity). The search was therefore aimed at including the greatest number of studies possible. Hence, the methodological evaluation criteria were not oriented toward the exclusion of weaker studies, but rather, to their correct evaluation.

The evidence deriving from single studies were summarised in charts that were specific for each question and type of study. The adopted charts were either NICE-developed or were developed by the Panel as required, when appropriate charts were lacking.

The adopted evidence-grading method is described in the *PNLG<sup>1</sup> Manuale metodologico* (methodological manual) (see [http://www.snlg.it/doc/Manuale\\_PNLG.pdf](http://www.snlg.it/doc/Manuale_PNLG.pdf)), which is based on six levels of evidence (I-VI) and five grades of recommendation (A-E).

The Panel attributed evidence level by considering each study's design and methodological evaluations, which were discussed by the Panel in the process of attributing grade of recommendation.

## Principles of good clinical practice

In the currently used hierarchy of evidence, expert opinion is considered to be a rather low level of evidence, to which one resorts in the absence of experimental evidence, or in the presence of particular key questions. In domains in which experimentation is unfeasible, however, the formulation of recommendations based on experience derived from best clinical practices can be quite helpful.<sup>1,2</sup> This type of principle was adopted in the present guidelines and is indicated by the following acronym: *BPC* (*Buona pratica clinica raccomandata*, i.e., recommended Good clinical practice).

## External revision

The team-defined document was sent to external experts with specific instructions to evaluate the document's legibility and clarity as well as its clinical significance and the applicability of the recommendations contained therein. This review group was composed of five psychiatrists and one psychiatric psychotherapist.

## Updating, implementation, monitoring, and evaluation

An update of the guidelines is foreseen by December 2009.

Multiple document circulation and active implementation techniques will be adopted based on the following approaches:

- diffusion of the initiative through the media and popular press articles;
- postal mailings to Autonomous regional and provincial healthcare departments, Local Health Authorities (*ASL*'s), hospitals, medical specialists, general practitioners, and opinion leaders;
- publications on internet sites (*SNGL*, *ASPs* [public health agencies], scientific societies,

healthcare agencies, etc...);

- scientific publications;
- Continuing Education in Medicine (*ECM*) in-service training courses;
- promotion of formal guideline adoption in Italian hospitals;
- national and international conference presentations;
- adaptation of guidelines to local contexts, by promoting integrated,

local health authority-level clinical pathways to care, with particular attention focussed on surmounting any barriers to implementation of the guidelines.

All guideline diffusion initiatives will be recorded to monitor the document's nationwide circulation.

Appendix 1 presents audit indicators to guide the process of monitoring guideline adoption locally at local health authority-, district-, and hospital levels.

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**Early intervention in  
high risk individuals  
and/or prodromal  
patients**

## **Question A1**

**What is the effectiveness of early intervention to identify high risk individuals and/or prodromal patients?**

**Raised titles: 290**

**Selected titles: 59**

**Rated titles: 24**

**Included titles:**

**2 guidelines**

**1 literature review**

**1 randomised controlled trial – RCT**

Defining the usefulness of identifying persons at risk of, or in the prodromal phase of schizophrenia means clarifying the effects of early identification and treatment interventions on the incidence, prognosis, and prognosis of the disorder. In other words, it must be demonstrated that this type of intervention can obviate a patient's transition to full-blown psychosis or can positively influence his or her prognosis. Moreover, to avoid lead time bias, the minimum follow-up required to demonstrate efficacy should be commensurate with whatever knowledge is available on the natural history of the illness.

The Canadian and Australian guidelines for the treatment of schizophrenia<sup>1, 2</sup> (proposed by a referee because they had not been yielded by the bibliographical search), provide a special section presenting moderate-level recommendations for the monitoring of high-risk individuals (ultra-high-risk mental state).

A literature review<sup>3</sup> evaluated studies concerning the primary prevention of schizophrenia. The three review-included titles (programmes conducted between 1984 and 1988 in Buckinghamshire, Great Britain; the Personal Assessment and Crisis Evaluation Service—PACE—study, developed in Melbourne, Australia; and the Bonn Early Recognition Study) investigated transition from the prodromal phase to full-blown psychosis. The studies did not yield notable findings, however—also because they presented numerous methodological problems (concerning / i.e., varying follow-up duration, use of historical controls, and inconsistent prodromal phase definition).

Indirect proposals concerning the use of Cognitive Behavioural Therapy (CBT), aimed at decreasing the probability of psychosis onset in at-risk individuals, were found in research<sup>4</sup> conducted with small samples and based on brief follow-up periods.

Currently, the literature presents no conclusive studies demonstrating the efficacy of intervention of efforts aimed at the early identification of at-risk or prodromal-phase individuals—either in terms of preventing illness onset or improving prognosis. The lack of evidence in this research area illustrates the need for follow-up studies directly aimed at evaluating efficacy or learning more about the natural history of the illness.

## **Recommendation**

**I/C** Current evidence does not allow for the recommendation of early diagnostic intervention for prodromal or at-risk patients, to prevent progression from prodromal to acute psychosis, or to improve prognosis.

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## Question A2

What instruments are available to identify high risk individuals and/or prodromal patients?

**Raised titles: 290**

**Selected titles: 58**

**Rated titles: 22**

**Included titles:**

**2 Cohort studies**

The possibility of identifying and treating individuals who are at-risk of, or in the prodromal-phase of schizophrenia depends on the availability of valid diagnostic tests. In other words, it is important to know the predictiveness of diagnostic criteria one use, to minimise the risk of false positives (individuals treated erroneously), which inevitably emerge when at-risk or prodromal-phase individuals are actively sought out.

Clinical tests (e.g., interviews and scales) are available, and, independently of their validity, present the strong point of good acceptability and ease of administration. Moreover, other tests, based on imaging techniques, can require highly sophisticated technology, are poorly accepted, and are unquestionably more costly.

The Comprehensive Assessment of at Risk Mental State (CAARMS) semi-structured interview, developed in Melbourne;<sup>1</sup> the Structured Interview for Prodromal Syndromes (SIPS), developed at Yale;<sup>2, 3</sup> and the associated Scale of Prodromal Symptoms (SOPS) have shown poor and mixed predictiveness (ranging from 17% to 50%) for full-blown psychosis starting from at-risk mental states, after follow-up periods ranging from 6 to 26 months.<sup>3, 4, 5, 6, 7</sup>

The Bonn Scale for Assessment of Basic Symptoms has shown moderate predictiveness in prodromal-phase individuals.<sup>8, 9</sup> In much the same way, Chapman's scales for measuring perceptual aberration, magical ideation, and in particular, social anhedonia have shown good predictiveness for the schizophrenia onset or schizophrenia spectrum disorder in individuals in suspected prodromal phase.<sup>9, 10, 11, 12</sup>

High scores on the Structural Interview for Schizotypy (SIS) and on the Rust Inventory of Schizotypal Cognitions (RISC) have been found to be associated with subsequent onset of schizophrenia<sup>13</sup> in individuals with high genetic risk (i.e., with at least two afflicted family members). It is important to note that no detection methodology has shown high specificity, with the exception of a high cut-off on the SIPS, which is associated, however, with rather low sensitivity.<sup>5</sup>

In at-risk mental state individuals, several studies have documented an association between different sizes of specific brain areas (hippocampus, hypophysis, medial temporal and right lateral cortices, right inferior frontal cortex, anterior and posterior cingulate, bilaterally) and subsequent onset of psychosis<sup>14, 15, 16</sup>--although one study did not show an association with anterior cingulate cortex morphology.<sup>17</sup> Differences in the size of the cerebellar and left temporal cortices have been found to be associated with subsequent onset of schizophrenia in persons with high genetic risk.<sup>18</sup>

Other associations have been observed between a decrease in immediate memory, ability to identify odours, spatial working memory<sup>19, 20, 21</sup> and subsequent psychotic onset in at-risk individuals, whereas no association with sustained attention has been observed.<sup>22</sup>

Reduced verbal memory has been found to be associated with subsequent schizophrenia onset in individuals at high genetic risk.<sup>13</sup>

Based on the available evidence, it is currently not possible to identify, with sufficient precision, which at-risk individuals will actually develop schizophrenia or a psychotic disorder in general.

## Recommendation

**III/C** Due to the clinical heterogeneity of the phenomenon, prodromal or at-risk patients who will progress towards acute psychosis remain unidentifiable. Clinical rating scales and imaging diagnostic techniques can support diagnosis, but are not recommended as screening methods.

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## **Question A3**

**What is the role of pharmacological therapy in high risk individuals and/or prodromal patients?**

**Raised titles: 251**

**Selected titles: 14**

**Rated titles: 3**

**Included titles: 3 randomised controlled trials – RCTs**

There is a dearth of data supporting the use of medications in asymptomatic individuals who are at risk of schizophrenia.

There is evidence of treatment efficacy in the use of atypical anti-psychotics in prodromal-phase patients; these findings, however, result from studies with small sample sizes, methodological limits, and all-too-brief follow-up periods.<sup>1, 2, 3</sup>

The use of antipsychotic medication for prodromal or at-risk patients to prevent the onset of psychotic disorder or to improve prognosis, is in doubt.

## **Recommendation**

**I/C** The use of antipsychotic medication for prodromal or at-risk patients, to prevent the onset of psychotic disorder or to improve prognosis, is in doubt.

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## **Question A4**

**What is the role of psychological (psychotherapeutic, psychoeducational, family, psychosocial) treatments in high risk individuals and/or prodromal patients?**

**Raised titles: 117**

**Selected titles: 41**

**Rated titles: 25**

**Included titles: 3 randomised controlled trials – RCTs**

Three RCT's investigated the role of Cognitive Behavioural Therapy in at-risk or prodromal-phase individuals.<sup>1, 2, 3</sup>

This form of therapy was observed to be effective in moderating patients' symptoms and helping them improve their social skills, identify dysfunctional thoughts, and minimising anxiety and depression related to prodromal phase distress. Only one study<sup>3</sup> based on 60 patients and 12 months of follow-up showed efficacy of Cognitive Behavioural Therapy in reducing the probability of psychosis onset in individuals at risk of the illness

Current evidence does not allow for the recommendation of specific psychological therapies for prodromal or at-risk patients to prevent the onset of psychotic disorder or improve prognosis.

Sufficient evidence is not yet available on the role of Cognitive Behavioural Therapy in reducing the transition rate from risk- or prodromal phase to full-blown illness, or in improving a patient's prognosis.

### **Recommendation**

**I/B** Cognitive Behavioural Therapy is recommended for prodromal or at-risk patients to moderate symptoms, improve social skills, identify dysfunctional thoughts, and minimise anxiety and depression related to prodromal phase distress. Yet, current evidence does not allow for the recommendation of specific psychological therapies for prodromal or at-risk patients, to prevent the onset of psychotic disorder or improve prognosis.

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## Question A5

What is the optimal design of services aimed at identifying and treating high risk and/or prodromal patients(in terms of facilities, personnel, and intervention methods)?

**Raised titles: 194**

**Selected titles: 24**

**Rated titles: 10**

**Included titles: 10 observational studies**

The studies selected provided detailed descriptions of six intervention programmes targeting in a psychotic risk phase individuals and which had either concluded or were underway at the time of the data search

The multi-modal Prevention and Early intervention Programme for Psychoses (PEPP) in Ontario, Canada,<sup>1</sup> was developed in 1997. It is based on the integration of medical and psychosocial forms of treatment and close collaboration among local- and regional area employment agencies, public institutions, schools, and generic associations. Although the programme caters to individuals at psychotic onset, it focuses on implementing local-and regional area information campaigns and collaborative efforts with healthcare risk management professionals.

The Australian Buckingham Integrated Mental Healthcare Project<sup>2</sup> is based on the focussed collaboration of general practitioners, mental health services, and various local- and regional area public organisations, such as schools, courts of law, prenatal wards, and cultural groups by adapting its methods to the various cultural origins of individuals participating in the programme.

The Personal Assessment and Crisis Evaluation (PACE) programme<sup>3</sup> operates in a clinic founded in 1994 in Melbourne, Australia, and provides(?) information and training activities concerning processes involved in the transition from pre-psychotic phase to psychosis. It caters to area communities and healthcare services and especially to young, at-risk individuals.

The Early Psychosis Prevention and Intervention Centre (EPPIC) programme<sup>4</sup> is more specific to the psychotic onset phase than it is for the risk phase; it caters to the entire community concerning aspects of prevention. The programme originated out of the authors' conviction that, although achievement of primary prevention is beyond our current knowledge, there is a positive association between reduction in Duration of Untreated Psychosis (DUP) and favourable prognosis. The programme is therefore based on the idea that early intervention through optimised support treatment can help lower rates of transition to full-blown psychosis and consequent, secondary impact of the mental illness.

The Early Psychosis Intervention Programme (EPIP) programme,<sup>5</sup> began in 2001 in Singapore; it is characterised by concentrated prevention and information efforts aimed at the general population. It does not exclusively target at-risk individuals, but also persons in more advanced illness phases. The programme also evaluates the potential benefits of supplementing psychological support treatment with low-dose anti-psychotic medication.

The Outreach And Support In South London (OASIS) programme<sup>6</sup> is a concentrated, multi-form information programme, which was introduced in London through the creation of a close-knit collaborative network of general social services. It exclusively targets prodromal-phase individuals, and admission to the programme is based on specific inclusion criteria. It originated and continues to operate as a 30-month-long experimental programme.

The Prevention through Risk Identification, Management and Education (PRIME) programme,<sup>7</sup>

developed by the Yale School of Medicine, exclusively targets at-risk individuals and compares patients simultaneously receiving pharmacological and psychosocial treatments with patients receiving psychosocial support only.

The Recognition And Prevention Program (RAP) developed in New York<sup>10</sup> began in 1998 and was developed with the purpose of identifying whether correlations might exist between the prodromal signs of psychosis and neurocognitive deficits, and to examine the efficacy of various types of risk-phase intervention.

Nearly all of the above-described programmes providing details on the topic maintain that the optimal design for services identifying and treating persons at risk of, or in the prodromal phase of schizophrenia is based on the criteria of: provision of information and training programmes on the distinctive aspects of mental disorders to general practitioners, local- and regional area healthcare service workers,<sup>1, 2, 5, 6, 7, 9</sup> the general population,<sup>1, 2</sup> and public institutions;<sup>2</sup> intervention methods that also ensure specificity, personalisation, and flexibility of treatment and create user-friendly treatment settings by ensuring the separation of these facilities from traditional mental health centres.<sup>3, 5, 9</sup>

## Recommendation

**VI/B** Services dedicated to identifying and treating high risk individuals and/or prodromal patients should present characteristics such as specificity, personalisation, and flexibility of intervention; a location independent of mental health centres; information and training programmes for general practitioners, local- and regional area healthcare workers, the population at large, and public institutions.

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**Early intervention in  
individuals with first  
episode psychosis**

## **Question B1**

**What is the effectiveness of timely diagnostic intervention and early treatment of first episode patients? What are the consequences of the duration of untreated psychosis (DUP) during the period following first episode?**

**Raised titles: 402**

**Selected titles: 55**

**Rated titles: 28**

**Included titles:**

**1 prospective study**

**1 systematic review**

**11 observational studies**

**3 metaanalyses**

**1 randomised controlled trial – RCTs**

Defining the usefulness of identifying patients with first episode psychosis means demonstrating the effects produced by early detection and treatment intervention on the natural history of the illness and, ultimately, on its prognosis.

The few studies available on the topic have either investigated the effects of early intervention on several outcomes considered to be prognosis indicators, or have tested the efficacy of early intervention in reducing the Duration of Untreated Psychosis (DUP), which appears to be correlated with a more benign prognosis and perhaps, with a better prognosis.

A prospective study conducted on 53 patients, with a 2-year follow-up<sup>1</sup> evaluated the efficacy of early intervention in reducing negative symptoms (emotional flattening, alogia, and abulia) and in improving cognitive performance.

A systematic review evaluated two secondary prevention studies.<sup>2</sup> In the purview of the Early Psychosis Prevention and Intervention Centre (EPPIC) programme conducted in Melbourne, the outcomes of patients included in the programme and of historical controls were compared two years after diagnosis. The programme produced two publications (one in 1996 and the other, in 1999), and in both instances the two groups' mean and median DUP's showed no significant differences. During the first follow-up year, however, patients included in the EPPIC programme experienced fewer hospitalisations, better quality of life (Quality of Life Score), and a reduced frequency of negative symptoms. It is interesting to note that these benefits were more marked in the subgroup of patients with a DUP of 1-6 months.

The authors accounted for the apparent contradiction between similar DUP's and better outcomes for patients enrolled in the programme by referring to the better quality of treatment that the patients in the structured programme presumably were receiving. In any event, the findings suggest an interaction between DUP and treatment, given that the enhanced treatment effects were associated with brief DUP's.

The Early Treatment and Intervention of Psychosis (TIPS) project, conducted in Norway, conversely allowed for the comparison of patients from a single geographical area (Rogaland), who had been recruited before and after implementation of an early detection programme based on various types of integrated intervention. Early detection reduced the DUP, with respect to historical controls; lowered the patients' mean age; and was associated with less severe psychopathology at the moment of diagnosis. Interestingly, the schizophrenia/schizophreniform disorder ratio was much lower in earlier identified individuals than it was among controls.

Intervention tested within the scope of the TIPS project consisted of an integrated strategy, including efforts aimed at increasing awareness in the population at large, schools, and general practitioners, as well as the establishment of a team of experts (Early Detection Team), whose task was to identify individuals at psychotic onset.<sup>3</sup> After 3 months of follow-up<sup>4</sup>, the authors observed a shorter DUP for earlier identified individuals than for controls, and a general improvement in general clinical and social functioning, as measured with the Positive And Negative Syndrome Scale (PANSS) and Global Assessment of Functioning Scale (GAF).

Conversely, the Canadian Prevention and Early intervention in Psychosis Programme (PEPP) study,<sup>5</sup> showed no DUP reduction and found greater symptom severity for earlier identified individuals than for historical controls. The authors accounted for this apparent discrepancy by referring to the brief duration of the programme, which they hypothesised had resulted in the recruitment of many prevalent cases and cases eluding routine diagnosis, with consequently longer DUP's. The overdiagnosis hypothesised by the authors, however, was not shown by significant detection rate differences in the two groups compared.

The relation between Duration of Untreated Psychosis (DUP) and its clinical characteristics is crucial to demonstrating the efficacy of early intervention, as one can reasonably expect that the implementation of programmes dedicated to early diagnosis of the illness will /can result in DUP reduction.

One metanalysis<sup>6</sup> characterised DUP as an independent prognostic variable, which (if of brief duration) is associated with a better response to pharmacological treatment and lower negative symptom severity. Significant correlations between DUP and positive symptomatology—i.e., delusions, hallucinations, and impaired neurocognitive functions—were not observed.

Another metanalysis<sup>7</sup> showed a modest correlation between DUP and outcomes, which, however, was not immediately observable, but evident over time (6-12 months of follow-up).

A metanalysis published in the British Journal of Psychiatry<sup>8</sup> found an association between DUP and remission of positive symptoms, but not a causal relation. There were no data confirming a relation between DUP and neurotoxic effects, i.e., no findings that provided confirmation for the hypothesis that a longer DUP produces organic brain lesions. Results yielded by a randomised controlled trial,<sup>9</sup> showed no significant correlations between DUP and cognitive functioning measured post-onset.

Some studies have found correlations between DUP and positive symptomatology<sup>10, 11</sup> and between DUP and negative symptomatology,<sup>12</sup> as opposed to other studies yielding no significant correlations.<sup>13</sup>

Evidence has emerged showing that a DUP of brief duration is correlated with improved management of delusions, but not of hallucinations,<sup>14</sup> and with shorter response times to pharmacological therapy.<sup>15</sup> Longer DUP duration has shown evidence of being linked to worse outcomes<sup>10</sup> and lower quality of life.<sup>11</sup> In fact, higher quality of life levels have been observed only after very early intervention and with DUP's of less than 3 months.<sup>16</sup>

No consistent data on correlations of DUP with quality of life and social and global functioning have been shown.<sup>17, 10, 15, 13</sup>

There is evidence of the efficacy of structured early detection and treatment programmes for individuals with first episode schizophrenia. Efficacy--considered in terms of improvement in prognosis--is presumably mediated by a reduction in DUP and by the quality of treatment that specialised centres are able to provide.

Further studies aimed at investigating the efficacy of early intervention in detection are necessary, by focussing on types of intervention tested, duration of follow-up, and evaluated outcomes. These studies should also avoid using surrogate outcomes (outcomes one supposes are a programme's goals, such as morbidity as an indicator of mortality, briefness of DUP as an indicator of better prognosis, etc...), whose relation with actual outcomes is controversial. Complicating the evaluation of strategies, however, are many cases that, for various reasons, elude routine diagnosis and are detected only when early identification intervention is implemented. The different types of intervention tested should be subjected to empirical verification over time, after implementation, so as to avoid the DUP dilution and worsening of experimental arm outcomes that is produced by inclusion of prevalent cases.

## **Recommendation**

**I/B** Identification and treatment of first episode psychosis patients through structured early intervention programs is recommended. Efficacy, considered as improvement in prognosis, is presumably mediated by a reduction in the DUP and by the quality of delivered care that specialised centres are able to provide.

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## Question B2

What instruments are available to identify first episode patients?

**Raised titles: 234**

**Selected titles: 60**

**Rated titles: 54**

**Included titles:**

**1 metanalysis**

**1 diagnostic study**

**3 prospective studies**

**46 observational studies**

**1 expert review**

The possibility of setting up facilities and activities aimed at identifying and treating schizophrenic individuals depends on the availability of valid diagnostic tests. In other words, to minimise the risk of false positives (individuals identified/treated erroneously), which inevitably emerge when patients with first episode psychosis are actively sought out, one must have a good idea of the predictiveness of the diagnostic criteria one uses. Specifically, in addition to the validity of diagnostic criteria, it is important to demonstrate the stability of the diagnosis of psychosis over time, i.e., to examine the frequency with which the diagnosis of schizophrenia made at illness onset is confirmed at a later date.

Three diagnostic studies,<sup>1, 2, 3</sup> based, respectively on 24, 48, and 18 follow-up months, demonstrated the good diagnostic accuracy of the Structured Clinical Interview for DSM IV – SCID and its good stability of schizophrenia diagnosis.

In a small prospective study based on 6 months of follow-up, the SCID was used to make the initial diagnosis, and a regression model was used to calculate the odds of diagnostic confirmation for each item examined with several scales (the Brief Psychiatric Rating Scale - BPRS, Scales for Assessment of Negative Symptoms - SANS, Scales for Assessment of Positive Symptoms - SAPS, the Hamilton Depression Rating Scale - HDRS). High levels of anhedonia and hallucination showed evidence of predicting confirmation of schizophrenia for individuals with first episode psychosis after 6 months of follow-up.<sup>4</sup>

Morphological brain modifications, verifiable through magnetic resonance techniques, have been associated with first illness episodes. For example, a metanalysis of cross sectional studies.<sup>5</sup> revealed increased volume of the right and left lateral ventricles and of the third ventricle, and reduced volume of the right and left hippocampus in individuals at their first episode.

Numerous observational studies using nuclear magnetic resonance techniques<sup>6-32</sup> and computerised axial tomography<sup>33</sup> have shown hypofrontality; reduced hippocampus, cortex, and cerebellum volume; and other morphological brain modifications, in individuals at their first episode, as compared to controls. Electroencephalographic modifications<sup>34</sup> and reflex disorders<sup>35</sup> have also been found in individuals with first episode psychosis.

One expert review<sup>36</sup> examined cognitive functioning in patients with psychotic onset and identified deficits in their verbal learning, memory, attention, and psychomotor speed.

Instruments such as the WAIS, the Iowa Gambling Task, and the Trail Making Test revealed impairment of general and specific cognitive functioning<sup>37</sup> in the prefrontal area,<sup>38</sup> as well as several neuropsychological functions, such as memory, attention, psychomotor speed, and spatial abilities (examined with the PANSS scale and the California Verbal Learning Test – CVLT)<sup>39-42</sup> and

olfactory abilities, as evaluated by the Smell Identification Test.<sup>43</sup>

In patients assessed with various diagnostic instruments (Neurological Evaluation Scale, SCAN, Hidelsberg Scale, SCID, PANSS, etc...), the presence of neurological soft signs (NSS) was associated with first episode<sup>44, 45</sup> and correlated well with prognosis.<sup>46</sup>

Other studies<sup>47-52</sup> have shown no morphological, metabolic, or cognitive modifications that were specific to schizophrenic patients at their first episode.

Of all the instruments examined, only the assessment scales can ensure adequate diagnostic accuracy. Although instruments assessing cognitive functioning and NSS presence can identify signs associated with psychotic onset, they have not demonstrated diagnostic accuracy.

Similarly, although imaging techniques (MRI and CT) detect many "typical" morphological signs of psychotic onset, they cannot be used for diagnostic purposes--due to the lack of evidence concerning their diagnostic accuracy as well as the poor feasibility and acceptability of the techniques themselves.

## Recommendations

**III/B** The diagnostic accuracy of clinical rating scales allows for recommendation of their use to identify first episode patients.

**III/C** Diagnostic imaging techniques can detect morphological brain modifications associated with psychotic onset. MRI and CT can therefore be used to support diagnosis, but are not recommended as screening methods to identify first episode patients.

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## Question B3

What is the role of pharmacological therapy in patients with first episode psychosis?

**Raised titles: 144**

**Selected titles: 42**

**Rated titles: 28**

**Included titles:**

**3 guidelines**

**4 randomised controlled trials – RCTs**

**6 observational studies**

**3 retrospective/prospective studies**

Numerous studies have investigated the efficacy of antipsychotic medication in individuals at illness onset, and most of this research has compared the effects of typical and atypical antipsychotics.

No fundamental differences have been observed between typical and atypical antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole) in terms of efficacy, but they do present a different side effect profile, in favour of atypicals, regarding extrapyramidal symptoms.<sup>1,2</sup>

Several randomised controlled clinical trials conducted with first-episode individuals have shown that, although presenting a limited advantage in terms of efficacy, olanzapine (as compared to haloperidol)<sup>3</sup> and risperidone (also as compared to haloperidol)<sup>4</sup> show a lower risk of extrapyramidal symptom induction.

Moreover, few cognitive functioning differences have been observed,<sup>5</sup> especially when comparing olanzapine and haloperidol at low doses.<sup>6</sup>

Compared to their superior tolerability profile in terms of extrapyramidal symptoms, atypicals present a greater risk of weight gain, especially olanzapine, as compared to haloperidol,<sup>8</sup> although individuals treated with olanzapine have shown better treatment compliance, as compared to patients treated with haloperidol.<sup>8</sup>

Another type of comparison examined low and high-dose haloperidol treatment and yielded equivalent efficacy, but with a greater low dose advantage for negative symptoms and tolerability.<sup>9</sup>

A retrospective comparison between risperidone and olanzapine showed no significant differences in positive symptom remission, but a significant presence of extrapyramidal symptoms in the risperidone group and significant weight gain in the olanzapine group was observed.<sup>10</sup> Two other, prospective studies compared treatment with olanzapine, risperidone, and atypical antipsychotics<sup>11</sup> with treatment using olanzapine and typical antipsychotics.<sup>12</sup> Significant improvement was observed for all types of treatment, but with less frequent extrapyramidal effects and greater weight gain in the olanzapine group. The best study compliance was observed in the typical antipsychotic experimental arm.

No significant differences in clinical improvement were observed in a study comparing risperidone use at high (4 mg) and low doses (2 mg), although there were fewer side effects for the low-dose group.<sup>13</sup>

Clozapine use has been found to be indicated for patients resistant to at least two consecutive antipsychotic treatments, especially in the presence of suicide risk.<sup>1</sup>

The most common side effects of typical drugs are therefore extrapyramidal symptoms (parkinsonism, dystonia, akathisia, tardive dyskinesia), with a 5% per-year-of-treatment risk of provoking persistent tardive dyskinesia. Atypical antipsychotics, conversely, are mostly responsible for side effects that are metabolic (weight gain, hyperglycemia, diabetes), endocrinologic

(increased prolactin levels and consequent sexual dysfunction), and cardiological (orthostatic hypotension and QT interval prolongation).

There is no evidence for the greater efficacy of atypical drugs as compared to typical drugs for individuals at onset or in the acute phase of schizophrenia, although some international schizophrenia treatment guidelines<sup>14-16</sup> recommend considering the use of atypical antipsychotics as a first treatment option. The efficacy of pharmacological therapy as compared to other types of treatment has not been tested.

## Recommendation

**I/A** Pharmacological therapy of first episode patients is recommended. The choice between typical and atypical antipsychotics must be evaluated on a case-by-case basis and must consider both the lower incidence of extrapyramidal symptoms and the higher risk of metabolic side effects associated with atypical antipsychotic medication.

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## **Question B4**

**What is the role of pharmacological therapy in the period following first episode psychosis?**

**Raised titles: 56**

**Selected titles: 8**

**Rated titles: 6**

**Included titles:**

- 1 non-randomised controlled clinical trial**
- 1 systematic review**
- 1 longitudinal study**
- 3 guidelines**

A systematic review<sup>1</sup> analysing several placebo-controlled trials lasting a maximum of 2 years showed the efficacy of pharmacological maintenance therapy. Relapse rates comparing placebo with pharmacological therapy (41 vs. 0%, 62 vs. 46%, 57 vs. 0%, 64 vs. 43%) varied, due to different definitions of relapse and different types of study design.

The relapse rate for individuals interrupting pharmacological therapy was 5 times higher than for non-interrupters.<sup>1</sup>

A review published in *Drugs* in 2003,<sup>2</sup> revealed that the relapse risk estimated at 40-50% during the first year of treatment discontinuation reached near totality after 5 years.

A study appearing in *Schizophrenia Research*,<sup>3</sup> with a 2-year follow-up, compared three maintenance strategies: continuous maintenance therapy, intervention based on relapse prodromes, and crisis intervention. Continued maintenance therapy relapse rates were very similar to those of prodromal intervention (25% and 21%, respectively), and both were lower than the crisis intervention rates (60%). Whereas maintenance therapy did not show any significant differences between the first and second years, an increase in relapse (42%) occurred during the second year of prodrome-based treatment. Hence, this latter treatment strategy, which had been effective in the first year, showed evidence of losing its advantage in the second year.

The various guidelines examined recommend that maintenance therapy be used for at least 1 or 2 years after first episode psychosis and can then be gradually discontinued.<sup>4, 5, 6</sup>

There is evidence of the benefits of pharmacological maintenance therapy for the remission of symptoms, aimed at reducing the probability of relapse in the short and intermediate term. Further studies are necessary to clarify the extent to which this type of therapy influences a patient's long-term prognosis.

## **Recommendation**

**I/A** There is clear evidence of the effectiveness of pharmacological therapy for schizophrenic patients in the period following psychotic onset, in reducing relapse rates. Antipsychotic medication is recommended for this specific phase of the pathology, but further studies are necessary to verify the impact of this therapy on long-term prognosis.

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## **Question B5**

**What is the role of psychological forms of treatment (psychotherapeutic, psychoeducational, family-, psychosocial) during the period following first episode?**

**Raised titles: 73**

**Selected titles: 8**

**Rated titles: 8**

**Included titles: 3 randomised controlled trials – RCTs  
1 non-randomised controlled trial  
1 longitudinal studies  
2 metaanalyses  
1 guideline**

The randomised Danish study, OPUS trial<sup>1</sup> compared an integrated treatment, based on antipsychotic pharmacological therapy and supplemented with social skills training and psychoeducational family treatment in an Assertive Community Treatment (ACT) regimen, with standard treatment based on antipsychotic pharmacological therapy.

After one year of therapy, the integrated treatment showed higher efficacy than the standard treatment did, as measured by SAPS and SANS scores on the psychotic dimension (OR=0.35, CI 95% 0.2-0.6, p=0.001) and the negative symptom dimension (OR=0.49, CI 95% 0.3-0.8, p=0.002). Moreover, the integrated treatment yielded a significantly lower percentage of patients with GAF scores of <30, and a lower percentage of homeless or jobless. Lastly, an advantage for the integrated treatment was also shown for the global measure defined by the authors as “any poor outcome” (OR=0.50, CI 95% 0.3-0.8, p=0.001).

Two British randomised studies, which were not included in the search strategy but were proposed by a Panel member, compared the efficacy of Cognitive Behavioural Therapy (CBT) with routine treatment for individuals at psychotic onset.

The first study,<sup>2</sup> conducted with 309 hospitalised patients, showed the efficacy of Cognitive Behavioural Therapy (CBT), after 18 months of follow-up, in reducing symptoms (based on the Positive and Negative Syndrome Scale - PANSS), but not for relapse or re-hospitalisation rates. Conversely, the second study,<sup>3</sup> conducted with only 21 patients and based on 6 months of follow-up, yielded inconclusive findings and showed a wide range of individual variability in CBT effects on patients at illness onset.

A non-randomised Australian study<sup>4</sup> did not achieve its aim of demonstrating greater benefits for patients treated with Cognitively Oriented Psychotherapy for Early psychosis - COPE) at first-episode, than for untreated individuals.

A Dutch study, conducted with individuals with recent psychotic onset,<sup>5</sup> attempted to evaluate the efficacy of family therapy in reducing “parental expressed emotion” after an approximately one-year-long intervention period and during an 8-year follow-up. Efficacy up to only the 34<sup>th</sup> treatment week was demonstrated, and only for “emotional overinvolvement”, but not for other parental expressed emotions.

A metaanalysis of randomised trials<sup>6</sup> (not selected by the search criteria adopted for the drafting of the present document but proposed by Panel members) showed the efficacy of intervention with families (especially of programmes aimed at treating individual families) in reducing schizophrenic patients' relapse rates and subsequent hospitalisation and in improving compliance with pharmacological therapy as compared with all the other types of treatment examined. Conversely,

CBT, was shown to improve mental state scores and to reduce drop-out rates at follow-up. In a further metanalysis<sup>7</sup>, the same authors observed a lack of benefits (in terms of relapse rates, compliance, quality of life, and social functioning) for schizophrenic individuals receiving social and cognitive forms of treatment.

Recommendations concerning the stabilisation phase of schizophrenia in the American Psychiatric Association guidelines<sup>8</sup> include family psychoeducational treatments, social skills training, and CBT.

## Recommendations

- I/A** Family psychoeducational treatment targeting single families and social skills training are recommended during the critical period following psychotic onset.
- I/B** A body of evidence allows for the recommendation of CBT in synergy with other treatment strategies.

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## Question B6

**What is the optimal design of services aimed at identifying and treating individuals with first episode psychosis or at assisting patients during the period following first episode (in terms of facilities, personnel, and intervention methods)?**

**Raised titles: 113**

**Selected titles: 14**

**Rated titles: 13**

**Included titles:**

**1 guideline**

**2 randomised controlled trials – RCTs**

**6 prospective/retrospective studies**

**4 dissertations, editorials, overviews**

Numerous international programmes, in particular Scandinavian (TIPS, Swedish Parachute Project)<sup>1, 2, 3, 4, 5</sup>; Australian (EPPIC, SAFE)<sup>3, 6</sup>; Dutch,<sup>7</sup>; British (EIS, FIRST)<sup>3, 9</sup>; Canadian (EPP, PDC, PEPP)<sup>3, 8, 11, 12</sup>; German<sup>10</sup>; and Italian<sup>11</sup> projects, underscore the importance of early intervention for individuals with first episode psychosis, but these findings only indirectly allow for the delineation of an optimal service design (considered in terms of facilities, personnel, and intervention methods).

Danish randomised controlled trials<sup>1,2</sup> and prospective studies<sup>4, 5, 8, 13</sup> have attributed the efficacy of integrated treatments to the design of early intervention services. Aspects relative to organisation (multidisciplinary teams, home care, availability of health-care professionals, personalised crisis plans, integrated case management with case-managers), and to methods (use of low dose atypical neuroleptics, psychoeducational intervention, social skills training, individual training opportunities, psychoeducational group intervention for families) are considered essential to ensuring the efficacy of early intervention.

Other, non-experimental studies have indirectly examined the concept of optimal service design. They focus on aspects such as the diffusion and consolidation of early intervention programmes<sup>6</sup>; criteria for satisfaction expressed by patients and families concerning care delivered for first episode psychosis<sup>7,9</sup>; ways in which individuals with first episode psychosis seek help; pathway delays to psychiatric care<sup>10</sup>; and time intervals between psychotic symptom onset and proper treatment.<sup>12</sup>

Conversely, the guidelines developed by the British IRIS (Initiative to Reduce the Impact of Schizophrenia) project, under the administration of the National Health Service (NHS) report indications for managing individuals with first episode psychosis. In any event, the guidelines are recommendations (derived from expert opinion and not from a systematic evaluation of the scientific literature), which are aimed at providing helpful information on managing individuals with first episode psychosis, in terms of diagnosis, therapy, and service design.<sup>14</sup>

Lastly, the OPUS trial,<sup>1</sup> a randomised Danish study, compared treatment based on standard antipsychotic pharmacological therapy with a form of integrated treatment based on antipsychotic pharmacological therapy, supplemented with social skills training and family psychoeducational treatment, in an Assertive Community Treatment regimen. After one year of therapy, the integrated treatment showed greater efficacy than the standard treatment did (a lower percentage of patients with GAF scores of <30 and a lower percentage of homeless and “jobless for the group receiving the ACT regimen).

The available literature therefore shows the importance of context (a specialised early intervention

team working within a non-targeted service can be effective in rural or broad-based contexts), accurate and comprehensive information for patients, flexibility of services, home care, and diffusion of information aimed at improving both the general population's and health-care workers' abilities ability to detect signs of schizophrenia onset.

There is some evidence for the efficacy of a specific type of design for services aimed at the early detection and treatment of individuals with first episode psychosis. The ACT regimen and the characteristics of multidisciplinary, home care, and flexibility are recommended as indispensable aspects for the good functioning of specialised services.

## Recommendation

**I/B** The Assertive Community Treatment regimen (ACT) and the characteristics of multidisciplinary, home care, and flexibility are recommended as indispensable elements for the good functioning of services specialised in the early detection and treatment of individuals with first episode psychosis.

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## **Appendices**

# APPENDIX 1: Indicators for evaluating early intervention in schizophrenia programmes, in Italian mental health departments<sup>1</sup>

## Introduction

The present indicator system is aimed at rendering the degree of application of the Early Intervention in Schizophrenia guidelines measurable. It was developed by the Italian Society of Psychiatric Epidemiology (SIEP) and is based on the experience acquired in the purview of the SIEP project, “Evaluation of the appropriateness and application of NICE guidelines for schizophrenia in Italian mental health departments” (*Valutazione dell’appropriatezza e dell’applicazione delle linee guida NICE per la schizofrenia nei Dipartimenti di salute mentale italiani*), coordinated by Domenico Semisa (Vice president, SIEP), Mirella Ruggeri (President, SIEP), and Antonio Lora (Treasurer SIEP); many of the indicators presented herein are derived from this project. Twenty Italian Mental Health Departments have participated in the SIEP project; for further information, see <http://www.siep.it>.

The proposed indicators allow for a self-evaluation process aimed at providing a measure of the actual degree of application of each recommendation in each specific service, as measured by its relative indicator. The self-evaluation results will help Mental Health Departments pinpoint the strong and weak points of the service under consideration and will promote discussion on causes of its limitations.

We would like to specify 2 aspects:

→ We are aware that each guideline is a product based on the state of the art at the moment of publication and that the recommendations must be periodically reviewed in terms of newly acquired knowledge (as already scheduled for the present guidelines). This process must also lead to updating of the proposed indicators. It is important to note, however, that the measure of practices as implemented by the indicators reported herein also has independent merit with respect to the guidelines. In fact, it allows for the description of early forms of intervention in schizophrenia conducted in mental health departments that will implement the self-evaluation process for various purposes.

→ The proposed indicators represent an initial version, which—although mostly already tested in the scope of the broader, above-cited SIEP project—will require future review and modification based on feedback from those implementing the self-evaluation process.

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## Indicators

Two sets of indicators are proposed:

1. indicators for recommendations pertaining to interventions of proven efficacy or inefficacy;
2. indicators for recommendations pertaining to intervention for which sufficient efficacy evidence is still unavailable.

The evaluation period for all the indicators is the solar year previous to the current year; instances of different observation periods are specified in the indicator.

For the definitions of types of facilities and types of intervention, readers are referred to "*Il sistema informativo nazionale per la salute mentale*" (the Italian "National Mental Health Information System"), approved by the State-Region-Autonomous Province Conference in its October 11<sup>th</sup> session, 2001.

Data marked by (#) appear several times on the indicator list as denominators: the same datum value must be maintained in the various indicators (e.g., if the number of patients in the care of a given Mental Health Department [MHD] is 40, the value must remain invariable each time the number of MHD patients is used as a numerator or denominator).

The general layout for each indicator is as follows:

<i>RECOMMENDATION</i>	<i>the NICE Recommendation from which the indicator is derived, with evidence level</i>
<b>INDICATOR</b>	<b>Number and name of indicator</b>
MEASURE	Either quantitative (e.g., a percentage) or qualitative (e.g., YES-NO)
NUMERATOR	For percentages
DENOMINATOR	For percentages
SOURCE	Description of information source
NOTES	Operative definitions and indications for calculating the indicator are presented in this area

When it is not possible to give the indicator a value, use:

- **not applicable = NA** (indicator not applicable in the context of reference, with reason given);
- not found = NF (not possible to obtain information).

### Data sources

The information sources used in the gathering of indicators are:

- The MHD information system, to gather data on patients in treatment and on types of intervention (e.g., number of contacts, number of patients receiving a specific type of treatment, etc...);
- MHD management, to establish the existence of procedures and guidelines;
- specific research conducted on Mental Health Centre (MHC) and/or Psychiatric Diagnosis and Treatment Service (PDTS) clinical records to survey several themes that cannot be analysed in other ways and if no data are currently available. The webpage [www.snlq.it/LG/019](http://www.snlq.it/LG/019) gives detailed instructions on how to conduct this type of research for each of the indicators;
- focus groups--the main information source for the degree of appropriateness of practices with respect to the recommendations. Two types of focus groups are recommended:
  1. multidisciplinary focus groups, characterised by the participation of all professional categories involved, together with patient- and family member representatives;
  2. specialised focus groups, characterised by the presence of only one type of professional category (e.g., focus groups relative to indicators examining pharmacological therapy indicators, which should be made up of psychiatrists).

The webpage [www.snlq-iss.it/LG/019](http://www.snlq-iss.it/LG/019) provides detailed instructions on how to organise and

conduct these focus groups.

The authors would like to thank the Consultant Group from the SIEP Project on the “Evaluation of the appropriateness and application of NICE guidelines for schizophrenia in Italian mental health departments” for their helpful comments on the indicator set from the above-cited project. The Group consisted of: Fabrizio Asioli, Andrea Balbi, Giuseppe Carrà, Massimo Casacchia, Giuseppe Corlito, Walter Di Munzio, Arcadio Erlicher, Alessandra Marinoni, Maurizio Miceli, Carla Moranti, Pierluigi Morosini.; the present work is based on this project, and several of the indicators reported herein have been derived from it.

The authors also express their gratitude to the reference persons in the 20 Italian mental health Services accepting to actively participate in the project.

They also wish to thank Giuseppe Carrà, Francesco Barale, and Alessandra Marinoni for having made the Italian edition of the NICE guidelines on schizophrenia available even before publication—guidelines they edited (*Schizofrenia. Linee guida cliniche complete per gli interventi fondamentali nella medicina di base e specialistica, Il Pensiero Scientifico Editore, 2004*) and without which much of SIEP’s activity in this field would not have been possible.

The authors are moreover grateful to Angelo Cocchi, Fabrizio Starace, Maurizio Bacigalupi, Massimo Casacchia, Giuseppe Corlito, Giovanni Neri, Giuseppe Tibaldi (members of the SIEP board from November 2003 to October 2007) for having promoted the start-up of the SIEP guidelines project and for having developed its conceptual framework of reference.

Finally, they wish to thank Angelo Picardi for his careful reading of and comments on the final version of the manuscript.

# 1. Indicators for recommendations pertaining to interventions of proven efficacy/inefficacy

**Question A5:** What is the optimal design of services aimed at identifying and treating high risk individuals and/or prodromal patients (in terms of facilities, personnel, and intervention methods)?

**RECOMMENDATION** *Early intervention service characteristics, such as specificity, flexibility, tailoring of treatments to prodromal patients' needs and autonomous location from mental health services, are recommended. Provision of information and advice to general practitioners, raising of local early-intervention awareness, and active dialogue with key representatives of prodromal services and with local populations are also recommended.*  
**VI/B**

**INDICATOR** **A5.1**  
**Informational and training activities for general practitioners, local- and regional area healthcare workers, the population at large, and institutions.**

**MEASURE** Score:  
0 = no informational and training activities for general practitioners, area healthcare workers, teachers and students, nor for the population in general;  
1 = no activities, but inclusion of these initiatives in next year's programming;  
2 = several specific, though not systematic, activities which have not yet been included in DMH (Department of Mental Health) programmed activities;  
3 = frequent informational activities, but not yet included in DMH programming;  
4 = stable and continuative informational activities included in DMH programming, with specific personnel.

**SOURCE** • DMH management or multidisciplinary focus group.

**Note:** The addition of an asterisk(\*) to an indicator number refers to the fact that the indicator was derived from the indicator system of the SIEP project, *Valutazione dell'appropriatezza e dell'applicazione delle guidelines NICE per la schizofrenia nei Dipartimenti di salute mentale italiani* (Evaluation of the appropriateness and application of NICE guidelines for schizophrenia in Italian mental health departments) (Semisa, Lora, & Ruggeri, for the SIEP Guidelines Group, publication in prep.).

**Question B1: What is the effectiveness of timely diagnostic intervention and early treatment of first episode patients? What are the consequences of the duration of untreated psychosis (DUP) during the period following first episode?**

*RECOMMENDATION Identification and treatment of first episode psychosis patients through structured early intervention programs is recommended. Efficacy, considered as improvement in prognosis, is presumably mediated by a reduction in the DUP and by the quality of delivered care that specialised centres are able to provide.*

**I/B**

**INDICATOR B1.1\***  
DMH services or initiatives for the early treatment of onset

**MEASURE**  
Score:  
0 = no activities for identification and implementation of targeted early treatment for schizophrenic onset  
1 = no activities, but these initiatives are included in next year's programming;  
2 = several specific, though not systematic, activities and not yet introduced into clinical routine;  
3 = activities aimed at patients in the current year, included in clinical routine and programmed by the DMS, with the presence of specific personnel; lack of specific facilities;  
4 = presence of specific facilities for the early treatment of schizophrenia onsets.

**SOURCE** • DMH management or multidisciplinary focus group.

**NOTES** The DMH presence of specific facilities for the early treatment of schizophrenic onset is substantiated by the existence of a physical site set aside for this activity and by personnel specialised in treating young patients at schizophrenic onset, for a defined time-work number.

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**INDICATOR B1.2\***  
**Receiving procedures and guidelines for treating patients at onset.**

**MEASURE**  
Score:  
0 = the DMH has no written receiving procedures, nor guidelines for treating patients at onset;  
1 = the DMH has written receiving procedures and/or guidelines for treating patients at onset available, but they are generic;  
2 = the DMS has detailed written receiving procedures, but guidelines for treating patients at onset are either lacking or are generic;  
3 = the DMS has detailed written receiving procedures and detailed guidelines for treating patients at onset; roles and responsibilities are not clearly defined (no written care pathway is available);  
4 = the same as number 3, but roles and responsibilities are clearly defined (there is a written care pathway).

**SOURCE** • DMH management.

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**INDICATOR B1.3\***  
**Practices for treating patients at onset.**

**MEASURE**  
Score relative to DMH worker implementation of differentiated activities specific to the DMH treatment of patients at onset:

- 0 = in no cases;
- 1 = in 25% or less of cases;
- 2 = in 26-50% of cases;
- 3 = in 51-75% of cases;
- 4 = in more than 75% of cases.

SOURCE

- Multidisciplinary focus group.

**Question B2: What instruments are available to identify first episode patients?**

*RECOMMENDATION*                      *The diagnostic accuracy shown by the assessment scales in formulating a schizophrenia diagnosis makes it possible to recommend their use for the early identification of individuals with first episode psychosis.*

**III/B**

**INDICATOR**                              **B2.1**  
**Use of clinical rating scales for identifying first episode patients**

**MEASURE**                                Score:  
0 = no use of assessment scales for identifying individuals with first episode psychosis;  
1 = use in less than 26% of cases;  
2 = use in 26%-50% of cases;  
3 = use in 51%-75% of cases;  
4 = use in more than 75% of cases.

**SOURCE**                                 • Multidisciplinary focus group;  
• clinical records.

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**INDICATOR**                              **B2.2**  
**Use of brain-imaging techniques (MRI or CT) to identify first episode patients**

**MEASURE**                                Score:  
0 = no use of brain-imaging techniques (MRI or CT) to identify individuals with first episode psychosis;  
1 = use in less than 26% of cases;  
2 = use in 26%-50% of cases;  
3 = use in 51%-75% of cases;  
4 = use in more than 75% of cases.

**SOURCE**                                 • Multidisciplinary focus group;  
• clinical records.

**Question B3: What is the role of pharmacological therapy in patients with first episode psychosis?**

**RECOMMENDATION** *Pharmacological therapy of first episode patients is recommended. The choice between typical and atypical antipsychotics must be evaluated on a case-by-case basis and must consider both the lower incidence of extrapyramidal symptoms and the higher risk of metabolic side effects associated with atypical antipsychotic medication*  
**I/A**

**INDICATOR** **B3.1\***  
**Guidelines for the pharmacological therapy of patients at onset.**

**MEASURE** Score:  
0 = the DMH has not adopted specific guidelines on this topic;  
1 = the DMH has not adopted specific guidelines on this topic, but has a project that includes their adoption;  
2 = the DMH-adopted guidelines are generic and include only a part of the recommendations;  
3 = the DMH-adopted guidelines include at least one of the two recommendations;  
4 = the DMH-adopted guidelines include both recommendations.

**SOURCE** • DMH management

**NOTES** It was found that, due to consideration of more recent data, the present recommendation's content differs in part from the NICE recommendation. The present indicator is therefore a modified version of the one used in the SIEP project guidelines.

**INDICATOR** **B3.2\***  
**Initial treatment with typical and atypical antipsychotics.**

**MEASURE** Percentage.

**NUMERATOR** a) Number of patients who—referred for the first time to the PDTS (Psychiatric Diagnosis and Treatment Service) or MHC (Mental Health Centre) in the previous year for a schizophrenic onset--were treated at the beginning with oral administration of a typical antipsychotic;  
b) Number of patients who--referred for the first time to the PDTS or MHC in the previous year for a schizophrenic onset--were treated at the beginning with oral administration of an atypical antipsychotic.

**DENOMINATOR** number of patients referred for the first time to the PDTS or MHC in the previous year for schizophrenic onset. (#)

**SOURCE** • DMH informational system;  
• MHC and PDTS clinical records.

**NOTES** It was found that, due to consideration of more recent data, the present recommendation's content differs in part from the NICE recommendation. The indicator is therefore a modified version of the one used in the SIEP project guidelines.

**Question B4:**        **what is the role of pharmacological therapy in the period following first episode psychosis?**

*RECOMMENDATION*        *Pharmacological therapy for schizophrenic patients in the period following psychotic onset is effective in reducing the relapse rates. The use of drugs in this specific phase of the pathology is recommended, but further studies are necessary to verify the impact of this therapy on long-term prognosis.*  
**I/A**

**INDICATOR**                **B4.1\***  
**Pharmacological maintenance therapy guidelines.**

**MEASURE**                Score for written antipsychotic drug maintenance therapy guidelines based on whether they include or do not include the following elements:  
- recommendation to continue treatment until [at least] one year has passed since an acute episode;  
- recommendation to consider the possibility of gradually discontinuing treatment and monitoring for signs and symptoms of relapse;  
- recommendation to monitor patients for which antipsychotics have been discontinued for at least two years after the last acute episode.  
0 = the DMH has not adopted specific guidelines on this topic;  
1 = the DMH has not adopted specific guidelines on this topic, but has a project that includes their adoption;  
2 = the DMH-adopted guidelines are generic and include only a part of the recommendations;  
3 = the DMH-adopted guidelines include most of the recommendations;  
4 = the DMH -adopted guidelines include nearly all of the recommendations.

**SOURCE**                • DMH management

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**INDICATOR**                **B4.2\***  
**Pharmacological maintenance therapy practices.**

**MEASURE**                Score based on frequency of application of pharmacological maintenance therapy recommendations.  
a) Duration of 1 year for post-crisis antipsychotic maintenance therapy:  
0 = in no cases or in very few cases (less than10%);  
1 = in 10%-25% of cases;  
2 = in 26%-50% of cases;  
3= in 51%-75% of cases;  
4 = in more than 75% of cases.  
b) In instances of decision to discontinue drug, gradual discontinuation:  
0 = in no cases or in very few cases (less than10%);  
1 = in 10%-25% of cases;  
2 = in 26%-50% of cases;  
3 = in 51%–75% of cases;  
4 = in more than 75% of cases.  
c) Symptomatology monitoring after drug discontinuation:  
0 = in none or very few cases (less than10%);  
1 = in 10%-25% of cases;  
2 = in 26%-50% of cases;  
3 = in 51% –75% of cases;  
4 = in more than 75% of cases.

**SOURCE**                • Specialised focus group.

**Question B5: What is the role of psychological forms of treatment (psychotherapeutic, psychoeducational, family-, psychosocial) during the period following first episode?**

*RECOMMENDATION* A body of evidence allows for the recommendation of CBT in synergy with other treatment strategies.

**I/B**

**INDICATOR** **B5.1\***  
**DMH competencies in the Cognitive Behavioural psychotherapy of psychosis.**

**MEASURE** Percentage per professional category (psychiatrists, psychologists, social workers, nurses).

**NUMERATOR** Number of workers qualified to implement Cognitive Behavioural Therapy in psychosis, per professional category.

**DENOMINATOR** Number of workers per professional category in service at 31/12.

**SOURCE** • DMH management.

**NOTES** Cognitive Behavioural Therapy is a form of psychological intervention conceived to help people to establish links between their thoughts, feelings, or actions and their current or previous symptoms and to re-evaluate their own perceptions, beliefs, or reasoning processes relative to target symptoms. Intervention should include at least one of the following aspects:

- monitoring of thoughts, feelings, and behaviour with respect to symptoms;
- assistance in developing other coping strategies for target symptoms;
- stress reduction.

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**INDICATOR** **B5.2\***  
**Patients in treatment with Cognitive Behavioural Therapy.**

**MEASURE** Percentage.

**NUMERATOR** Number of patients receiving Cognitive Behavioural psychotherapy in the previous year, subdivided by number of interventions received during the current year(0, 1-3, 4-10, >10).

**DENOMINATOR** Number of patients receiving DMH care in the previous year. (#)

**SOURCE** • MHC records;  
• DMH informational system.

**NOTES** A patient is defined as being in treatment if receiving at least three sessions of Cognitive Behavioural Therapy over the course of the current year.

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**INDICATOR** **B5.3\***  
**Guidelines on Cognitive Behavioural psychotherapy in psychosis.**

**MEASURE** Score for written guidelines based on whether they include or do not include the following elements:

- recommendation of Cognitive Behavioural Therapy for patients with schizophrenic disorders;
- recommendation of Cognitive Behavioural psychotherapy for patients with persistent psychotic symptoms;
- recommendation of Cognitive Behavioural Therapy for patients with poor

compliance;  
 • recommendation to follow therapy for at least six months and 10 sessions.  
 0 = the DMH has not adopted specific guidelines on this topic;  
 1 = the DMH has not adopted specific guidelines on this topic, but has a project that includes their adoption;  
 2 = the DMH-adopted guidelines are generic and include only a part of the recommendations;  
 3 = the DMH-adopted guidelines include most of the recommendations;  
 4 = the DMH-adopted guidelines include virtually all of the recommendations.

SOURCE • DMH management

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RECOMMENDATION *Treatment aimed at single families and certain types of psychosocial treatment are recommended in the period following first episode psychosis.*  
 I/A

INDICATOR **B5.4\***  
**DMH competencies for family psychoeducational intervention.**

MEASURE Percentage.

NUMERATOR Number of professionals qualified to implement family psychoeducational intervention per professional category (psychiatrists, psychologists, social workers, nurses).

DENOMINATOR Number of workers per professional category in service at 31/12.

SOURCE • DMH management.

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INDICATOR **B5.5\***  
**Intensity of family psychoeducational intervention.**

MEASURE Percentage.

NUMERATOR Number of patients with family members receiving psychoeducational intervention in the previous year, subdivided by the number of psychoeducational interventions received during the current year (0, 1-3, 4-10, >10).

DENOMINATOR Number of patients receiving DMH care, who live with family members (parents, brothers/sisters, partners, or children) (#)

SOURCE • DMH informational system.

NOTES Psychoeducational intervention with members of a single family or with more than one family is based on the use of a specific method and the attendant training of workers. This type of intervention generally has the aim of following defined programmes to inform family members about the nature, prognosis, and treatment of the patient's psychiatric disorder. Training is based on structured methods aimed at enhancing intra-family communication skills and increasing families' capacities to cope with problems and stress.  
 Psychoeducational intervention programmes can be conducted for either single families or groups of families and can be implemented with or without patients present.  
 The family groups meet at set times based on pre-arranged procedures to discuss problems involved in cohabitating with psychiatric patients and the best ways to cope with these difficulties. The procedure used to conduct these groups can be derived from techniques that differ from the

psychoeducational method.

It includes: informational and psychoeducational intervention with either single families or with groups of family members; non-psychoeducational intervention with groups of family members

It excludes: non-structured forms of intervention with family members (interviews with family members), family psychotherapies (family psychotherapy), group psychotherapies.

- The numerator for family intervention, is given by the number of families interested in this type of activity; if several family members participate in a group, they are contacted only once.

- The denominator is made up of the number of patients having at least one contact with the DMH during the current year and living with their family members (parents, brothers/sisters, partners, children).

**Question B6: What is the optimal design of services aimed at identifying and treating individuals with first episode psychosis or at assisting them during the period following first episode (in terms of facilities, personnel, and intervention methods)?**

*RECOMMENDATION*      *The Assertive Community Treatment regimen (ACT) and the characteristics of multidisciplinary, home care, and flexibility are recommended as essential elements for the good functioning of services specialised in the early detection and treatment of individuals with first episode psychosis.*  
**II/B**

**INDICATOR**      **B6.1  
Therapeutic continuity in the early treatment of individuals with first episode schizophrenia.**

**MEASURE**      Percentage.

**NUMERATOR**      Number of patients who, in the previous year, received at least one contact every 90 days during the 365 days following first contact.

**DENOMINATOR**      Number of patients in treatment.(#)

**SOURCE**      • DMH informational system.

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**INDICATOR**      **B6.2  
Home care in the early treatment of individuals with first episode psychosis.**

**MEASURE**      Percentage.

**NUMERATOR**      Number of patients who, in the previous year, received at least 3 home visits.

**DENOMINATOR**      Number of patients in treatment.(#)

**SOURCE**      • DMH informational system.

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**INDICATOR**      **B6.3  
Multidisciplinary in the early treatment of individuals with first episode schizophrenia.**

**MEASURE**      Percentage.

**NUMERATOR**      • Number of patients receiving MHC intervention from psychiatrists only.  
• Number of patients receiving MHC intervention from psychologists only.  
• Number of patients receiving MHC intervention from both psychiatrists and psychologists.  
• Number of patients receiving MHC intervention from psychiatrists and/or psychologists as well as from members of other professional categories (nurses, educators, social workers).

**DENOMINATOR**      Number of patients in treatment.(#)

**SOURCE**      • DMH informational system.

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**INDICATOR**      **B6.4  
DMH practices in the early treatment of individuals with first episode**

**psychosis.**

**MEASURE**

Score.

a) Patients with percentage of home (or residential) interventions equal to:

0 = none;

1 = less than 10%;

2 = 11-24%;

3 = 25-49%;

4 = 50% and more.

b) Patients receiving intervention from not only psychiatrists:

0 = none;

1 = less than 10%;

2 = 11-24%;

3 = 25-49%;

4 = 50% and more.

**SOURCE**

- Multidisciplinary focus group.

## 2. Indicators for recommendations pertaining to forms of intervention for whose efficacy sufficient evidence is still unavailable

**Question A1: What is the effectiveness of early intervention to identify high risk individuals and/or prodromal patients?**

*RECOMMENDATION* Current evidence does not allow for the recommendation of early diagnostic intervention for prodromal or at-risk patients to prevent progression from prodromal to acute psychosis, or to improve prognosis.  
**I/C**

**INDICATOR** **A1.1**  
**DMH services or initiatives for identifying individuals at-risk and/or in the prodromal phase of schizophrenia.**

**MEASURE** Score:  
0 = no activities aimed at identifying high risk individuals and/or prodromal patients;  
1 = no activities, but this type of initiative is included in next year's programming;  
2 = several specific though not systematic activities, which have not yet been included in the DMH activity programme;  
3 = activities targeting at-risk individuals over the current year, systematically included in the clinical routine and programmed by the DMH; lack of specific structures or teams with specialised personnel;  
4 = presence of specific facilities or teams with specialised personnel for identifying high risk individuals and/or prodromal patients.

**SOURCE** • Multidisciplinary focus group.

**NOTES** The presence in the DMH of specific facilities for the early treatment of schizophrenic onset is substantiated by the existence of a physical site dedicated to this activity and by personnel specialised in treating young patients at schizophrenic onset, for a defined time-work number.

**Question A2: What instruments are available to identify high risk individuals and/or prodromal patients?**

*RECOMMENDATION* Due to the clinical heterogeneity of the phenomenon, prodromal or at-risk patients who will progress towards acute psychosis remain unidentifiable. Clinical rating scales and imaging diagnostic techniques can support diagnosis, but are not recommended as screening methods.  
**III/C**

**INDICATOR** **A2.1**  
**Use of assessment scales for identifying individuals at-risk and/or in the prodromal phase of schizophrenia.**

**MEASURE** Score:  
0 = no use of assessment scales in activities aimed at the identification of high risk individuals and/or prodromal patients  
1 = assessment scales have been used in routine activities or in specific initiatives for identifying high risk individuals and/or prodromal patients.  
NA = there are no DMH activities aimed at identifying high risk individuals or prodromal patients.

**SOURCE** • Multidisciplinary focus group.

**Question A3: What is the role of pharmacological therapy in high risk individuals and/or prodromal patients?**

*RECOMMENDATION*            *The use of antipsychotic medication for prodromal or at-risk patients to prevent the onset of psychotic disorder or to improve prognosis, is in doubt.*  
**I/C**

**INDICATOR**                    **A 3.1**  
**Use of pharmacological therapy in high risk individuals and/or prodromal patients.**

**MEASURE**                      Score:  
0 = no use of pharmacological therapy in high risk individuals and/or prodromal patients;  
1 = use in less than 26% of cases;  
2 = use in 26%-50% of cases;  
3 = use in 51%-75% of cases;  
4 = use in more than 75% of cases;  
NA = there are no DMH activities aimed at identifying high risk individuals and/or prodromal patients.

**SOURCE**                        • Multidisciplinary focus group;  
• clinical charts.

**Question A4: What is the role of psychological (psychotherapeutic, psychoeducational, family, psychosocial) treatments in high risk individuals and/or prodromal patients?**

*RECOMMENDATION* Cognitive Behavioural Therapy is recommended for prodromal or at-risk patients to moderate symptoms, improve social skills, identify dysfunctional thoughts, and minimise anxiety and depression related to prodromal phase distress. Yet, current evidence does not allow for the recommendation of specific psychological therapies for prodromal or at-risk patients to prevent the onset of psychotic disorder or improve prognosis.  
**I/B**

**INDICATOR** **A4.1**  
**Use of specific forms of psychological treatment (CBT) in at-risk and/or prodromal patients**

**MEASURE** Score:  
0 = no use of specific forms of psychological treatment (Cognitive Behavioural Therapy) in at-risk individuals and/or in the prodromal phase of schizophrenia;  
1 = use in less than 26% of cases;  
2 = use in 26%-50% of cases;  
3 = use in 51%-75% of cases;  
4 = use in more than 75% of cases;  
NA = there are no DMH activities aimed at identifying high risk or prodromal phase individuals

**SOURCE** • Multidisciplinary focus group;  
• clinical records.

## APPENDIX 2: Italian programmes

**1. “Programma 2000”.** This initial early detection and intervention programme was started up at the beginning of 1999 at the Department of Mental Health in the *Niguarda Ca’ Granda* Hospital, Milan, Italy. It made a crucial contribution to promoting information on and awareness of the “early psychosis” approach through publications, informative events, training courses, conference participation and organisation, and the creation of a scientific society, the AIPP (*Associazione italiana per l’intervento precoce nelle psicosi* - the Italian Association for Early Intervention in Psychosis), in association with IEPA (the International Early Psychosis Association).

From its inception, *Programma 2000* developed as an intervention/research initiative, by developing clinical activities based on scientific evidence and research activity concurrently with events in the international scientific community. In *Programma 2000*, multimodal assessment was used to evaluate 247 young people with their families, 144 of whom were taken in charge by the specific, multidimensional programme: results for the programme’s various follow-ups are published periodically.

**2. Piano regionale salute mentale della Lombardia (DGR del 17.5.2004)--the Lombardy Regional Health Plan, according to the Regional Government Decree of 17.5.2004).** In point 3.2, *Modelli di intervento per rispondere a bisogni con rilevanza sociale* (Intervention Models for responding to social needs), a chapter is dedicated to the topic of early intervention in psychosis by specifying that, “the Detection and Early Intervention in Psychosis Project is formulated by the DMH and presented and approved at the site of the affiliated Local Health Authorities’ (ASLs’) coordinating authority. In defining the project, the DMH identifies a specialised, internal “functional team”. The procedures, which must include the programme’s evaluation procedures and aims, must be carried out by respecting local specificity and organisational autonomy”. Three of the innovative programmes funded by the Plan are dedicated to the topic and led, in the year 2006, to the start-up of activities at DMHs in Vimercate (Desio, Sesto San Giovanni, and Vimercate), Legnano (Legnano and Magenta), and in the private domain, by ICOS, a collaboration and support company located in Milan, Italy.

**3. The Tuscany region’s Progetti sperimentali per la salute mentale (Experimental Mental Health Projects).** In 2007, the region of Tuscany acknowledged and funded four initiatives (at Local Health Units – USLs - in Grosseto, Florence, Massa, and Siena), in the purview of “Experimental Mental Health Projects”, with the aim of setting up intervention/research activities concerning psychotic onset.

**4. L’individuazione e l’intervento precoce nelle psicosi. Un approccio preventivo alla schizofrenia (Detection and early intervention in psychosis. A preventive approach to schizophrenia).** At the end of 2006, the Ministry of Health’s Centre for Disease Control (CCM), approved this biennial project (which began in March 2007) aimed at the implementation and evaluation of clinical programmes. It is coordinated by the *Niguarda Ca’ Granda* Hospital in Milan (Programma 2000) and involves the Mental Health Departments of the Catanzaro ASL 7, the Salerno ASL 1, the *Roma D USL*, and the Grosseto USL 9.

**5. L’individuazione e il trattamento precoce delle psicosi: esiti clinici e implicazioni economiche per i Servizi di salute mentale (The detection and early treatment of psychosis: clinical outcomes and economic implications for mental health services).** In 2006, this study was assigned to the Lombardy region and delegated to the *Niguarda Ca’ Granda* Hospital in Milan (leader), with the participation of the following hospitals: the Legnano Public Hospital, the Vimercate Public Hospital, the Salvini Hospital in Garbagnate Milanese, and of the Italian National Institute of Health in Rome.

The main goals of the study (started up in the Autumn of 2006) are: 1. implementation of a detection and early intervention programme for severe mental illness, through conduction of: i) an information and awareness campaign for the population at large, schools, general practitioners, and for key youth agencies operating locally and regionally; ii) implementation of an early treatment

programme for cases detected with a model based on individualised treatment projects for patients taken in charge; 2) evaluation of the implemented programme from the perspective of clinical outcomes (symptomatology, days of hospitalisation), social outcomes (social disability, family burden), and socioeconomic impact (costs, user satisfaction).

**6. The Picos Project.** Il Psychosis Incident Cohort Outcome Study is a project promoted by the Division of Psychiatry and Clinical Psychology, University of Verona, coordinated by Mirella Ruggeri, Antonio Lasalvia, and Michele Tansella; it began in 2004 and is funded by the Veneto region and by other institutions. It is a multicentric study examining the outcomes of new cases of psychosis coming to the attention of the Veneto Region's Mental Health Services, which cover an area of approximately 4 million inhabitants. It includes clinical-epidemiological, genetic, and brain imaging assessment.

The programme is also conducted in collaboration with the London Institute of Psychiatry, with the main aims of developing a predictive model for onset psychosis outcomes and identifying the role of biological, psychological, and environmental factors.

7. In addition to the above-described programmes, several already begun programmes, in the start-up phase, or in the planning phase were presented at the first national AIPP conference (Milan, 26th November, 2006). (They are listed in alphabetical order by location, see box.

8. *Programma 2000* has activated three main lines of research on outcomes, costs and efficacy, and--in the purview of a collaborative effort with the Central Institute of Mental Health in Mannheim, Germany--on the validation of ERIRAOS instruments aimed at identifying psychotic risk factors.

Moreover, research is underway in the domain of "structured clinical practice" concerning neurocognitive deficits and on subjective quality of life indicators.

*La Fondazione CeRPS* (The CeRPS Foundation) (Salerno) and the *ASL Salerno 1 DMH* have conducted a study on the predictability of psychiatric crises, by focussing on psychotic onset.

An investigation of the opinions of physicians and psychiatrists (early intervention experts and non-experts) concerning intervention during the pre-psychotic phase has been conducted by researchers at the University of Modena and Reggio Emilia in Italy, in collaboration with the University of Melbourne, Australia.

Location	Project
Andria	Programme for the detection and early intervention in psychosis programme (begun in 2005) at the Andria CMH (DMH ASL BAT/1-regione Puglia).
Bari	The <i>Nessun Dorma</i> Project (University of Bari and AUSL Bari 3), aimed at constructing collaborative pathways to care among public, private, university, and local- and regional area sectors for investigating susceptibility to schizophrenia and evaluating early forms of intervention.
Bologna	A programme activated in September 2003 to develop and implement specific forms of early intervention, includes collaboration between the specialised multidisciplinary team and general practitioners at the <i>Borgo-Reno</i> MHC, under university management.
Como	Screening and intervention model concerning the population with at-risk mental states and at psychotic onset, experimentally conducted from 2002 to 2004 in the Sant'Anna Hospital DMH.
Genoa	An outcome study still underway in the ASL 3 (in collaboration with the Savona ASL), implemented through <i>Programma 2000</i> , has led to the development of specific programme in a Genoese MHC.
L'Aquila	The SMILE Project ( <i>Servizio di monitoraggio e intervento precoce per la lotta agli esordi della sofferenza mentale e psicologica dei giovani</i> ) (Monitoring and early intervention in the

fight against the onset of mental and psychological suffering in young people) was activated in 2006 c/o the *Servizio psichiatrico universitario di diagnosi e cura* (University Psychiatric Services for Diagnosis and Treatment).

Rome

In addition to the above-described programme for the *Roma D* DMH (which already had a programme underway prior to the CCM project), the *Roma E* DMH has begun research/intervention on the detection of high-risk mental states and the optimum treatment of psychotic onset, in collaboration with the University of Rome *La Sapienza*. As to the City of Rome, a university-managed activity with specific hospital aspects has started up at the *Tor Vergata* University Polyclinic.

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