# Clinical Practice Guideline for Schizophrenia and Incipient Psychotic Disorder

**CLINICAL PRACTICE GUIDELINES IN THE NHS.**
MINISTRY OF HEALTHCARE AND CONSUMER AFFAIRS

**NOTE:**

More than 5 years have passed since the publication of this Clinical Practice Guideline, and **its validity has not been reviewed**.

Therefore, **it is unclear whether its recommendations remain valid**; they should therefore be treated with caution and applied in accordance with **clinical judgement and the individual circumstances of each patient**.

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Clinical Practice Guidelines in the NHS

**Number 2006/05-2**

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This CPG is an aid for decision-making in healthcare. It is not in any way an obliged requirement to adhere to every aspect of this CPG nor does it replace the clinical judgement of health care professionals.

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# Presentation

**Presentation of the Clinical Practice Guideline for schizophrenia and incipient psychotic disorder**

In order to ensure that clinical decisions are adequate, efficient and safe, healthcare professionals with updated knowledge and skills are required.

Although scientific information is more accessible than ever, the large number of references, lack of time and need to grade the importance of scientific evidence make certain tools aimed at supporting clinical decision-making necessary. Clinical Practice Guidelines (CPGs) provide answers to the most relevant questions regarding a patient with a specific pathology and present scientific evidence in the form of graded recommendations based on the quality of the studies that support them.

Given that CPGs facilitate the thousands of clinical decisions made daily in healthcare and that they are a tool to improve health outcomes, the Quality Agency supports their development, dissemination and use, while ensuring that CPGs developed in Spain are high quality.

In the year 2003, the National Health System's Interterritorial Council created the HealthGuide project, which aims ultimately to improve evidence-based clinical decision-making by means of training activities and the configuration of a Clinical Practice Guidelines (CPG) register in the NHS. Since then, the HealthGuide project has assessed dozens of CPGs in accordance with explicit criteria generated by its scientific committee, registered these CPGs and disseminated them throughout the Internet

In early 2006, the Directorate General of the National Health System Quality Agency elaborated the Quality Plan for the NHS, a plan that encompasses twelve strategies.

The objective of this Plan is to increase cohesion of the NHS and aid in guaranteeing maximum quality healthcare to all citizens, regardless of their place of residence.

The plan's tenth strategy is aimed at improving clinical practice, its objectives being the reduction of variability in clinical practice and the promotion of the development and use of CPGs. GuíaSalud and the CPG development program are responding to the objectives set forth in the Quality Plan, the former in terms of the creation of a registry, training and consultancy, and the latter in terms of the creation of new guidelines.

In 2006, the development of eight CPGs on prevalent pathologies related with health strategies was assigned to different agencies and experts groups. This updated clinical

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practice guideline on schizophrenia and incipient psychotic disorder is part of this assignment.

Additionally, the establishment of a common CPG development methodology within the NHS was requested. This assignment was shaped into a Methodological manual for the development of CPGs, which has been available to all professionals since November 2007. It is the reference methodological manual employed for the development of all guidelines created in this program.

At present, fourteen more guidelines are in the process of being developed, in collaboration with the same institutions and with the participation of the scientific societies involved.

In 2007 the HealthGuide project was reworked and the Clinical Practice Guidelines Library was created. This project delves deeper into the development of CPGs and includes other services and products of Evidence-Based Medicine that are aimed at supporting clinical decision-making. It also emphasises diffusion, dissemination and implementation of CPGs to boost their use, as well as the assessment of health outcomes in the population.

Schizophrenia and other forms of psychosis represent an important public health problem, given that these disorders can severely affect the psychological and social development of patients and their family and social environment.

However, scientific advances in the past few years have ignited a renewed sense hope in regards to its treatment and rehabilitation of patients. Likewise, recent studies demonstrate that clinical course can vary with early and specific interventions adapted to the early phases of these disorders.

In this sense, the World Health Organisation (WHO), together with the International Association of Incipient Psychosis, made a public declaration in 2005 to promote early intervention and the recovery of young people with early psychosis.

This CPG on schizophrenia and incipient psychotic disorder is also an update of the guideline published in 2003 and incorporates more contents, including information on incipient psychotic disorders. It aims to provide professionals and users of healthcare services with rigorous information on available scientific evidence for the treatment of these disorders, thus facilitating the development of preventive, therapeutic and rehabilitation interventions that improve the clinical course, prognosis and quality of life of affected patients and their family and social environment.

**Pablo Rivero Corte**
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# Authorship and Collaborations

The Mental Health Forum and the Agency for Health Technology Assessment and Research have worked together on the updating of this Clinical Practice Guideline. The working group that has developed the CPG is comprised of a coordinator and a development group. There follows a list of group members, collaborators and external reviewers who have collaborated in the development of the CPG are:

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**Declaration of Interests**:

All members of the working group (coordinator and development), as well as all external reviewers, have declared no conflict of interests by completing a form designed to this end (annex 5). This guideline is editorially independent from the funding agency.

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# Key Questions

The following section presents the clinical questions that the working group deemed should be addressed in the Clinical Practice Guideline (CPG) according to the type of intervention.

## Pharmacological Interventions

Should antiparkinson drugs be used preventively with second generation antipsychotics?

What side effects should be taken into account when administering second generation antipsychotics?

Are there any differences in terms of efficacy between first and second generation antipsychotics?

Are there any differences in terms of efficacy between Consta type antipsychotics and classic depots?

What is the efficacy of maintenance electroconvulsive therapy (ECT)?

Is the use of antidepressants justified in schizophrenia?

What factors are involved in adherence to treatment?

Effects of cannabis on the onset and course of schizophrenia.

Effects of cocaine on the onset and course of schizophrenia.

What antipsychotics have been proven effective at reducing negative symptoms?

## Psychosocial Interventions

### a) Psychological Interventions

Does specific treatment produce greater benefits than other psychological interventions?

What are the most effective formats for initial treatment?

Are there any advantages to the concomitant or sequential combination of a specific intervention with other psychological interventions?

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## b) Psychosocial Rehabilitation

Does the specified treatment produce greater benefits than other psychological treatments?

What are the most efficient formats for treatment (for example, group-based or individual treatment)?

Is there any advantage to the concomitant or sequential combination of a specific intervention with other psychological interventions?

What configuration/s most favours and promotes recovery?

What service provision model promotes paid employment?

## c) Modalities of care to the community

What does assertive community treatment consist of?

What patient profile is it aimed at?

What types of community-based treatments are available?

What are the differences between the different modalities of care to the community?

Is there any scientific evidence to determine that one type of treatment is superior to another?

What are the outcomes of these treatments?

What is the recommended length of these treatments?

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# Summary of Recommendations*

## 1. Pharmacological intervention

### General aspects

| | |
|---|---|
| **A** | Whenever possible, antipsychotic medication should be prescribed in a non-coercitive manner in combination with psychosocial interventions that include adherence-promoting strategies[1]. |
| **A** | Antipsychotic medications are indicated in nearly all patients who experience an acute relapse; the selection of medication should be guided by the individual characteristics of each patient.[2] |
| **C** | Weight and body mass index should be measured at the beginning of treatment, then every month for six months, and after that every three months. Consultation with a die titian is advisable, as well as encouraging regular physical exercise. It may also be necessary to consider a drug with a smaller risk of weight gain if weight does not change or is significant. Pros and cons should be assessed with the patient, and he/she should be provided with psychosocial support.[1] |
| **C** | Fasting plasma glycaemia and lipid profiles should be measured at baseline and at regular intervals over its course.[1] |
| **C** | An optimum initial assessment should include magnetic resonance imaging, neurocognitive assessment, neurological exam of neurological and motor disorders, an electrocardiogram, height and weight measurement (body mass index), illegal substance detection tests, lipid profiles and fasting plasma glycaemia (and/or HbA1c).[1] |

### Prescription of antipsychotics and side effects

| | |
|---|---|
| **A** | Pharmacological treatments should be prescribed with extreme caution in patients who have not undergone prior treatment, under the basic principle of producing the least harm possible, while obtaining the maximum benefit. This means a gradual introduction, after careful explanation, of low doses of antipsychotic medication together with antimania or antidepressant drugs when these syndromes are present.[1] |
| **A** | In patients who initiate treatment for the first time, second-generation antipsychotic medication is recommended given that it is justified due to its better tolerance and lower risk of tardive dyskinesia.[1] |
| **A** | The use of oral second-generation medication such as risperidone, olanzapine, |

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| | |
|---|---|
| | quetiapine, amisulpride and aripiprazole is recommended as the first and second line of treatment in the first episode of psychosis. Initial doses should be low and then be gradually increased little by little at spaced out intervals only if response is low or incomplete. Secondary discomfort, insomnia and restlessness should be initially treated with benzodiazepines. Other symptoms such as mania and severe depression require specific treatment with mood stabilisers and antidepressants.[1] |
| **C** | These doses probably will not have an early effect (during the first days) on discomfort, insomnia and behavioural disorders secondary to psychosis. Hence, a safe, supportive context, and regular and sufficient dose of benzodiazepines will provisionally represent essential components in the management of specialised nursing care.[1] |
| **C** | If the risk-benefit relationship changes in certain patients due to, for example, weight gain, impaired glucose tolerance or sexual side effects associated with the development of second generation agents, an alternative first or second generation antipsychotic drug should be reconsidered.[1] |
| **C** | In emergency situations it is recommended to avoid the first choice use of drugs that tend to undermine the future adherence to treatment due to the production of undesirable side effects that generate an aversive subjective effect. First generation drugs should be used only as a last resort in these circumstances, particularly haloperidol, given that they produce more rigidity than sedation.[1] |
| **C** | If in the first episode of non-affective psychosis there are side effects, such as weight gain or metabolic syndrome, the use of a conventional antipsychotic is recommended. If response is insufficient, other causes should be assessed. If there are no side effects, doses should be increased. If adherence is poor, analyse the reasons, optimize the doses and provide treatment compliance therapy.[1] |

## Technical aspects of prescription

| | |
|---|---|
| **A** | Maintenance of pharmacotherapy is recommended for the prevention of relapse in stable and stabilisation phases, with doses that are always within the recommended treatment range for first and second generation antipsychotics.[2] |
| **B** | Antipsychotic medication for the treatment of a first episode of psychosis should be maintained for at least two years after the first recovery from symptoms.[2] |
| **B** | In a first episode of psychosis, dosage should be initiated in the lower half of the treatment range; second generation antipsychotics are indicated due to the lower short and long term risk of extrapyramidal side effects.[2] |
| **B** | The use of clozapine is recommended in cases of persistent aggressiveness.[2] |

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|---|---|
| **B** | The administration of multiple antipsychotic drugs, such as the combination of first and second generation drugs, should not be used except during transition phases of switching from one medication to another.[1] |
| **C** | Antipsychotic drugs, whether second or first generation, should not be prescribed simultaneously, except for brief periods of time during a transition phase.[3] |
| **C** | The combination of two antipsychotics is not recommended, given that it could increase the risk of side effects and pharmacokinetic interactions.[3] |
| **C** | The recommendation to combine an antipsychotic drug, a mood stabiliser and a benzodiazepine or antidepressant could be totally justified by the characteristics of comorbid symptoms, which are extremely common in psychotic disorders.[1] |
| **C** | If parenteral treatment is deemed necessary, intramuscular administration is preferable to intravenous, from the point of view of safety. Intravenous administration should only be used in specific circumstances.[3] |
| **C** | Vital signs should be monitored after parenteral administration of treatment. Blood pressure, pulse rate, body temperature and respiratory rate should be recorded at regular intervals, established by the multidisciplinary team, until the patient is active again. If he/she is asleep or seems to be so, more intensive monitoring is required.[3] |
| **C** | Depot drugs should be reserved for two groups. Firstly, for those who clearly and voluntarily choose this administration route. Second generation injectable drugs are preferable due to their better tolerability and lower risk of tardive dyskinesia. Secondly, for those who, despite a series of comprehensive psychosocial interventions aimed at promoting adaptation and adherence, repeatedly fail to adhere to the necessary medication and present frequent relapses. This is even more pressing when the consequences of relapses are severe and entail substantial risk both for the patient and for others.[1] |

## Resistance to antipsychotic treatment

| | |
|---|---|
| **A** | Patients who are taking first generation antipsychotic drugs and who still present persistent positive or negative symptoms, or who experience uncomfortable side effects, should switch to oral second generation antipsychotic medication under close surveillance of a specialist.[1] |
| **A** | If the risk of suicide is high or persistent despite treatment for depression, if antidepressant treatment is ineffective, or if depression is not severe, the immediate use of clozapine should be considered.[1] |
| **A** | Second generation medication is recommended for patients who relapse in spite of good adherence to first generation antipsychotic medication, although other reversible |

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|---|---|
| | causes of relapse should be taken into account.[1] |
| **A** | If the patient is resistant to treatment, clozapine should be introduced with safety guarantees on the very first administration.[1] |
| **A** | When there is no response to treatment with adequate administration of two different antipsychotics, the use of clozapine is recommended.[2] |
| **B** | Depot antipsychotic drugs should be considered for those patients who present poor adherence to medication.[2] |
| **C** | If schizophrenia symptoms do not respond to first generation antipsychotics, the use of a second generation antipsychotic should be considered before diagnosing treatment-resistant schizophrenia or introducing clozapine. In these cases, the introduction of olanzapine or risperidone can be assessed. It is recommended to inform the patients.[3] |
| **C** | The addition of a second antipsychotic to clozapine could be considered in people resistant to treatment in whom clozapine alone has not been proven to be sufficiently effective.[3] |

## Comorbidity and coadjuvant medications

| | |
|---|---|
| **B** | It is possible to introduce antidepressants as complementary treatment to antipsychotics when depressive symptoms fulfil the syndromic criteria of major depression or are severe, causing significant discomfort or interfering with the patient's functionality.[4] |
| **B** | An episode of major depression in the stable phase of schizophrenia is an indication for treatment with an antidepressant drug.[2] |

# 2. Psychosocial interventions

| | |
|---|---|
| **C** | The selection of a certain approach will be determined by the patient, his/her clinical situation, needs, capacities and preferences, as well as by the resources available at that time.[5] |
| **C** | It is recommended that psychosocial interventions be carried out by professionals who have specific training, sufficient experience, qualifications (backed by supervision and technical expertise), as well as availability and constancy in order to maintain a long-term alliance.[6] |

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## 2.1. Cognitive-Behavioural Therapy

| | |
|---|---|
| **A** | Cognitive-behavioural therapy (CBT) is recommended for the treatment of psychotic symptoms that are persistent despite receiving adequate pharmacological treatment.[3] |
| **A** | CBT should be indicated for the treatment of positive symptoms of schizophrenia, especially hallucinations.[7] |
| **A** | CBT is recommended as a treatment option to aid in the development of insight and to increase adherence to treatment.[7] |
| **A** | CBT is recommended to prevent the evolution to psychosis in early intervention.[8] |
| **A** | CBT is recommended as a treatment option to prevent the prescription of drugs and reduce symptomatology in the management of incipient psychosis.[8] |
| **A** | CBT, together with standard care, is recommended in the acute phase to accelerate recovery and hospital discharge.[1] |
| **B** | CBT should be considered for the treatment of stress, anxiety and depression in patients with schizophrenia and consequently the techniques employed should be adapted to other populations accordingly.[2] |

## 2.2. Supportive psychotherapy

| | |
|---|---|
| **C** | It is recommended to develop the therapeutic alliance by providing emotional support and cooperation, given that this alliance plays an important role in the treatment of patients with schizophrenia.[9] |
| **C** | Supportive therapy is not recommended as a specific intervention in the normal management of patients with schizophrenia if other interventions whose efficacy has been proven are indicated and available. In spite of this, patient preferences should be acknowledged, especially if other more effective psychological treatments are not available.[9] |

## 2.3. Psychodynamic psychotherapy

| | |
|---|---|
| **C** | Psychoanalytical and psychodynamic principles may be useful to help professionals understand the experience of patients with schizophrenia and their interpersonal relationships.[3] |

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## 2.4. Psychoeducation

| | |
|---|---|
| **A** | The routine implementation of psychoeducational interventions for patients and family members in treatment plans is recommended.[10] |
| **C** | It is recommended to transmit information gradually depending on the needs and uncertainties of the patient and his/her family and the phase of the disorder the patient is in.[3] |

## 2.5. Family intervention

| | |
|---|---|
| **A** | Family Intervention (FI) programs are recommended to reduce the burden on the family, improve social functioning of the patient and reduce economic cost.[11,12] |
| **A** | The application of FI therapy is recommended in patients who are moderately or severely disabled and, especially, in those with long evolution of the disorder. In patients with recent onset of the disease, each situation will have to be individually assessed.[11,12] |
| **A** | FI should be offered to families who live together or who are in contact with patients with schizophrenia, especially those who have relapsed or present relapse risk, and also in cases of persistent symptomatology.[3] |
| **A** | Psychoeducational FI, based on the management of expressed emotion, is recommended to avoid relapses and improve the prognosis of the disease (its effects are maintained at 24 months).[11-16] |
| **A** | Programs should be applied in groups comprised of family members of similar patients, taking expressed emotion into account and should include the patient to the greatest possible extent. These programs should be added to standard treatment and should never last under six months in order for them to be effective.[11,12] |
| **A** | Patients should be included, whenever possible, in FI sessions given that it significantly reduces relapses.[3] |
| **A** | Prolonged FI (over six months) is recommended to reduce relapses.[3] |
| **A** | Patients and their families usually prefer single family interventions rather than multifamily group interventions.[3] |
| **A** | Programs should always include information for the families regarding the disease along with different strategies, such as stress coping strategies or problem-solving training.[17,18] |

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|---|---|
| **B** | Referral to patient and carer social networks is recommended.[1] |
| **B** | FI programs should last more than nine months and include characteristics of commitment to attend the program, support and development of skills and should not simply provide information or shared knowledge.[2] |
| **C** | It is recommended to transmit information gradually depending on the needs and uncertainties of the patient and his/her family and the phase of the disorder the patient is in.[3] |

## 2.6. Cognitive rehabilitation

| | |
|---|---|
| **A** | The application of cognitive rehabilitation therapy, in all its modalities, is recommended as a technique that improves cognitive functioning in a wide range of clinical conditions of the patient with schizophrenia.[19] |
| **A** | The application of cognitive rehabilitation therapy in the daily environment of the patient with schizophrenia is recommended.[20] |

## 2.7. Social skills training

| | |
|---|---|
| **A** | The application of social skills training (based on the problem-solving model) is recommended for severely or moderately impaired patients.[21] |
| **B** | Social skills training should be available to patients with difficulties and/or stress and anxiety related to social interaction.[2] |

## 2.8. Training in activities of daily living

| | |
|---|---|
| **B** | Training in activities of daily living, based on scientific evidence, should be available to patients who have difficulties with daily functioning tasks.[2] |

## 2.9. Occupational insertion support

| | |
|---|---|
| **A** | It is recommended to encourage people with schizophrenia to find employment. Mental health specialists should actively facilitate it and specific programs that |

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| | |
|---|---|
| | incorporate this intervention should be widely established.[1] |
| **A** | Supported employment programs are recommended for the occupational insertion of patients with schizophrenia, given that better outcomes are obtained when compared to other occupational rehabilitation interventions.[22,23] |
| **A** | It is recommended to provide occupational support to moderately or mildly disabled patients and who are in the stable or maintenance phase.[24,25] |
| **C** | Mental health services, in collaboration with social and health care staff and other relevant local groups, should facilitate access to employment opportunities, including an array of support modalities adapted to the different needs and abilities of people with schizophrenia.[3] |

## 2.10. Housing resources

| | |
|---|---|
| **B** | It is recommended that housing resources focus on the interaction between the patient and his/her environment, activating the individual's personal resources and community resources with the aim of achieving as much autonomy as possible.[26] |
| **C** | If possible, patient preferences in terms of housing and resource selection should be favoured, acknowledging the right of the patient to live in an environment that is as normalized as possible, articulating the necessary training programs and providing proper support so that the patient can access and remain in the aforementioned setting.[27] |

# 3. Modalities of care and intensive follow-up in the community

| | |
|---|---|
| **A** | It is recommended that patients be treated in the least restrictive setting possible, while ensuring safety and enabling effective treatment.[4] |

## 3.1. Community-based mental health teams

| | |
|---|---|
| **A** | Outpatient management in a community mental health centre is recommended for patients with severe mental disorder given that it decreases deaths by suicide, dissatisfaction with care delivery and treatment dropout.[29] |

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| | |
|---|---|
| **A** | Community management with a comprehensive care plan for patients with severe mental disorder is recommended. The patient should be included in decision-making, emphasising his/her ability to improve his/her degree of satisfaction and social recovery.[30] |
| **C** | Outpatient management in a community mental health centre that provides pharmacological treatment, individual, group and/or family therapy, psychoeducational measures and different intensities of individualized treatment for stable patients with relatively mild disability is recommended.[28] |

## 3.2. Case management and assertive community treatment

| | |
|---|---|
| **A** | Case management is recommended for community-based management of patients with severe mental disorder with the aim of increasing linkage with services and therapeutic compliance.[31] |
| **A** | Intensive case management is recommended in patients with severe mental disorder who make use of hospital services with the aim of reducing this consumption.[33] |
| **B** | Assertive community treatment and intensive case management programs are recommended in patients with schizophrenia who frequently seek care.[32] |
| **C** | Intensive care management and community-based support services, in addition to the administration of psychoactive drugs and psychotherapy, are recommended for patients who present early onset schizophrenia (before the age of 18).[34] |

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# 1. Introduction

This CPG on schizophrenia and incipient psychotic disorder is an update and expansion of the guideline edited in the year 2003. The update has been carried out by means of a new systematic review of scientific evidence that appeared after 2002, and new contributions derived from research on the early phases of schizophrenia and incipient psychotic disorder have been taken into account for the expansion of contents. Both aspects have advised the modification of content order, particularly contents relating to healthcare interventions and the classification of the phases of these disorders. As will be evidenced, it has been decided to subdivide the clinical course and corresponding recommendations into two big phases: early phases of psychosis and phases of schizophrenia.

Given that the document herein presented is an update, it has maintained some coherence with the CPG published in 2003 and differs to some extent in terms of the format and methodology criteria established within the framework of the CPG Program for the development of the Quality Plan of the NHS.

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# 2. Scope and objectives

The basis of clinical practice is mainly clinical judgement, that is, the array of knowledge and experiences acquired by clinical professionals throughout their professional trajectory and which is expressed in every action and in the decision-making process in the case of each individual patient.

However, the quantitative and qualitative development of scientific research in the general medical field and in the psychiatric field in particular make it difficult for professionals to remain updated on knowledge that keeps exponentially expanding and diversifying.

Therefore, it is necessary to provide all health care professionals who are involved in the management of patients with schizophrenia with updated and reliable information on the advances provided by research that are applicable to the clinical field. Better use of this information will be ensured if it is expressed as a CPG, meaning it is formulated as "a series of recommendations designed to help health care professionals and patients select the best option in the diagnosis and treatment of specific clinical conditions in specific circumstances".[35]

The development of a CPG applicable to schizophrenia and incipient psychotic disorder requires the fulfilment of precise elaboration conditions and a methodology that guarantees a systematic review of available scientific evidence.

Furthermore, the development of a recommendations guideline must necessarily consider the conditions of real clinical practice where recommendations must be applied; that is, all those elements that condition clinical judgement and health care practice, such as the specific characteristics of health care professionals in terms of training, experience and specific technical knowledge; the characteristics of the population cared for, in particular the acceptability of therapeutic proposals and informed consent; and, lastly, the conditions that surround the health care act such as accessibility, availability of resources and material conditions of the care.

For all these reasons, we aim to provide a guideline that responds to both, the technical requirements and methodological rigour in terms of the systematic review and development of recommendations, as well as to the consideration of applicability conditions inherent to our health care setting, and particularly those related to the mental health network of public use.

## Objective

The **objective** of this CPG is to provide recommendations for the management of patients with schizophrenia and incipient psychotic disorder that are preferably applicable in public use mental health services. This CPG develops recommendations on diagnostic, therapeutic and rehabilitation interventions, with the aim of aiding professionals in decision-making. Hence, it aims to tailor treatment to each patient's specific situation, providing several therapeutic and rehabilitation options for each phase of the disorder and the idiosyncratic characteristics of each patient.

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The main **users** of this CPG are psychiatrists, psychologists, nurses, social workers and educators, occupational therapists, psychiatric aides and other mental health professionals. It may also be useful to family physicians, nurses and other primary care professionals who are involved in the management of patients with schizophrenia.

As in the previous CPG, the working group agreed for the CPG update to focus on adult patients diagnosed with schizophrenia and also to include a new section on **early intervention in psychosis**, which can initiate in childhood or adolescence and also in adulthood. The CPG provides a broad view of schizophrenia and has addressed the diagnosis, treatment and rehabilitation of this health problem.

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# 3. Methodology

## 3.1. Introduction

The *Clinical Practice Guideline for the Management of Patients with Schizophrenia* was edited and presented in December 2003. Two years after its publication, a bibliographic review process was initiated, and the need for the guideline's updating was analysed, resulting in the development of this CPG that updates certain aspects and complements other relevant topics that were not addressed in the first edition.

Given that the update has substantially changed the initial content, and has even incorporated a new chapter, it has been decided not to highlight changes in the text. Despite this, new recommendations have been shaded to distinguish them from reviewed recommendations.

## 3.2. Working group members

The development group for the update of the CPG was composed of professionals from different fields involved in this disorder. Hence, not only psychiatrists participated in this process, but also psychologists, nurses, social workers and occupational therapists, comprising a multidisciplinary team that contributed new perspectives. Likewise, two members of the Catalan Agency for Health Technology Assessment and Research (CAHTA) also participated, providing methodological support.

The working groups that contributed to the development of the CPG were:

a) **Coordinator group**: comprised, in part, by the members who developed the previous CPG and who, led by a coordinator, carried out the organization of the CPG, the establishment of the scope and objectives, the formulation of clinical questions, as well as methodological and support aspects to aid the development group.

b) **Development group**: composed of health care professionals who were in charge of the review and synthesis of the scientific literature, as well as the development of the recommendations that had to be updated. The members of this group were divided into four subgroups that addressed the different aspects covered in the CPG: biological treatment and somatic management, psychosocial interventions, psychosocial rehabilitation and modalities of care to the community.

In the authorship and collaborations chapter the affiliation and specialty of the members of the working group (coordinator and development) is presented.

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# 3.3. Review and synthesis of the biomedical literature

A general bibliographic search was carried out for CPGs and recommendations on the management of schizophrenia and incipient psychotic disorder in the main medical and psychology databases: *Pubmed/Medline*, *The Cochrane Database of Systematic Reviews*, *The Cochrane Controlled Trials Register, The Health Technology Assessment Database, Database of Abstracts of Reviews of Effects (DARE),* Psycinfo, Psicodoc and CPG directories such as the *National Guidelines Clearinghouse, the Scottish Intercollegiate Guidelines Network* (SIGN), the *New Zealand Guidelines Group*, the *National Institute for Clinical Excellence* (NICE), the CPG INFOBASE and EBM Guidelines. The same search terms used in the previous CPG were applied (annex 7). The search period spanned from the completion of the previous CPG (2002) to July 2007.

In the bibliographic search 11 CPGs or consensus documents with recommendations for the treatment of schizophrenia were identified.[1-4,36-42] With the aim of obtaining the highest quality CPGs, the AGREE questionnaire for CPG assessment was applied to the documents identified, and the contributions of each CPG were analysed (annex 6). Finally, four CPGs were selected, serving as the basis for this update. However, other aspects of interest were examined in the other CPGs, such as specific pharmacological[40] or first episodes content.[41] The following table lists the selected CPGs:

| Selected clinical practice guidelines | Abbreviation used |
|---|---|
| Schizophrenia. Full national clinical guideline on core interventions in primary and secondary care. National Collaborating Centre for Mental Health. National Institut for Clinical Excellence (NICE). The Royal College of Psychiatrists & The British Psychological Society. London, 2003.[3] | NICE (2003) |
| McGorry P, Killackey E, Lambert T, Lambert M, Jackson H, Codyre D, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. Aust N Z J Psychiatry. 2005; 39(1-2):1-30.[1] | New Zealand (2005) |
| Practice guideline for the treatment of patients with schizophrenia (Second Edition). American Psychiatric Association; Steering Committee on Practice Guidelines. 2004.[4] | APA (2004) |
| Clinical practice guidelines. Treatment of schizophrenia. Can J Psychiatry.2005; (50) 13 Suppl 1: 7S-57S.[2] | CPG (2005) |

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It should be noted that the main recommendations of the selected CPGs were extracted and compared with recommendations from the previous CPG, enabling the addition, replacement or elimination of some of the prior recommendations. In order to facilitate the subsequent consensus work of the group, the corresponding values of the grades of recommendation of each

selected CPG and this CPG were determined, taking the scientific evidence scale employed by each one of them into account.

Additionally, with the aim of updating and expanding contents, several specific searches were performed, according to the area of intervention and some aspects that had not been addressed in the previous CPG, such as incipient psychotic disorder. These searches were conducted in the main medicine and psychology databases: *Pubmed/Medline*, *The Cochrane Database of Systematic Reviews, The Cochrane Controlled Trials Register, The Health Technology Assessment Database, Database of Abstracts of Reviews of Effects (DARE), Science Citation Index,* Psycinfo, etc., and pages of different organizations, scientific societies, etc., were reviewed. A search was conducted for potential systematic reviews of the scientific evidence (SRSE) and, in some cases, randomised clinical trials (RCT), covering the 2002-2007 period. The different searches and main strategies of each one of them can be consulted in annex 7. Furthermore, other manual searches of bibliographic references included in selected articles, or through other access channels. The bibliographic references obtained were managed using the Reference Manager program, which facilitated the detection of duplicates and the management of references in the development of the document

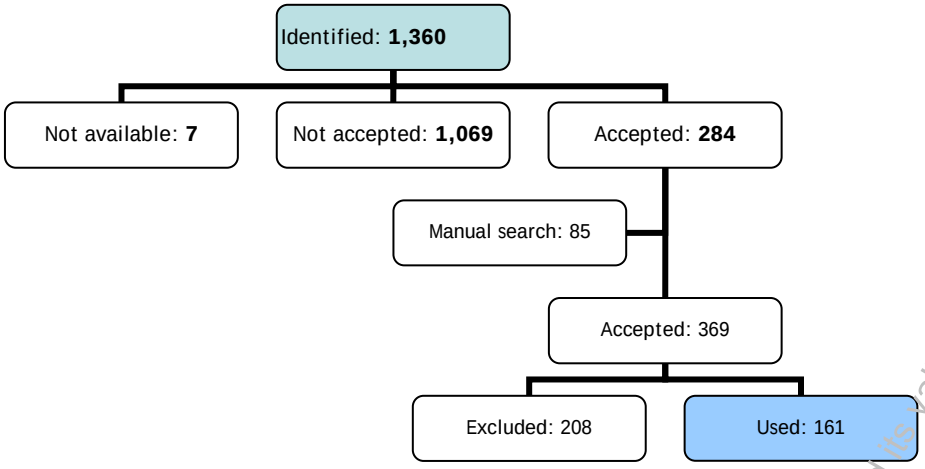
The following step was to perform a first selection of the scientific literature by reading the titles and summaries of recovered documents, which met the inclusion and exclusion criteria determined by the group (based on the clinical questions established, the study period, language, etc.). Finally, the last selection was carried out after the critical reading of the complete text of the studies included (Figure 1). In cases of greater difficulty or methodological doubts, two independent reviewers performed the selection. The information extracted from the articles and their quality assessment was synthesized in tables of scientific evidence.

The selection, review and synthesis of the biomedical literature were carried out by the four previously mentioned subgroups, according to the type or area of intervention. Likewise, each subgroup selected and reached consensus on the recommendations that were going to be formulated based on those extracted from the selected CPGs and from the scientific articles that completed the information. Annex 1 presents the scale with the levels of evidence and the classification of recommendations used in this project.

In this update, the recommendations extracted from the selected CPGs maintain the grade of recommendation, even though they do not incorporate the level of scientific evidence that is already referenced in the original CPG.

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**Figure 1. Selection process of references identified in the bibliographic search**




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## 3.4. Presentation formats

The presentation formats of the CPG update that have been agreed upon are:

- A complete version. Core document that is the result of the work carried out by the working group applying the methodology that has been mentioned in the previous section.

- A summarized version. Summary that stems from the complete version, containing the main points of interest, recommendations and algorithms of clinical practice.

- A quick version. Easy-to-use document, with the main recommendations and algorithms of clinical practice.

- A version for patients. Document aimed at people with schizophrenia and their families, friends or people they are involved with.

The CPG update will be published in electronic format (available at www.aatrm.net and www.guiasalud.es) and in paper format.

## 3.5. External review

The external review was performed by professionals from different fields and national health care settings, as well as by some representatives from schizophrenia foundations (see chapter on authorship and collaborations). All reviewers received an assessment questionnaire. The form used and a summary of the responses obtained are presented in annex 8.

Finally, the changes suggested by the reviewers were discussed in the working group for later modification, applying the external review method of *The schizophrenia patient outcomes research team* (PORT) studies. That is, recommendations were modified only if they were supported by scientific evidence, meaning opinion by itself was not considered sufficient enough reason to modify the recommendation.[43] In this sense, recent bibliography (outside the

time range selected for the initial review and synthesis of the biomedical literature) has been included, given that the relevance of the contents justified their inclusion in the CPG.

## 3.6. Performance of the pilot test

In the previous CPG, a pilot test was performed in which 22 professionals from different fields (psychologists, psychiatrists, nurses and social workers) and different community mental health centres, day hospitals and psychiatry services of general hospitals participated. In order to approve the CPG, they were delivered the document with an assessment questionnaire and a letter explaining the process to be followed to analyze both the presentation format and the feasibility of application and acceptance of recommendations. They were requested to use the CPG in their clinical practice over a period of two weeks and subsequently conduct their assessment. The suggestions obtained were incorporated into the format of algorithms and in a new pamphlet design, achieving the main objective: to improve the presentation of the CPG before its edition and publication.

Given that this CPG updates and complements specific aspects, the working group did not deem the performance of a new pilot test necessary.

## 3.7. Review and/or update planning

Once the updated CPG is published, the same review procedure described in this document will be followed: in two years, a new bibliographic search will be conducted to decide if it is necessary to update or modify the guideline. If an update is necessary, the indications of the GuiaSalud Clinical Practice Guideline Update Manual shall be followed. The updated version is expected to be available four or five years after the publication of this edition.

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# 4. General overview

## 4.1. Definition

Schizophrenia is a severe psychotic mental disorder characterized by significant disturbances of mental functioning. It has also been called "early dementia", "intrapsychic discordance" or "autistic dissociation of personality".[44]

Historically, at the end of the 19th century, the different clinical manifestations of schizophrenia were called "dementia praecox" by Morel, in France, "hebephrenia" (demential state in young people) by Hecker, in Germany, and "catatonia", referring to psychomotor disorders, by Kalhbaum. Kraepelin combined all these types into one nosological entity that he defined as "early dementia". He distinguished three clinical forms: simple or hebephrenic, catatonic or paranoid, the latter characterized by delusions.[45]

Many authors from that time period already recognized that it had less to do with dementia than it did with dissociation of psychic life, which loses its cohesiveness. It is this notion that is reflected in the concept of "schizophrenia" developed by Bleuler in 1911. [46] This process is characterized by a deficitary syndrome of dissociation and by a secondary syndrome of generation of ideas, feelings and delusional activity. The current definition was developed based on this conceptualization.

The term schizophrenia refers to a series of psychotic disorders, characterized by the presence of positive psychotic symptoms at some point of their evolution, and where negative and cognitive symptoms are associated with a variable degree of disability. Their basic manifestations consist of a mixture of characteristic signs and symptoms. Symptoms affect multiple psychological processes, such as perception (hallucinations), ideation, loss of connection with reality (delusions), thought processes (loose associations), feelings (flat affect, inappropriate affect), behaviour (catatonia, disorganization), cognition (attention, concentration), motivation and judgement. There is no symptom that, by itself, is pathognomonic of schizophrenia. These psychological and behavioural characteristics are associated with several types of impairment. The characteristic symptoms of schizophrenia have often been classified into two big categories –positive and negative symptoms (or deficits)-, to which a third category has been recently added, disorganization. Not all symptoms described are present in every patient diagnosed with schizophrenia. They are not specific, given that they also occur in other diseases. The disorder is characterized by great heterogeneity amongst different individuals and variability in each of them over time. It is also associated with increased incidence of general medical diseases and mortality, especially by suicide, which occurs in up to 10% of patients.[47]

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# 4.2. Natural history and course

The onset of schizophrenia can occur during adolescence –even during childhood– or in adulthood. It affects both sexes in a similar way. However, in males, the most frequent age of onset is at the beginning of the third decade of life, whereas in women, it is at the end of the second decade of life or beginning of the third. Generally, women are more prone present late onset schizophrenia. Onset may be acute or insidious. In the clinical course of most patients acute psychotic episodes alternate with stable phases of total or partial remission. This disorder, which is often chronic, can be characterized by three phases which overlap with no clear or absolute limits between them. These phases comprise the structure to integrate the therapeutic approaches described in this CPG.

- **Acute phase (or crisis).** During this phase, patients present severe psychotic symptoms, such as delusions and/or hallucinations, and severely disordered thinking; and, overall, are not able to properly take care of themselves. Often, negative symptoms also become more intense.

- **Stabilization phase (or postcrisis).** During this phase, the intensity of acute psychotic symptoms decreases. This phase can last six or more months after the onset of an acute episode (or crisis).

- **Stable phase (or maintenance phase).** Symptomatology may have disappeared or be relatively stable and, if persistent, is almost always less severe than in the acute phase. Some patients may be asymptomatic; others may present non-psychotic symptoms, such as tension, depression or insomnia. When negative (deficits) and/or positive (delusions, hallucinations or thought disorders) symptoms persist, they are often present in non-psychotic attenuated forms (for example, illusions instead of hallucinations or overestimated ideas rather than delusions).

Prior to the relapse of a patient who is in the stable phase, there is usually a prodromal period in which there may be non-psychotic dysphoric symptoms, attenuated forms of positive symptoms or idiosyncratic behaviours. The prodromal period may last between several days and several weeks, but may sometimes last for several months. Most longitudinal studies on schizophrenia suggest that its course is variable; in some patients there are no new episodes, in most of them there are exacerbations and remissions, and a small portion of them present a severe chronic psychotic state. Given the differences that exist in diagnostic criteria used in the studies that have been conducted, it is not possible to elaborate an exact and complete summary of the long-term evolution of schizophrenia.

Complete remission (restoration of the function that existed prior to the onset of the disorder) is not frequent in this disease. Of the patients who continue to suffer the disease, some seem to maintain a relatively stable course, whereas others present progressive worsening associated with severe disability. In the initial phase of the disease, there may be increasing negative symptoms that manifest mainly as prodromal disturbances. Subsequently, positive symptoms appear. Given that positive symptoms respond especially well to treatment, it is common for these symptoms to decrease with treatment; however, negative symptoms may persist. It has

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been suggested that negative symptoms may intensify in some patients over the course of the disease.

The course of the disease may vary depending on whether treatment is instaured in early stages and on the health care response that the patient with schizophrenia obtains early on in the course of disease. Additionally, in relation to treatment, the evolution of scientific progress (development of new drugs, genetic studies, design of new psychosocial approaches, new treatment areas, etc.) gives hope to the future of treatment of patients with schizophrenia and their families.

During the 1990s interest in the first episodes of mental disorders grew, which led to placing greater attention on the initial phases of established severe mental disorders. In the field of psychotic disorders, interest focused on disorders such as schizophrenia, bipolar disorder, and others shifted to increased interest in the first episodes of psychosis. This interest was based on the hypothesis that an initial treatment of more severe mental disorders would improve their clinical course, and, therefore, their prognosis. This idea was strengthened by the knowledge that very long periods of time would elapse between the onset of a psychotic disorder and its acknowledgement and therapeutic intervention, which would be called duration of untreated psychosis. The reduction of this period would entail the possibility of secondary prevention.

This position gradually gave way to an interest focused on the prodromal manifestations of psychotic disorders, resulting in different conceptualizations and operative definitions of these manifestations, such as prepsychosis, preschizophrenia, hypopsychosis, prodromal symptoms or mental states at risk. The recognition of populations with these clinical characteristics could facilitate early intervention. The initial methodology followed to identify the psychopathological characteristics of psychotic disorder prodromes was the retrospective study of preceding symptoms and signs. In the 90s, Häfner and collaborators developed a standardized instrument, the "Interview for the Retrospective Assessment of the Onset of Schizophrenia" (IRAOS).[48] Likewise, other authors used retrospective descriptions to characterize psychotic prodromes, based on basic symptoms, or other similar methodologies.[49,50]

Another research line focused on the clinical manifestations which preceded a relapse (relapse prodromes) in patients diagnosed with schizophrenia.[51] Yung and McGorry, based on the previous retrospective and relapse prospective studies, developed the theory that the manifestations of psychotic prodromes could be divided into eight subtypes: 1. Neurotic symptoms; 2. Mood-related symptoms; 3. Volition changes; 4. Cognitive changes; 5. Physical symptoms; 6. other symptoms; 7. Behavioural changes and 8. Attenuated (subthreshold) or isolated psychotic symptoms. The most frequently reported prodromal symptoms in retrospective studies were: reduced concentration and attention, reduced impulse and motivation, depression, sleep disorders, anxiety, social isolation, distrust/suspicion, functional deterioration and irritability.[50]

The category of attenuated (subthreshold) or isolated psychotic symptoms corresponds to experiences that are similar to psychotic features, but differ from true psychotic symptoms in terms of intensity, frequency and/or duration.[52] As can be easily assumed, not all symptoms will be present in all patients or continuously in the same individual, and there is wide variability in how they present.

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More recent works have focused on the prospective identification of prodromes, once their clinical characteristics have been identified, to enable both research and intervention. However, it must be taken into account that prodromal manifestations are not specific, and can be caused by different clinical conditions, such as major depression, substance abuse, somatic diseases, or a psychotic disorder.[52] Amongst non-specific prodromes, the following should be highlighted: changes in the sense of "I", feelings of tiredness, lethargy, lack of motivation, depression, anxiety, preferred isolation, eccentricity and difficulty studying or at work. [53] More specific prodromal manifestations include: unusual ideas or beliefs, distrust/suspicion, grandiosity, sensation that the appearance of things has changed and difficulty thinking clearly. In young people the first symptoms are social withdrawal, anxiety and worry. Also, attenuated or isolated psychotic manifestations are not necessarily deterministic of a true psychotic disorder.

The concepts of at risk mental states (ARMS) and high and ultra high risk mental states (HRMS/UHR) have been introduced to describe these populations.[50] High risk populations are characterized by the presence of initial psychotic symptoms. Furthermore, three high risk subtypes have been established: 1. Presence of attenuated (subthreshold) psychotic symptoms; 2. History of brief and limited psychotic symptoms, and 3. Positive family history of psychosis and persistent low functional level. These criteria have been tested in different studies to confirm their validity[54] and to assess in a detailed manner threshold and subthreshold psychotic phenomena, as well as other signs and symptoms that appear in psychotic prodromes, including negative, dissociative and so-called "basic" symptoms.

Hence, when considering the natural history and course of schizophrenia, one cannot ignore all the research conducted in the past few decades which establishes a sequence from the prodromal phase until the establishment of schizophrenia and posterior evolution. In this sequence two big moments are considered: the first, which includes the early phases of psychosis, and the second, which encompasses the different phases of schizophrenia. This classification enables the subdivision of these moments into the following phases:

a. **Early phases of psychosis**, which include the high risk mental state or prodromal phase, the first psychotic episode phase and the recovery phase and critical period.

b. **Phases of schizophrenia**, which include the acute phase, the stabilization phase and the stable phase.

# 4.3. Epidemiology

The prevalence of schizophrenia over the course of a lifetime is variable, but results from the majority of studies establish an overall mean rate of less than 1 case per 100 inhabitants.[55] The disorder seems to be uniformly distributed throughout the world, even though there may still be some pockets with high or low prevalence.[47]

In regards to indidence, the *First episodes of schizophrenia in Cantabria* study reported that the incidence of schizophrenia in the 15-54 years risk age was 1.9/10,000 inhabitants per year, and that there were no statistically significant differences between sexes.[56] Mean age of disease onset is 26 years, and it is significantly higher in women than in men.

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Given that the onset of schizophrenia usually occurs in early stages of life and is often chronic, the costs derived from this disorder are considerable. In the United States, according to the review of studies conducted by the American Psychiatric Association (APA) schizophrenia accounted for 2.5% of the total direct costs of health care; that is, 16,000-19,000 million dollars in 1990. Indirect costs derived from factors such as the loss of productivity and the burden on the family were estimated to be approximately 46,000 million dollars. Furthermore, unemployment rates can reach 70-80% in severe cases and it is calculated that schizophrenic patients constitute 10% of the population in permanent disability.[47]

A review of studies examined data regarding the frequency of this disorder. The incidence of schizophrenia, its prevalence and the first psychotic episodes are successively described below.[57]

**A. Incidence of schizophrenia**. The international multicenter study performed by the World Health Organization (WHO) to determine the ratios of incidence in eight locations of seven countries and the publication of the preliminary report showed that the incidence of schizophrenia ranged from 7 to 14 for every 100,000 inhabitants per year. The authors concluded that the results supported the notion that schizophrenia occurs with comparable frequency in different populations.[58, 59]

However, a review of 158 studies performed between 1965 and 2001 in 32 different countries enabled the establishment of a mean annual incidence of 15.2 per 100,000 inhabitants per year, with higher rates ranging from 7.7 to 43.0 per 100,000 inhabitants per year in developed countries. Two independent systematic reviews showed differences in incidence depending on the patient's sex, with significantly higher rates for males (male-female ratio 1.42/1.00). There were also higher incidences in urban areas versus rural areas, migratory status and birth month, with higher incidences in winter months.[60-62]

Later studies demonstrated heterogeneity in the causes of incidence of schizophrenia and other psychotic syndromes based on the AESOP study performed in three centres in the United Kingdom with a population of 1,600,000 inhabitants. Schizophrenia presented higher incidence in males (2.3/1.0); psychotic disorders were more frequent in black and minority ethnic groups, and differences related to age and geographical area were also reported. The authors conclude that there are independent and significant variations in schizophrenia and other psychoses in terms of gender, age, ethnic group and geographical area.[63]

**B. Prevalence of schizophrenia**. A SRSE of 188 studies published between 1965 and 2002 on the prevalence of schizophrenia in 46 countries reported that prevalence ranges from 4 to 7/1,000, depending on the type of estimation employed, although there were substantial differences between different geographical areas. The same review found raised prevalence in migrant populations.[64]

**C. Frequency of first psychotic episodes**. A study performed in rural Ireland on first psychotic episodes between 1995 and 2003, focused on the incidence of schizophrenia, bipolar disorder, mania and major depressive disorder with psychotic episodes, yielded an annual incidence of all forms of psychosis of 31.6/100,000 inhabitants per year, with higher values in males. For schizophrenia, incidence was 7.0; for schizoaffective disorders, 2.0; and for

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schizophreniform disorder, 1.8. Affective psychoses presented an incidence of 11.6/100,00 inhabitants per year, and for brief psychotic disorder, delusional disorder and other psychotic disorders, incidence was 9.3/100,000 inhabitants per year. [65] These data contrast with the results obtained in the study performed in Cantabria that was described at the beginning of this chapter.[56]

Lastly, mortality in schizophrenia should be considered from an epidemiological perspective, given that mortality in schizophrenic patients is consistently and significantly higher, in a two to three fold higher proportion, than that of the general population. The causes of this raised mortality should be sought in different factors such as suicides and violent deaths, non-cardiac natural deaths, cardiovascular diseases and use of antipsychotics and polypharmacy.[66]

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# 5. General overview of the management of schizophrenia and incipient psychotic disorder

In order to establish the general guidelines for the management of schizophrenia and incipient psychotic disorder, diagnosis and the pertinent assessment are firstly considered. Secondly, the general aspects of psychiatric management and its components, such as the therapeutic alliance, monitoring, care provision and selection of the scope of treatment, are developed.

## 5.1. Diagnosis and assessment

### 5.1.1. Diagnosis

An initial, complete diagnostic study should be performed on every patient, including:

- Psychiatric and general medical history.
- Psychosocial history and family psychiatric history.
- Examination of the mental state.
- Physical assessment that includes a neurological examination.
- The necessary complementary examinations to rule out disorders that resemble an incipient psychotic disorder or a schizophrenic disorder, determine the presence of associated disorders, establish baseline characteristics for the administration of antipsychotic drugs and guide habitual medical care if necessary should be performed. Patients who abuse alcohol or other drugs or who present alcohol- or drug-induced psychosis should receive specific treatment. The risk of inflicting injury on oneself or on others and the presence of hallucinations issuing orders should be assessed and proper precautions taken whenever the safety of the patient or others is uncertain .[47]

In order to diagnose mental disorders in our setting, the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR, and the tenth revision of the International Classification of Diseases' (ICD-10) Classification of Mental and Behavioural Disorders are employed.

#### *DSM-IV-TR Classification criteria for schizophrenia*

The DSM-IV-TR classification establishes the following criteria:[67]

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**Criterion A. Characteristic symptoms**: two (or more) of the following[a], each present for a significant portion of time during a 1-month period (or less if successfully treated): 1) delusions; 2) hallucinations; 3) disorganized speech, incoherence; 4) catatonic or grossly disorganized behaviour; 5) negative symptoms, for example, affective flattening, alogia, or avolition.

**Criterion B. Social/occupational dysfunction**: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

**Criterion C. Duration**: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

**Criterion D. Schizoaffective and mood disorder exclusion:** Schizoaffective Disorder and Mood Disorder with Psychotic Features have been ruled out because either:

a. No major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms, or

b. If mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

**Criterion E. Substance/general medical condition exclusion:** The disorder is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

**Criterion F. Relationship to a pervasive developmental disorder:** If there is a history of autistic disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

- **Classification of longitudinal course according to the DSM-IV-TR:** determined by whether the course is continuous or episodic and by the presence of psychotic symptoms.

[a] Only one symptom from Criterion A is required if delusions are strange, consist of a voice that continuously comments on the individual's thoughts or behavior, or if two or more voices talk to each other.

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- **Episodic With Interepisode Residual Symptoms** (episodes are defined by the re-emergence of prominent psychotic symptoms); also specify if: With Prominent Negative Symptoms.
- Episodic With No Interepisode Residual Symptoms.
- Continuous (prominent psychotic symptoms are present throughout the period of observation); *also specify if:* With Prominent Negative Symptoms.
- Single Episode In Partial Remission; *also specify if:* With Prominent Negative Symptoms.
- Single Episode In Full Remission.
- Other or Unspecified Pattern.
- Less than one year since the onset of the first active-phase symptoms.

- **Schizophrenia subtypes according to the DSM-IV-TR:** defined according to the type of presentation seen during the most recent episode and can be therefore modified over time.
  - Paranoid type, in which preoccupation with delusions or auditive hallucinations are a prominent characteristic.
  - Disorganized type, in which disorganized speech and behaviour and flattened or inappropriate affect are prominent.
  - Catatonic type, in which characteristic motor symptoms stand out.
  - Undifferentiated type, which is an unspecific category, used when symptoms are present but are not sufficiently formed or specific enough to classify in the other subtypes.
  - Residual type, in which there are no positive symptoms but there are other remaining signs of disturbance (for example, negative symptoms or attenuated positive symptoms).

Although the prognosis and therapeutic implications of these subtypes are variable, the disorganized type tends to present the most impairment and the paranoid type the least.[47]

## *ICD-10 Schizophrenia classification criteria*

The ICD-10, like the DSM-IV-TR, indicates that there are no patagnomonic symptoms, but certain associated psychopathological phenomena that are especially significant for the diagnosis of schizophrenia. These phenomena are:[68]

1) Thought echo, thought insertion or withdrawal, and thought broadcasting.

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2) Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception.

3) persistent delusions of other kinds that are culturally inappropriate and completely impossible, such as religious or political identity, or superhuman powers and abilities (e.g. being able to control the weather, or being in communication with aliens from another world).

4) Persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without clear affective content, or by persistent over-valued ideas, or when occurring every day for weeks or months on end.

5) Breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms.

6) Catatonic behaviour, such as restlessness, posturing, or waxy flexibility, negativism, mutism, and stupor.

7) "Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance; it must be clear that these are not due to depression or to neuroleptic medication.

8) A significant and consistent change in the overall quality of some aspects of personal behaviour, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.

- **ICD-10 Diagnostic guidelines:** The normal requirement for a diagnosis of schizophrenia is that a minimum of one very clear symptom (and usually two or more if less clear-cut) belonging to any one of the groups listed as (1) to (5) above, or symptoms from at least two of the groups referred to as (5) to (8), should have been clearly present for most of the time during a period of 1 month or more. Conditions meeting such symptomatic requirements but of duration less than 1 month (whether treated or not) should be diagnosed in the first instance as acute schizophrenia-like psychotic disorder and are classified as schizophrenia if the symptoms persist for longer periods. The first symptom on the list above is only applied to simple schizophrenia and requires a minimum of one year duration.

- **ICD-10 Course classification:** continuous; episodic with progressive defect; episodic with stable deficit; episodic with complete remissions; incomplete remission; other; course uncertain, period of observation too short.

- **ICD-10 Course subtypes:** paranoid schizophrenia, hebephrenic schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, postschizophrenic depression, residual schizophrenia, simple schizophrenia, other schizophrenia, and unspecified schizophrenia.

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### *Classification and grouping of psychotic symptoms*

In addition to the classifications described, symptoms are also frequently classified and group into three categories: positive symptoms (delusions and hallucinations), negative symptoms (affective flattening, alogia, avolition/apathy and attention difficulties) and "disorganization" symptoms (which include disorganized speech, thought disorder, disorganized behaviour and attention deficit). Positive symptoms are the most relevant features in the acute phases of these disorders, whereas negative symptoms and cognitive impairment are the deterministic symptoms in social and occupational dysfunction. Negative symptoms and cognitive impairment are extremely important, clinically speaking and in terms of rehabilitation, given that they affect the patient's ability to work, relationships with others and emotional ties; that is, the patient's capacity to develop a life in normal circumstances.

## 5.1.2. Differential diagnosis

The following aspects of the differential diagnosis are considered:[28,69]

Differential diagnosis for schizophrenia should be performed to distinguish it from other psychic, organic and/or toxic clinical pictures.

In terms of psychic clinical pictures, it should be distinguished from schizoaffective disorder; mood disorder with psychotic features; schizophreniform disorder; brief psychotic disorder; delusional disorder; pervasive developmental disorder; schizotypal, schizoid or paranoid personality disorders; borderline personality disorder; dissociative hysterical psychosis, and puerperal psychoses.

Differential diagnosis relating to organic medical conditions should be carried out with brain tumours (frontal, temporal); temporal lobe disease; epilepsy; viral encephalopathy-encephalitis; brain abscesses; postencephalitis; thyrotoxicosis; acute intermittent porphyria; and psychotic disorder due to delirium or dementia.

Finally, as far as substance abuse clinical pictures, the following should be taken into account: chronic consumption of cannabis, amphetamines, LSD, digital, steroids, alcoholic hallucinosis, and others.

## 5.1.3. Clinical condition and continued assessment

It is important to assess, at the very least, these four critical circumstances: risk of inflicting injuries on self or on others; access to means to carry out suicidal or homicidal objectives; presence of hallucinations that issue orders; and self-care abilities.[47]

## 5.1.4. Comorbidity with other mental disorders

The symptoms of other mental disorders, especially depression, but also obsessive and compulsive symptoms, somatic preoccupations, dissociative symptoms and other anxiety or mood symptoms, can be present in schizophrenia. Whether they are symptoms or disorders

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associated with this disease, these manifestations can significantly worsen prognosis and often require specific care and therapeutic planning.

## 5.1.5. Comorbidity with substance- and alcohol-use related disorders

The use and dependency of alcohol and other substances should be assessed. Together with general medical conditions, the most frequently associated disorder seems to be substance use, especially the consumption of alcohol and stimulants, such as cocaine and amphetamines; other frequently used substances are nicotine, cannabis, phencyclidine and LSD.[47]

## 5.1.6. Comorbidity with other diseases and past medical history

The general state, along with cardiac function, medications and other treatments the patient is receiving, should be assessed. The most frequent concomitant clinical pictures and risk factors that should be assessed and treated are: obesity, HIV risk behaviours, tobacco smoking and hypertension.[4]

Based on the specific circumstances of each case, the assessment of medical complications or substance use, diabetes and cardiovascular problems should be considered. If necessary, the general practitioner should be consulted.

In a patient who presents a first crisis, laboratory tests should be requested: basic analyses to perform the differential diagnosis with other disorders that may appear to be schizophrenia, analyses to rule out the presence of toxic substances, general biochemistry, complete haemogram and urine analysis.[28]

Depending on the circumstances of each patient, the following complementary tests should also be considered: pregnancy test, electrocardiogram, computerized tomography or magnetic resonance imaging, neuropsychological studies and general psychometry.

## 5.1.7. Psychiatric history

It is important to assess at least four of these circumstances: prior episodes, danger to the patient or other people, response to prior treatments and prior use of substances.

## 5.1.8. Psychosocial history and family psychiatric history

Based on expert consensus, it is important to record the frequency and quality of the social relationships maintained by the patient throughout his/her life, as well as the current significant relationships. The assessment of family structure and relationship patterns is important to establish a therapeutic plan. It is essential to assess the factors related with social and family relationships that may represent elements of stress or vulnerability, as well as those which may serve as protection factors.[70]

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Information on premorbid function should also be retrieved, including employment history, the highest occupational and/or educational level attained, occupational functioning, significant relationships in the work place, and specific difficulties.

### 5.1.9. Annual general check-ups

According to McEvoy and collaborators, the following recommendations apply to all patients: medical history and physical exploration that includes size and weight, blood pressure and complete hemogram.[28]

Based on the circumstances of each patient, the following tests and examinations are recommended: general biochemistry, electrocardiogram, dental check-up, pelvic examination/Pap smear, rule out the presence of toxic substances, tuberculin test, lipid profile, mammography, prostate specific antigen and blood test to rule out hepatitis and detect HIV.

Coordination with the primary care physician during examinations is important given that his/her role is key in the detection and quick referral of relapses, as well as in the follow-up of the general health state.

## 5.2. Psychiatric management

### 5.2.1. General overview

In the development of a treatment plan for a patient with schizophrenia or incipient psychotic disorder cross-sectional issues, such as the current clinical condition, and longitudinal issues, such as clinical course and frequency, severity, treatment and consequences of previous episodes, should be taken into account.

Whenever possible, patient and family should be involved in the treatment plan in active collaboration by means of an integrated approach of appropriate pharmacological and psychosocial interventions.

The general objectives are the improvement of the clinical course, as well as the reduction of the frequency, severity and psychosocial consequences of the episodes. A further aim will be to optimize psychosocial functioning between episodes. Specific objectives will depend on the phase of the disorder and the patient's specific characteristics.

### 5.2.2. Components of psychiatric management

Treatment of the patient with schizophrenia or incipient psychotic disorder is facilitated by overall knowledge of the patient, which includes the assessment of his/her objective and subjective needs; objectives; intrapsychic conflicts and defences; coping styles; personal capacities; and biological, interpersonal, social and cultural factors which affect the patient's adaptation.

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Professionals who are involved in the care of the patient must work to develop an **integrated and coordinated treatment plan** given that they several professionals and services frequently take part in care, both simultaneously and successively.

The main elements that comprise the therapeutic plan are related with its influence on the evolution of the disease and treatment efficacy. It also includes issues that are present in the treatment of all psychiatric diseases.[4]

- **Symptom assessment and establishment of a diagnosis**
  For treatment to be effective and appropriate, precise and pertinent diagnostic and clinical evaluations should be performed. In the case of schizophrenia, diagnosis has significant consequences on the short and long term planning of treatment.

- **Development of a treatment plan**
  Once the diagnosis and clinical and psychosocial circumstances of the patient have been assessed, a treatment plan should be formulated and applied. This process entails the selection of therapeutic modalities, the type of treatment or specific treatments and their context. Depending on the severity of the clinical situation and due to the fact that sometimes the information on the patient's history and the clinical assessment are progressively obtained, it is possible that the process may have to be repeated and modified for as long as the patient-physician relationship lasts.

- **Establishment of the therapeutic alliance and stimulation of treatment compliance**
  It is essential for the psychiatrist who treats the patient to establish and maintain a supportive therapeutic alliance, from which treatment will be carried out. This alliance provides very important information to the psychiatrist and increases the patient's trust and desire to collaborate with treatment.

- **Education and therapy for the patient and family**
  Working with patients so that they learn to recognize early symptoms of relapse prevents a complete exacerbation of the disease. Informing the family on disease characteristics and providing them with strategies to cope with the disease can reduce relapses and significantly increase the patient's quality of life.

- **Treatment of comorbid diseases**
  There are several psychiatric, social and medical disorders that are much more frequent in people with schizophrenia than in the general population. The therapeutic team should assess this disease periodically. Some frequent comorbidities, such as major depression, substance-induced disorders and post-traumatic stress disorder, can often be detected by performing clinical examinations and talking to the patient and close friends and family, as well as by carrying out longitudinal observation of the patient's behavioural patterns.

- **Social circumstances and functioning of the patient**
  The patient's social circumstances and functioning can greatly influence treatment compliance and the response to treatment. Living conditions, the family's participation, the source and amount of income, the legal situation and relationships with close people can be

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both stressful and protective situations. Hence, they are aspects that psychiatry professionals could explore periodically.

- **Integration of treatments administered by different physicians**
  Many patients with schizophrenia receive several treatments that are often administered by different physicians. This situation could potentially lead to the fragmentation of therapeutic efforts for those patients who normally have difficulties planning and organizing.

- **Treatment documentation**
  Most people with schizophrenia are treated by many different physicians over the course of their disease. This is a result of changes in the treatment setting (hospital, out-hospital settings, assertive community treatment, etc.), the availability of programs, their place of residence and health care staff. Given that in order to plan treatment it is essential to have detailed knowledge of the patient's treatment history and the treatments that he/she is currently receiving, it is crucial to maintain good documentation.

| | |
|---|---|
| **A** | A therapeutic alliance enables the psychiatrist to acquire essential information regarding the patient and enables the patient to gain trust in the psychiatrist and the desire to cooperate in treatment. The identification of the patient's objectives and aspirations and relating them with results promotes treatment adherence, together with the therapeutic relationship. [4] |

# 5.3. Development of the therapeutic plan

## 5.3.1. Design of the therapeutic plan

Firstly, and if possible, the short-, mid- and long-term objectives of the therapeutic plan should be established. Secondly, the type of treatment or intervention to be carried out should be taken into account with the participation of the patient and his/her family. The different alternatives of pharmacological treatment (antipsychotics and other coadjuvant drugs) and psychosocial interventions (psychological and relating to psychosocial rehabilitation) are then described. Thirdly, the setting where treatment will be applied will be determined based on the clinical state, the phase of the disorder and the treatment chosen.

In order to reach treatment objectives, it is recommended to assess positive and negative symptomatology, depression, suicidal ideation and behaviour, substance abuse, medical comorbidities, post-traumatic stress disorder and an array of potential community adjustment problems, including being homeless, isolation, unemployment, victimization and involvement in the criminal justice system.[4]

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## 5.3.2. Choosing the treatment setting

Patients should be seen in the least restrictive setting possible, where safety is ensured and an effective treatment can be applied. In this sense, patients with schizophrenia should be seen in several settings. The selection of the setting for treatment should be based on the patient's clinical situation, his/her preferences and those of his/her family, the demands of the treatment plan and the characteristics of available treatment settings. Different settings differ in terms of the availability of different therapeutic possibilities, degree of support, limitation of and protection from harmful behaviour, working hours, capacity to manage psychotic or severely agitated patients, and general setting and philosophy of treatment.[47]

- **Factors to consider when choosing the intervention setting**

Some of the criteria that should be taken into account when choosing the most appropriate intervention setting at each moment are:

- The patient's psychopathological state
- Risk of aggression to self or others
- Need for hospitalization
- Intervention modality or required interventions
- Autonomy and capacity for self-care
- Family support
- Access to support and social resources in the community
- Patient and family preferences

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# 6. Types and scopes of intervention

The approach to schizophrenia and early phases of psychotic disorder demands a careful selection from the different types of interventions available, their proper articulation, as well as the most appropriate scope of intervention.

To address this issue, studies such as Falloon's, aimed at the implementation of treatments integrated with scientific evidence, have been developed. [71] According to this author, any person with a schizophrenic disorder should receive a combination of optimum antipsychotic treatment, educational strategies aimed at the patient and his/her environment, cognitive behavioural strategies to improve occupational and social objectives, reduction of residual symptoms and assertive home-based care.

In the following section we present the analysis of different types of intervention and a study on the different care settings offered in the community.

## 6.1. Pharmacological intervention

Pharmacological treatments are usually an essential element of treatment in patients with schizophrenia or initial psychotic episodes. Drugs are used to treat acute episodes, to prevent future episodes and to improve symptoms in between episodes. Antipsychotic drugs are the main pharmacological treatment for these patients. However, other drugs, such as mood stabilizers and other coadjuvant medications, are also useful in certain patient subgroups.[2-4,72]

### 6.1.1. Antipsychotic drugs

The main medications for the treatment of schizophrenia and other psychotic disorders are antipsychotic drugs, which were introduced into clinical practice during the 1950s. Due to their characteristics, effects on psychotic symptoms and side effect profiles, they have been classified into two large groups: first-generation or conventional antipsychotics, and second-generation or atypical antipsychotics. The analysis of both groups, which is presented below, has acknowledged the considerations on pharmacological treatments included in the different clinical practice guidelines examined, as well as those that appear in the Therapeutic Prescription Guideline (TPG) with information regarding authorized drugs in Spain, the Spanish adaptation of the British National Formulary, published by the Spanish Drug and Health Product Agency (2006)[b]. The TPG has been especially acknowledged in terms of the dosage of the different drugs assessed, both in the elaboration of the text and in the different prescription and comparative tables developed. In this sense, and with regard to the recommendation regarding doses over the indicated high limit, it is understood that "unless otherwise specified,

[b] Possible updates appearing on the oficial website in 2008 have been taken into account.

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the doses indicated are those that have been authorized; in other words, higher doses are not authorized". [73]

## *A) First generation (or conventional) antipsychotics*

First generation antipsychotics encompass a series of pharmaceutical specialities that are characterized by treating psychotic symptoms. The following first generation antipsychotics are currently authorized in Spain: chlorpromazine, clotiapine, haloperidol, levomepromazine, perphenazine, periciazine, pimozide, sulpiride, thioproperazine, trifluoperazine and zuclopenthixol.

These drugs are classified into three groups based on their antipsychotic potency: a) high potency (e.g., haloperidol); b) moderate potency (e.g., perphenazine); c) low potency (e.g., chlorpromazine).

They are effective at reducing most positive symptoms (hallucinations, delusions, odd behaviour), and, to a lesser degree, negative symptoms (apathy, affective flattening, alogia, avolition), when compared to relatively ineffective drugs.

Given that these drugs have a very high safety therapeutic margin, overdosing is rarely fatal if there are no pre-existing medical problems or simultaneous consumption of alcohol or other drugs. In case of overdosing, respiratory depression and hypotension present the highest risk.

Administration can be oral, fast acting intramuscular or long acting depot; the short acting intramuscular preparation achieves maximum concentration faster. Depot medications are especially useful in the maintenance phase (table 3, annex 2).

The effective dose of an antipsychotic drug is closely linked to its affinity for dopamine receptors (especially $D_2$ receptors) and its tendency to cause extrapyramidal side effects.

High potency drugs have a greater affinity for dopamine receptors than low potency drugs do, and require much lower doses. High potency drugs are prescribed more frequently than low dose drugs (even though they have a higher tendency to produce extrapyramidal side effects), and are administered more safely via intramuscular route as they rarely cause hypotension.[74] An adequate dose can be obtained in two days. It has been demonstrated that high doses of high potency antipsychotics are not more effective nor have a faster action than moderate doses and are associated with a higher incidence of side effects. [74]

Low potency drugs produce sedation and orthostatic hypotension and the dose should be gradually increased. They can cause a wide array of side effects, many of them a consequence of the pharmacological effects on neurotransmitter systems in regions other than where the medication is intended to exercise its therapeutic effects.

In the section below there is a brief description of each first generation antipsychotic drug, in conformity with the characteristics and uses as established in the TPG. Posology guidelines are presented in table 4, annex 2. Likewise, a comparative table has been developed for standard dosage intervals for adults based on the recommendations of the TPG[73], as well as a comparative table of standard dosage intervals for adults according to the APA's[4] and the

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Canadian Psychiatric Association's (CPG) CPGs, [2] those recommended by the World Federation of Societies of Biological Psychiatry (WFSBP) [75,76] and PORT[40], and, finally, those from two reference publications in the Spanish setting: RTM-III[77] and Chinchilla[78] (table 5, annex 2).

- **Chlorpromazine**

It is also indicated for mania, as brief complementary treatment of severe anxiety, psychomotor agitation, restlessness and violent or dangerously impulsive behaviour.

The usual maintenance oral dose is 75-300 mg/day depending on the response obtained, with a starting dose of 25 mg, three times a day, or 75 mg at night. The treatment of psychosis requires up to 1 g/day.

In deep intramuscular injection, dose ranges from 25-50mg every 6-8 hours. This administration route is recommended for acute symptom relief.

- **Clotiapine**

It is indicated for schizophrenia, acute and chronic psychosis, mania and insomnia in psychotic patients.

It is administered orally, with a starting dose of 120-160 mg at bed time. The maximum dose is 360 mg/day.

For treatment of insomnia, the dose is 20-60 mg taken at bed time. In this case, the maximum dose is 360 mg/day.

- **Haloperidol**

It is indicated for mania, as brief complementary treatment of severe anxiety, psychomotor agitation, restlessness and violent or dangerously impulsive behaviour.

Aside from the characteristic precautions and contraindications of conventional antipsychotics, it can also cause subarachnoid haemorrhaging and metabolic disorders such as hypopotasemia, hypocalcemia or hypomagnesemia.

The most frequent side effects are strange pigmentation and photosensitivity reactions. Its extrapyramidal effects include dystonia and akathisia, especially in patients with thyrotoxicosis, hypoglycemia and inadequate secretion of the antidiuretic hormone, and, rarely, weight loss. It presents less sedative and antimuscarinic or hypotensive effects than other conventional antipsychotics.

It is administered in oral, intramuscular or intravenous form. The starting oral dose is 1.5-3 mg, 2 to 3 times daily, if the patient has a severe or resistant disorder. In refractory schizophrenia up to 30 mg/day may be required.

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The maintenance dose should be adjusted to the lowest effective dose, 5-10 mg/day, depending on the response obtained. In elderly or weakened people, the initial dose should be half of an adult dose.

The starting dose for intramuscular or intravenous injection is 2-10mg, taken every 4-8 hours depending on the response obtained, with a maximum daily dose of 18 mg. Patients with severe disorders sometimes require a starting dose of up to 18 mg.

- **Levomepromazine**

Caution should be exercised with those patients who receive high initial doses. It is recommended that these patients remain in a face up supine position.

Elderly people have a higher risk of suffering postural hypotension, so this drug is not recommended in outpatients over the age of 50, unless the risk of hypotensive reaction has been assessed.

One of the most important side effects is an increased sedimentation rate.

It is administered orally, with a starting dose of 25-50 mg/day taken in divided doses. Dose can be increased based on the patient's needs. In bedridden patients, the starting dose is 100-20 mg/day, generally taken in three doses. Dosage can be increased, if necessary, up to 1 g/day.

- **Perphenazine**

It is indicated for mania, as brief complementary treatment of severe anxiety, psychomotor agitation, restlessness and violent or dangerously impulsive behaviour.

Aside from the characteristic precautions and contraindications of conventional antipsychotics, it can also cause agitation and restlessness in elderly people.

It has a less sedative effect. It produces extrapyramidal side effects, especially dystonia, that are more frequent at higher doses. It may rarely cause systemic lupus erythematous.

It is administered orally, with a starting dose of 4 mg, 3 times daily, adjusted according to the response obtained. The maximum dose is 24 mg/day.

- **Periciazine**

It has a more sedative effect. There are side effects at the beginning of treatment, such as hypotension, and also respiratory depression.

It is administered orally, with a starting dose of 75 mg/day, taken in divided doses; dose should be increased each week by 25 mg phases, according to the response obtained. The normal daily maximum dose is 300 mg/day.

It is also used as brief complementary treatment for severe anxiety, psychomotor agitation and violent or dangerously impulsive behaviour. In these cases the initial recommended dosage is

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15-30 mg/day, taken in two separate doses, taking the higher doses at bed time and adjusting dosage according to the response obtained.

- **Pimozide**

It is recommended to perform an ECG before initiating treatment and every year during follow-up. If the QT interval is prolonged, treatment should be reviewed and dosage discontinued or reduced under careful surveillance.

This drug should not be administered with other antipsychotics, not even those that are long acting, tricyclic antidepressants or drugs that prolong the QT interval, such as certain antipaludics, antiarrhythmics and some antihistaminics, nor with any other drugs that cause electrolyte imbalances (especially diuretics).

It is contraindicated in people with a past medical history of arrhythmia or congenital prolonged QT.

The most frequent side effects are severe arrhythmias, glycosuria, and sometimes hyponatremia. It has a less sedative effect.

The recommended starting dosage is 2mg/day, which should be increased at intervals of no less than a week apart and at 2 to 4 mg increments until satisfactory response is obtained. Normal dosage range is 2-20 mg/day.

For the treatment of monosymptomatic hypochondriac psychosis and paranoid psychosis, the recommended starting dose is 4 mg/day, which should be increased at intervals of no less than a week apart and at 2 to 4 mg increments, according to the response obtained. Dose should not exceed 16 mg/day.

- **Sulpiride**

Caution should be exercised in the administration of this drug in patients who are excited, agitated or aggressive, given that low doses can aggravate symptoms.

It is contraindicated in people diagnosed with porphyria.

The recommended dose range is 200-400 mg/day, two times daily. Maximum dose is 800 mg/day if there are mostly negative symptoms and 2.4 g/day if there are mostly positive symptoms.

- **Thioproperazine:**

It is indicated for patients with schizophrenia, anxiety, delirium and mania.

The most frequent side effects are pancytopenia, thrombocytopenia, hyperthermia and anorexia.

It is administered orally and the therapeutic dose range is 30-40 mg/day, taken in 3-4 doses.

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- **Trifluoperazine:**

It is indicated as brief complementary treatment of psychomotor agitation, restlessness and violent or dangerously impulsive behaviour.

The most frequent side effects at doses higher than 6 mg/day are pancytopenia, thrombocytopenia, hyperthermia and anorexia.

The starting dose is 5 mg, twice daily, or 10 mg once daily in a modified release form; dose should be increased by 5 mg at one week, and thereafter at three day intervals, according to the response obtained.

- **Zuclopenthixol acetate:**

This drug is indicated for brief treatment of acute psychosis, mania or exacerbations of chronic psychosis.

It is contraindicated in patients diagnosed with porphyria.

If administration is intramuscular, the recommended mean dose is 50-150 mg in one deep injection into the gluteus maximus muscle or into the external side of the thigh.

It is recommended to repeat the injection, if necessary, after 2 or 3 days (another dose may be necessary 1-2 days after the first injection). The maximum accumulative dose is 400 mg per cycle, and the number of injections should not exceed four. Treatment should not last longer than two weeks. If maintenance treatment is required, the patient should be switched to an oral antipsychotic to be taken 2-3 days after the last injection or to a longer acting antipsychotic injection (depot) that is administered at the same time together with the last injection of zuclopenthixol acetate.

- **Zuclopenthixol dihydrochloride:**

It is indicated in schizophrenia and other psychoses, especially those associated with agitation, aggressiveness or hostility.

It is contraindicated in patients diagnosed with porphyria and in patients who present apathy or withdrawal states.

The most frequent side effects are pollakiuria or urinary incontinence and weight loss (less common than weight gain).

This drug is administered orally, with a starting dose of 20-30 mg/day, in divided doses. Dose should be increased to a maximum of 150 mg/day, if deemed necessary. The standard maintenance dose range is 20 to 50 mg/day.

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## *Side effects of first generation (or conventional) antipsychotics*

Several side effects as presented by the APA's CPG[4] are individually described below:[4]

**a) Sedation**

Sedation is a very common side effect of first generation antipsychotics. This effect may be related to the antagonist effects of these drugs on histamine, adrenergic and dopamine receptors.

Sedation is more pronounced in the early phases of treatment because the continuous administration of these drugs increases patient tolerance to sedative effects. In the case of agitated patients, it is possible that the sedative effects of these drugs at the beginning of treatment may present a therapeutic advantage. Persistent sedation, such as day drowsiness and sleeping for hours, can interfere with social, recreational and occupational function. Reducing the daily dose, administering one dose at night instead of several doses throughout the day or using a less sedative antipsychotic drug may be effective at reducing the intensity of sedation.

**b) Neurological effects. Extrapyramidal side effects.**

The neurological side effects are: acute extrapyramidal side effects, such as drug-induced Parkinsonism, dystonia and akathisia; chronic extrapyramidal side effects, such as tardive dyskinesia and dystonia, and the neuroleptic malignant syndrome.

Acute extrapyramidal side effects are signs and symptoms that appear within the first few days and weeks of antipsychotic medication use, are dependent on dose and reversible if dose is reduced or administration is completely discontinued.

Chronic extrapyramidal side effects are signs and symptoms that appear within months or years of antipsychotic medication use, are not so clearly dependant ton dose and may persist after medication discontinuation.

Over 60% of patients who receive intensive treatment with a first generation antipsychotic present some type of clinically significant extrapyramidal side effect.[79-81]

**Drug-induced Parkinsonism** is characterized by the presence of symptoms mimicking idiopathic Parkinson's disease (rigidity, tremor, akinesia and bradykinesia) and is the most frequent presentation of extrapyramidal side effects. These symptoms appear within the first few days and weeks of antipsychotic medication use and are dose-dependant.

Akinesia or bradykinesia are characteristic symptoms of drug-induced Parkinsonism that affects both motor and cognitive function.

In patients with akinesia, depressive symptoms may also be observed; it is the so-called "akinetic depression".

**Acute dystonia** is characterized by spastic contraction of isolated muscle groups. Dystonic reactions occur in 10% of patients who initiate treatment.

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Risk factors include young age, male gender, use of high potency drugs, high doses and intramuscular administration. It frequently occurs after the first doses of medication and in 90% of cases within the first three days.

It can affect several areas of the body, but most frequently develops in the neck muscles, the larynx, eyes and torso; the terms "torticollis", "laryngospasm", "oculogyric crisis" and "opisthotonos" are used to describe the dystonic reactions of specific body regions. These reactions have a sudden onset and cause a great deal of discomfort. In some patients, these reactions, for example the laryngospasm, can be dangerous and even life-threatening.

These reactions respond quickly to the administration of anticholinergic or antihistaminic medication. Parenteral administration has a quicker effect than oral administration. Oral administration of anticholinergic anti-parkinsons medication can be later used to prevent relapses.

**Akathisia** is characterized by somatic agitation, which is manifested subjectively and objectively in 30% of patients treated with first generation antipsychotics, and is less frequent with low potency antipsychotics.

Patients usually report inner restlessness and the irresistible urge to move several parts of the body.

In mild akathisia, the patient is able to control body movements, but in more severe forms the patient will not stop walking while standing and is unable to remain seated. This secondary effect is often very uncomfortable and frequently results in poor adherence to antipsychotic treatment; if left untreated, it can cause dysphoria. It can also contribute to aggressive or suicidal behaviour.

Effective treatments for akathisia include central action β-blockers, propanolol (30-90 mg/day). When these drugs are administered, blood pressure and heart rate should be monitored for different doses.

The **neuroleptic malignant syndrome** is characterized by a triad of symptoms: rigidity, hyperthermia and autonomic instability, hypertension and tachycardia. It is associated with elevated blood concentration of creatine-kinase.

Prevalence is less than 1% of patients treated. Its diagnosis often goes unnoticed and it can be fatal in 5-20% of untreated patients.

Onset can be sudden, often within the first week or after increasing the dose.

Risk factors are: acute agitation, young age, male gender, prior neurological incapacity, physical disease, dehydration, fast increase of antipsychotic dose, administration of high potency drugs and intramuscular preparations.

Treatment with antipsychotics should always be interrupted and supportive treatment provided to maintain hydration and treat fever, as well as cardiovascular, renal and other symptoms. Its treatment requires, in most cases, hospitalization.

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**Tardive dyskinesia** is a disorder characterized by abnormal hyperkinetic involuntary movements caused by prolonged exposure to antipsychotic medication. It can affect neuromuscular function in any part of the body, but is especially common in the orofacial region.

Schizophrenia itself can be associated with risk of spontaneous dyskinesia that cannot be distinguished from drug-induced dyskinesia.

Tardive dyskinesia occurs at an annual rate of 4 to 8% of adult patients treated with this type of antipsychotics.

Risk factors are: elderly age, antipsychotic-induced Parkinsons symptoms, female gender combined with postmenopausal state, diagnosis of mood disorder (major depressive disorder), concomitant medical diseases (diabetes) and use of high antipsychotic doses.

Most patients have mild symptoms but 10% present moderate or intense symptoms. A frequent and severe variant of tardive dyskinesia is tardive dystonia, which is characterized by the onset of spastic muscle contractions instead of choreoathetotic movements. Tardive dystonia is often associated with greater distress and physical discomfort.

The therapeutic options for tardive dyskinesia are to use a second generation antipsychotic or reduce the dose of the currently used drug, in which case there may be an initial increase of dyskinetic symptoms (withdrawal dyskinesia). With prolonged exposure to first generation antipsychotics, without reducing the dose after the onset of tardive dyskinesia, the probability of reversibility decreases but does not disappear.

**c) Anticholinergic and antiadrenergic effects**

The side effects of first generation antipsychotics (and, in the case of joint administration, with the anticholinergic side effects of antiparkisonians) can produce a variety of peripheral side effects, such as dry mouth, blurred vision, constipation, tachycardia, urinary retention and thermoregulating effects. Anticholinergic side effects can appear in 10-50% of treated patients. It should be noted that more anticholinergic side effects have been reported with the use of chlorpromazine than with haloperidol.

Although the majority of anticholinergic side effects are mild and tolerable, this type of effects can be particularly problematic in older patients (e.g., older man with prostatic hypertrophy). The conditions of anticholinergic effects are severe in very few cases.

Anticholinergic effects are learning and memory disturbances, and impaired, slowed down cognition. The symptoms of anticholinergic toxicity are confusion, delirium, drowsiness and hallucinations. It is more likely that these symptoms appear with drugs whose anticholinergic effects are more potent, or due to the administration of anticholinergic antiparkinson's drugs, and also in elderly or medically debilitated patients.

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## *Other side effects*

**Convulsions:** First generation antipsychotics can reduce the threshold of convulsion and trigger the onset of widespread tonic-clonic convulsions. The low potency of these antipsychotics is associated with a higher risk. In the case of low potency antipsychotics, convulsion frequency is associated with dose, and higher doses are associated with higher risk. With normal doses, the rate of convulsion is below 1%, although in the case of patients with a history of idiopathic or drug-induced convulsions there is increased risk.

**Allergy and skin:** Allergic skin reactions are fairly frequent with first generation antipsychotics. Treatment interruption or the administration of an antihistaminic is usually effective at decreasing these symptoms.

**Liver:** This type of drugs also produces elevated concentration of liver enzymes and cholestatic jaundice. Jaundice has been reported in 0.1 to 0.5% of patients who take chlorpromazine. This side effect usually occurs within the first month of treatment and generally requires treatment interruption.

**Ophthalmologic:** Pigmentary retinopathies and corneal opacities may develop with the chronic administration of low potency drugs, such as chlorpromazine, especially at high doses (e.g. over 800 mg/day of thioridazine –already withdrawn from the market-). For this reason, patients using these drugs should undergo periodic ophthalmologic exams.

**Blood:** The administration of antipsychotic drugs can cause side effects on blood, such as leukopoiesis inhibition. This type of effects includes benign leukopenia and agranulocytosis, which is more severe. Chlorpromazine is the cause of benign leukopenia in over 10% of patients and agranulocytosis in 0.32%.

**Cardiovascular:** The most significant cardiovascular effects are orthostatic hypotension, tachycardia and prolonged QT interval with haloperidol.

**Weight gain:** Most antipsychotics produce weight gain; up to 40% of treated patients gain weight.

The prevention of weight gain should be a priority, given that many patients have difficulties losing weight. When the patient has gained weight, he/she should be advised to diet and exercise, or be referred to a dietician.

**Sexual function:** Erectile dysfunction occurs in 23-54% of men. Other effects include ejaculation disorders in men and loss of libido or anorgasmia in both sexes. Furthermore, in certain antipsychotics retrograde ejaculation has been reported, likely as a result of antiadrenergic and antiserotonergic effects. Dose reduction or treatment interruption usually leads to symptom reduction or disappearance. If it is not possible to reduce the dose or administer an alternative drug, yohimbine or cyproheptadine can be used.

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## *Pharmacological interaction of first generation (or conventional) antipsychotics*

Numerous pharmacological interactions that result in significant clinical effects can occur in patients who receive antipsychotic medication. Certain heterocyclic antidepressants, most selective serotonin reuptake inhibitors (SSRIs), some betablockers and cimetidine can increase blood concentration of antipsychotics and side effects. On the other hand, barbiturates and carbamazepine decrease blood concentration by acting upon cytochrome P-450 enzymes.[4]

## *B) Second generation (or atypical) antipsychotics*

At present the following second generation antipsychotics are authorized in Spain: clozapine, risperidone, olanzapine, paliperidone, sertindole, quetiapine, ziprasidone, amisulpride and aripiprazole.

In this section each second generation antipsychotic has been described. Posology guidelines presented in the TPG have also been included (table 6, annex 2)[73], as well as a comparative table for normal dosage intervals for adults according to recommendations from the TPG,[73] the APA's CPG[4] and the CPG,[2] those recommended by the WFSBP[75,76] and PORT[40], and finally, those from two consultation publications in Spain: RTM-III[77] and Chinchilla[78] (table 7, annex 2).

In regards to the side effects of atypical antipsychotics (AASEs) the TPG lists weight gain, dizziness, postural hypotension (especially during the initial dose adjustment) which can be associated with reflex syncope or tachycardia of some patients, extrapyramidal symptoms (overall, mild and transitory, which respond to dose reduction or to an antimuscarinic drug) and, sometimes, tardive dyskinesia after long-term treatment (medication should be discontinued at the onset of the first signs). Hyperglycaemia and, sometimes, diabetes can occur, especially with clozapine and olanzapine; weight and blood glucose monitoring enable the detection of hyperglycemias. The neuroleptic malignant syndrome has been rarely reported.

- **Amisulpride**

This drug presents high selective affinity for $D_2$ and $D_3$ receptors; at low doses (50-300 mg) it is a presynaptic $D_2$, $D_3$ antagonist with efficacy on negative symptoms, and at high doses (400-1200 mg) it is a postsynaptic $D_2$ antagonist, with efficacy on positive symptoms.[82]

Dosage range is 400-800 mg/day, taken in two doses. The most frequent side effects are extrapyramidal (dyskinesia, akathisia) and present low incidence, with weight gain and prolactin increase similar to that of other neuroleptic drugs.[69] Aside from AASEs, insomnia, anxiety, agitation, drowsiness, digestive disorders such as constipation, nausea, vomiting and dry mouth and, occasionally, bradycardia, have been reported; convulsions have rarely been reported.[73]

QT may increase and lead to the risk of ventricular arrhythmias (cardiologic study).[78] Its administration is oral.

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- **Aripiprazole**

First partial agonist with affinity for $D_2$ receptors. It is a partial $5HT_{1A}$ agonist, $5HT_{2A}$ antagonist and modulator of the DA/5HT system, and is effective for positive, negative and mood symptoms, reducing extrapyramidal symptoms and excitability-hostility.[83]

It has a low risk of side effects and extrapyramidal effects, does not produce weight gain or psychosexual effects (does not affect prolactin), nor does it alter the metabolism of cholesterol, triglycerides or glucose. It does not present QT disturbances. It may produce headaches, insomnia or agitation-anxiety. [78] Aside from AASEs, nausea, vomiting, dyspepsia, constipation, akathisia, drowsiness, tremors, asthenia, blurred vision; more rarely tachycardia, convulsive crises; very rarely hypersialorrhea, pancreatitis, chest pain, agitation, speech disorder, cramps, rhabdomyolysis, priapism and altered thermoregulation.[73]

In agitated patients this drug may be combined with benzodiazepines.[84] It is administered orally (tablets and orally disintegrating tablets) with a dose range of 10-15 mg/day.

- **Clozapine**

This drug presents antagonist activity for $D_1$ and $D_2$ dopamine receptors, as well as for 5-HT, adrenergic, histamine and muscarinic receptors. It is the antipsychotic drug with the lowest incidence of extrapyramidal side effects and may produce agranulocytosis that may be fatal in 1% of patients.

A multicenter RCT demonstrated that it was effective in patients resistant to first generation antipsychotic treatment and in patients who do not tolerate the extrapyramidal effects of these drugs, especially tardive dyskinesia.[85] In these patients, it was effective at reducing both positive and negative symptoms (**level of scientific evidence Ib**).[86]

Therapeutic doses range from 200-450 mg/day with a starting dose of 12.5 mg, once or twice daily; it should be slowly increased at daily increments of 25-50 mg/day initially and subsequently at weekly increments of 50-100 mg. The maximum dose is 900 mg/day.

It is used when there is resistance to two antipsychotics from a different family. Its use is contraindicated in patients with prior hypersensitivity to clozapine; a history of drug-induced granulocytopenia/agranulocytosis; white blood cell count lower than 3,500/$mm^3$; altered bone marrow function; alcoholic, toxic psychoses and comatose states; respiratory collapse and/or depression of the central nervous system due to any cause; severe liver, kidney or heart disease.

Before initiating treatment, an analysis of white blood cell count and formula should be performed to ensure that only patients with normal white blood cell count receive this treatment. Weekly white blood cell counts should be performed over the first 18 weeks and subsequently every month for at least the entire duration of clozapine treatment. A white blood cell count lower than 3,500 $mm^3$ and a neutrophil granulocytes count lower than 2,000-1,5000/$mm^3$ will entail twice weekly white blood cell counts, and a decrease to under 3,000 white blood cells/$mm^3$ and 1,500/$mm^3$ neutrophils, the immediate discontinuation of treatment. Values under 2,000 white blood cells/ $mm^3$ and 1,000 neutrophils/ $mm^3$ indicate the need for hospitalization and haematology surveillance (table 8, annex 2).

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Patients should be advised to inform their physician on any symptom of fever or infection. Patients in whom treatment has been discontinued due to agranulocytosis should not be treated with clozapine again.

The most frequent side effects are sedation, weight gain, hypersalivation, tachycardia, hypotension and fever; the first three are especially frequent and occur in most patients, especially in the first phase of treatment. Aside from AASEs, constipation (gastrointestinal obstruction), hypersalivation, dry mouth, nausea, vomiting, anorexia, tachycardia, ECG changes, hypertension, drowsiness, headaches, tremors, convulsions, fatigue, thermoregulation disturbance, urinary incontinence and retention, leukopenia, eosinophilia, leukocytosis; blurred vision; sweating; agranulocytosis, with less frequency; rarely dysphagia, hepatitis, cholestatic jaundice, pancreatitis, circulatory collapse, arrhythmia, myocarditis, pericarditis, thromboembolism, agitation, confusion, delirium, anaemia; very rarely, parotid hypertrophy, intestinal obstruction, cardiomyopathy, myocardial infarction, respiratory depression, priapism, interstitial nephritis, thrombocytopenia, thrombocythemia, hyperlipidemia, narrow angle glaucoma, fulminant hepatic necrosis and skin reactions.[73]

Clozapine is also associated with the risk of dose-related convulsive crises: 1-2% with doses below 300 mg/day, 3-4% with doses below 600 mg/day and 4-5% with doses between 600-900 mg/day.

- **Olanzapine**

This drug is chemically similar to clozapine, with moderate affinity for $D_4$, $D_2$ and 5-HT, and lower affinity for adrenergic, histamine and muscarinic receptors, acting upon positive and negative symptoms[c].

It is used at 5-20 mg/day doses, with a starting dose of 10 mg. The most frequent side effects, affecting over 25 of patients, are: confusion, dry mouth, akathisia and insomnia; and, less frequently, dyspepsia, anxiety, nausea, tremors, orthostatic hypotension and diaphoresis.[69] Aside from AASEs, transient antimuscarinic effects (very rarely, quick onset of narrow angle glaucoma); drowsiness, speech disorder; exacerbation of Parkinson's disease, abnormal gait, hallucinations, asthenia, increased appetite, increased body temperature, elevated triglyceride concentration, oedema, hyperprolactinemia (however, rare clinical manifestations), urinary incontinence; eosinophilia; less frequently, hypotension, bradycardia, photosensitivity; rarely, convulsions, leukopenia, rash; very rarely, thromboembolism, hypercholesterolemia, prolonged QT interval, hypothermia, urinary retention, priapism, thrombocytopenia, neutropenia, rhabdomyolysis, hepatitis, pancreatitis; in intramuscular form, reactions at the injection site, sinus arrest and hypoventilation.[73]

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[c] Even though its efficacy for these symptoms has not been clearly demonstrated.[87]

Doses over 10 mg/day increase the probability of extrapyramidal symptoms. It may cause worrying weight gain ranging from 3.5 to 12 kg in the high dose interval. [69] It may temporarily elevate prolactin and liver enzymes in the first few weeks of treatment.

It is available in oral tablets and in quick dissolution absorption form, and as an intramuscular injection.

- **Paliperidone**

- It is an active metabolite of risperidone which blocks serotonergic 5HT2A, dopaminergic D2 and adrenergic α receptors$_1$. It is available in extended release tablets.

Dose range is 3 to 12 mg daily. The recommended dose is 6 mg taken by mouth, once a day in the morning. The most frequent side effects are headaches, and less frequently, other nervous system, cardiovascular, gastrointestinal disorders, weight gain and additional adverse reactions that have been reported for risperidone.

- **Quetiapine**

It presents affinity for 5-HT, $\alpha_1$, $\alpha_2$, $H_1$, $D_1$ and $D_2$ receptors, thus presenting an affinity profile that differs from first and second generation (or atypical) antipsychotics.

The average dose is 300-450 mg/day taken in two doses. The recommended starting dose is 25 mg, twice daily, then 50 mg twice daily the second day, 100 mg twice daily the third day and 150 mg twice daily the fourth day. It is an effective treatment for positive and affective symptoms, and improves cognitive function, hostility and aggressiveness. [88]

The most frequent side effects are: sedation, dizziness, headache, insomnia, orthostatic hypotension and weight gain. All of them present low incidence.[69] There is low incidence of extrapyramidal effects[87] and there is no elevated prolactin. Aside from AASEs, drowsiness, dyspepsia, constipation, dry mouth, mild asthenia, rhinitis, tachycardia; leukocytopenia, neutrocytopenia and sometimes eosinophilia; elevated blood concentration of triglycerides and cholesterol; decreased blood concentration of thyroid hormone; possible prolonged QT interval, rarely oedema; very rarely, priapism.[73]

Quetiapine is available in oral tablets and long acting tablets.

- **Risperidone**

It is a potent antagonist of 5-$HT_2$ and $D_2$ receptors and of adrenergic $\alpha_1$ y $\alpha_2$ receptors to a lesser degree. $5HT_2$ blocking improves dopamine receptor blocking in schizophrenia. It has limited affinity for ß-adrenergic and muscarinic receptors, and high affinity for $\alpha_1$ and $H_1$. It is used to treat both positive and negative symptoms[c] and is well tolerated.[78]

The recommended dose is 4-6 mg/day and a single daily administration is possible due to its plasma half-life, with maintenance of effectiveness and tolerance.[69] The recommended starting dose is 2 mg once or twice a day, increasing the dose up to 4 mg on the second day in one or two doses.

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In a study that compared risperidone with clozapine in resistant patients, it was demonstrated that both drugs were equally effective, but risperidone was better tolerated, and caused less sedation and weight gain[89]

Risperidone is associated with dose-dependant extrapyramidal symptomatology, which is minimal at the therapeutic dose interval. In the initial dose adjustment period, transient orthostatic hypotension and reflex tachycardia (due to ß-adrenergic activity) may develop.[69]

Infrequent side effects include sedation, erectile dysfunction, slight weight gain, decreased sexual drive, and increased prolactin (galactorrhea and menstrual disturbances). Aside from AASEs, insomnia, agitation, anxiety, headache; less frequently, dizziness, concentration disturbances, fatigue, blurred vision, constipation, nausea and vomiting, dyspepsia, abdominal pain, hyperbilirubinemia (and galactorrhea, menstrual disturbances, gynecomastia), priapism, urinary incontinence, tachycardia, hypertension, oedema, rash, rhinitis, cerebrovascular accidents, neutrocytopenia and thrombocytopenia; rarely, convulsions, hyponatremia, thermoregulation disturbances and epistaxis.[73]

It is available in tablets and in fast dissolving presentation and in extended release intramuscular injection (Consta).

- **Sertindole**

This drug presents affinity for 5-$HT_{2C}$, 5-$HT_{2A}$, D2, $\alpha_1$ and $\alpha_2$ receptors, but not for histamine receptors, thus probably causing less sedation. Its antipsychotic efficacy has been proven to be superior to placebo.[87]

The most frequent side effects are: nasal congestion, postural hypotension (generally during dose escalation), sedation, tachycardia, decreased ejaculation volume in 20% of treated males (with no associated decreased libido or erectile dysfunction) and weight gain. Aside from AASEs, peripheral oedema, dry mouth, rhinitis, dyspnoea, paresthesias; rarely, convulsions, hyperglycemia.[73] Clinical trials show that sertindole is better tolerated than haloperidol and produces fewer extrapyramidal effects.[69,87] It is should be mentioned that electrocardiogram results yielded that 3% of patients treated with this drug presented prolonged QT which was greater than or equal to 500 msec without associated ventricular tachyarrhythmia, but presenting the possibility of vulnerability to develop ventricular arrhythmia (*torsades des pointes),* which may be fatal.[47,69] This possibility led to the cautionary withdrawal of this drug from the market in 1998 and later reintroduction after several favourable studies in 2006, with the recommendation to perform follow-up electrocardiograms.

Optimum dose seems to be in the 12-20 mg/day range, with a starting dose of 4 mg/day and 4 mg increments every 4-5 days.[69]

- **Ziprasidone**

This drug presents affinity for 5-$HT_{2A}$ receptors and moderate antagonism for $D_2$, strong antagonism for 5-$HT_{1D}$ and 5-$HT_{2C}$ receptors and agonism for 5-$HT_{1A}$, moderate antagonism of adrenergic and histamine receptors, and minimal antagonism of muscarinic receptors. This pharmacological mechanism is associated with elevated efficacy for treating positive and

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negative symptoms, with minimal extrapyramidal effects and effects on prolactin.[90] It does not interact with lithium, oral contraceptives, carbamazepine, antacids or cimetidine.

The recommended normal dose is 80 mg/day taken in two 40 mg doses when administered orally and up to 40 mg/day in up to three consecutive days when administered as intramuscular injection. The maximum dose is 160 mg/day taken in two doses.[73]

The most frequent side effects are: headache, drowsiness, nausea and dyspepsia. It does not produce significant weight gain and presents a low incidence of extrapyramidal effects (akathisia). It may slightly and temporarily elevate prolactin. Electrocardiogram monitoring is required due to the risk of increased QT.[78] It also present AASEs.[73]

Ziprasidone is presented in oral and intramuscular forms.

## *Frequent side effects of second generation antipsychotics*

**Metabolic syndrome**

The metabolic syndrome refers to a group of medical disorders including obesity, hyperglycaemia and hypertriglyceridemia, usually associated with resistance to insulin. These factors can lead to ischemic cardiopathy, diabetes and diseases associated with excess weight.[91]

In order to diagnose metabolic syndrome, three of the following disorders must be present: a) abdominal obesity (abdominal perimeter > 102 cm in men and > 88 cm in women), b) hypertriglyceridemia (blood triglycerides > = 150 mg/dl), c) reduced high density lipoprotein cholesterol (HDLc < 40 mg/dl in men and < 50 mg/dl in women), d) high blood pressure (130/85 mmHg) or e) elevated fasting glycaemia (110 mg/dl).[92]

It has been documented that some second generation antipsychotics, especially clozapine and olanzapine, produce significant weight gain[93,94] and in some cases diabetes,[95-97] which is more prevalent in schizophrenia than in the general population,[98] with the possibility to present risk factors prior to antipsychotic treatment.[99,100]

Hence, periodic physical follow-ups are highly advisable: blood pressure, glycaemia, and abdominal perimeter and blood cholesterol and triglyceride values.[91,96,101]

Sedative, hypotensive anticholinergic effects and weight gain are frequent with all atypical antipsychotics. Clozapine is associated with an elevated incidence of anticholinergic and sedative effects, and can produce convulsions and agranulocytosis. Clozapine and olanzapine produce more weight gain and hyperglycaemia, risperidone has more extrapyramidal effects and produces higher prolactin increases and maybe QT prolongation, and quetiapine and sertindole prolong the QT interval.[102]

On the other hand, a retrospective study has reported that prolonged QT interval and sudden cardiac death can be a result of both typical and atypical antipsychotics and are related with dosing.[103] The incidence of prolonged QT interval according to the results of the CATIE clinical trial (Clinical Antipsychotic Trials of Intervention) is 3%, while the incidence of sudden death in patients treated with antipsychotics is 3 per 1,000.

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## 6.1.2. Other coadjuvant drugs

Although the APA's CPG (2004) includes the use of other drugs to boost the therapeutic efficacy of antipsychotics and to treat residual symptoms, including positive, negative and affective symptoms, the efficacy of these treatments in patients with schizophrenia is a topic of discussion.

- **Lithium**

There is some scientific evidence that the use of lithium salts to boost antipsychotic treatment in patients with resistant symptomatology can increase antipsychotic response and reduce negative and affective symptoms. The lithium dose administered should obtain a blood concentration of 0.8-1.2 meq/l.

The side effects of lithium are: polyuria, weight gain, cognitive disturbances, tremor, sedation, impaired coordination, gastrointestinal disturbances, hair loss, benign leukocytosis, acne and oedemas.

The combination of an antipsychotic treatment with lithium can produce confusion and disorientation and increase the likelihood of developing the neuroleptic malignant syndrome.

- **Benzodiazepines**

These drugs may be useful in the acute phase as coadjuvant treatment for psychotic agitation, enabling a reduced dose of antipsychotics.

Its side effects include sedation, ataxia, cognitive impairment and in some patients behavioural disinhibition. The possible abuse of these drugs should be monitored, and it should be acknowledged that the combination of these drugs with clozapine and levopromazine can be dangerous and contraindicated.[104,105]

- **Anticonvulsants**

These drugs may be effective as coadjuvant treatment to antipsychotics in patients with abnormal electroencephalograms that indicate convulsive activity and in patients with agitated or violent behaviour.

The use of carbamazepine with clozapine is not recommended due to the potential of both drugs to produce agranulocytosis.

Carbamazepine and valproate reduce blood concentration of antipsychotics as a result of liver enzyme induction.

- **Antidepressants**

SSRIs are especially used when there is a post-psychotic depression which is difficult to differentiate from negative symptoms produced by first generation antipsychotics. Overall, evidence pointing to the efficacy of antidepressants in the treatment of negative symptoms is

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very moderate and most studies have been performed using first generation antipsychotics.[106] Two studies demonstrated the efficacy of fluvoxamine and clomipramine in the treatment of obsessive-compulsive symptoms in schizophrenia.[106]

Additionally, major depression and obsessive-compulsive disorder are comorbid disorders that frequently develop in patients with schizophrenia who would possibly respond to antidepressants. However, some antidepressants (those which inhibit catecholamine reuptake) can potentially maintain or exacerbate psychotic symptoms in some patients.[4]

## 6.1.3. General recommendations for antipsychotic treatments

International medical literature[107-114] has extensively addressed treatments with antipsychotic drugs, especially assessing their efficacy, effectiveness and side effects. Each drug has been analyzed individually as much as it has been compared to other drugs, particularly in the case of first and second generation antipsychotics. The objective of this assessment is to formulate recommendations on the use of these drugs.

A main issue for recommendations on the use of antipsychotic treatments is choosing one or another, particularly when it is a first psychotic o schizophrenic episode. When choosing medication, different criteria overlap such as the degree of response of symptoms, side effects that may develop patient preferences and administration route. All of these factors should be taken into account.

The comparison of the different CPGs selected has yielded the following general recommendations. According to the APA's CPG, second generation antipsychotics should be the drugs of choice in acute phases, mainly because the risk of causing extrapyramidal side effects and tardive dyskinesia is lower.[106] The NICE's CPG concludes that the evidence considered suggests that second generation antipsychotics are, at least, as effective as traditional drugs in terms of general response rates. There is also evidence suggesting that these drugs may vary in their relative effects on positive and negative symptoms and relapse rates. However, there is insufficient data to differentiate the assessment of the overall impact of each atypical antipsychotic for people with schizophrenia. Likewise, it determines that the conclusions that can be extracted from most studies are limited due to the lack of long-term follow-up.[3,115] The RANZCP CPG[1] considers that there is minimal evidence indicating that second generation antipsychotics are more effective than first generation antipsychotics in the acute treatment of positive symptoms, even though they seem to be more effective at preventing relapse. Available data suggest, but do not prove, greater efficacy for negative and neurocognitive symptoms. Greater importance is granted to the fact that new antipsychotics are much better tolerated and produce less motor side effects, including tardive dyskinesia.

The CPG of the Canadian Psychiatric Association[2] determines that there are no clear and consistent differences between first and second generation antipsychotics in relation to therapeutic response to positive symptoms, with the exception of clozapine in the treatment of resistant patients.

Second generation drugs have a wider spectrum of therapeutic effects, with a small but significant effect on negative symptoms and cognitive deterioration. It also considers the

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significant differences between first and second generation antipsychotics in the side effects profiles. Second generation antipsychotics produce fewer neurological side effects, both extrapyramidal side effects and tardive dyskinesia, but may also have a greater tendency to cause metabolic side effects (weight gain, dyslipidemia or metabolic syndrome), even though the evidence is based especially on clinical experience and on the publication of non-randomized studies.[2] Hence, the recommendation reached is to use second generation antipsychotics, particularly at the beginning of pharmacological interventions.

The Canadian CPG establishes the following general principles for pharmacological treatments:[2]

- Pharmacotherapy with antipsychotic medication is an essential component of the treatment plan for the majority of patients with schizophrenia.
- Psychosocial interventions act synergically with drugs to optimize adherence to treatment and achieve successful community life. The use of both interventions is recommended in the treatment of the disorder.
- Medication should be individualized because individual response to treatment is highly variable. The current problem and the patient's prior response to pharmacotherapy should be considered, including efficacy and side effects. Patients with a first psychotic episode generally require lower doses, as do elderly patients.
- The use of simple therapeutic guidelines, such as one daily administration, promote adherence to treatment.
- Dosage should be maintained within the recommended range, and the reasons for altering this range should be clearly documented and justified.
- The simultaneous use of more than one antipsychotic is not backed by available scientific evidence.
- Regular and periodic assessments are just as necessary when patients respond to medication, when their response fails, and when they develop side effects. Standardized scales are useful tools for initial and subsequent assessments.

Moore, based on the study of five guidelines, algorithms and consensus of North American experts which include the APA's CPG, the *Expert Consensus Guideline on Treatment of Schizophrenia*, el *Texas Medication Algorithm Project (TMAP) Schizophrenia Algorithm*, *PORT* and the *Schizophrenia Algorithm* of the *International Psychopharmacology Algorithm Project* has gathered the general recommendations shared by nearly all of them, and which coincide with the CPGs used in this document:[116]

1. Preferable use of second generation antipsychotics for the first episode of schizophrenia.
2. Use of clozapine after one or two failed attempts with other antipsychotics.
3. No use of combined antipsychotic drugs, except as a last resort.

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The study developed by the CATIE group considers that the relative efficacy of second generation antipsychotics (atypical) in comparison with older drugs has not been addressed in depth, even though new drugs are being used more frequently. A first generation antipsychotic, perphenazine, was compared with several more recent drugs in a double blind trial. 1,493 patients with schizophrenia from 57 centres in the United States participated in this study, and were randomly assigned to the olanzapine (7.5 to 30 mg daily), perphenazine (8 to 32 mg daily), quetiapine (200 to 800 mg daily), or risperidone (1.5 to 6.0 mg daily) groups over a maximum period of 18 months. Once approved by the FDA, ziprasidone was also included (40 to 160 mg daily). The main objective consisted in defining differences in the overall efficacy of these five treatments. The study concluded that most patients in all groups dropped out of the assigned treatment due to lack of efficacy, intolerable side effects or other reasons. Olanzapine was associated with lower dropout rates. The efficacy of perphenazine was, apparently, similar to the efficacy of quetiapine, risperidone and ziprasidone. Olanzapine was associated with increased weight gain and increased glucose and lipid metabolic values. [117]

In another study linked to the CATIE project it was determined that, after two months of antipsychotic treatment in patients with schizophrenia who were randomly assigned to pharmacological treatment with olanzapine, perphenazine, quetiapine or risperidone, all groups obtained small but significant improvements in neurocognition.[118] No differences were detected amongst any two drugs including the atypical antipsychotic perphenazine.

Second generation antipsychotics are perceived as more effective, presenting fewer side effects and seem to be preferred by patients. However, most of the scientific evidence available derives from clinical trials on the short-term efficacy on symptoms. Hence, the CUTLASS research group (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) designed a controlled, randomised trial with the aim of confirming the hypothesis that in some patients with schizophrenia who require treatment changes, second generation antipsychotics, aside from clozapine, are associated with improved quality of life at one year when compared to first generation antipsychotics.[119] This pragmatic multicenter study which did not receive funding with commercial interests assessed patients at 12, 26 and 56 weeks based on the intention to treat analysis. The main hypothesis of significantly improved quality of life after one year follow-up was refuted. Participants in the group that received first generation antipsychotics showed a tendency to improved quality of life and symptomatology. Participants did not indicate any preference for any one type of drug; costs were similar. In conclusion, people with schizophrenia that have switched medication due to clinical reasons, do not present disadvantages at one year in terms of quality of life, symptoms or care-related costs with the use of first generation drugs versus second generation drugs, excluding clozapine.

Lewis et al. developed the second part of the previously mentioned CUTLASS2 study.[120] The project design included a controlled, randomized trial that was also pragmatic, open and multicenter, and was focused on the effectiveness of clozapine versus other second generation antipsychotics in the treatment of schizophrenia. Evaluators were blind to treatment condition, the sample follow-up lasted one year and there was no funding from the pharmaceutical industry. The trial was more focused on the relative clinical efficacy of second generation antipsychotics, excluding clozapine, than on the individual efficacy of each drug, given that these drugs are generally grouped together in clinical guidelines. The authors determined that in patients with schizophrenia who respond poorly to treatment with two or more antipsychotic

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drugs, there is scientific evidence supporting initiating treatment with clozapine instead of other second generation antipsychotic drugs from the point of view of improved symptoms over one year.

Results were mirrored in the CATIE and CUTLASS studies, and surprised both groups of researchers. In both trials, the main hypothesis was refuted and second generation antipsychotics were not proven to be more effective (with the exception of olanzapine in the CATIE study). Furthermore, these drugs did not produce fewer extrapyramidal side effects. In both trials, clozapine was the most effective drug for treatment-resistant patients.[120]

A meta-analysis of 150 double-blind studies (most of them short-term) with a total of 21,533 patients with schizophrenia was recently published comparing the efficacy of different antipsychotics versus haloperidol.[85] Given the uncertainties regarding the supposed superiority of second generation antipsychotics to first generation antipsychotics, a meta-analysis of clinical trials was conducted with the aim of comparing the effects of these two types of drugs in patients with schizophrenia. Nine second generation antipsychotics were compared with first generation antipsychotics with several variables: overall efficacy (primary endpoint), positive symptoms, negative symptoms, depressive symptoms, relapses, quality of life, extrapyramidal effects, weight gain and sedation. It was determined that second generation antipsychotics differ from each other in many properties and are not a homogeneous group. This meta-analysis provides information to individualize treatment based on efficacy, side effects and cost.

On the other hand, when research is focused on first psychotic episodes a certain short term advantage is observed in terms of effectiveness for second generation antipsychotics versus first generation drugs, as is described below.

A double blind, randomized clinical trial compared the efficacy of olanzapine versus haloperidol in acute phase in patients with a first psychotic episode.[112] At 12 weeks of treatment, psychopathological, psychosocial, neurocognitive, and brain morphology and functioning measures were taken. As was observed in other studies, olanzapine and haloperidol were both effective at reducing acute psychopathological symptomatology of the first psychotic episodes. However, olanzapine presented several advantages in its therapeutic response. Specifically, patients treated with olanzapine presented a greater reduction of symptomatological severity and a lower rate of treatment-induced Parkinsonism and akathisia. Additionally, permanence in the study was higher with olanzapine. It should be noted that permanence in the study in this type of population is important due to its high relapse risk. The authors indicate the need for long-term results in order to determine if atypical antipsychotics really are better in a first psychotic episode.

Following in this line, in the year 2005 Schooler et al. performed a study on the long term efficacy of risperidone versus haloperidol in patients with a first psychotic episode.[121] They designed a double-blind randomized study comprised of a sample of 555 patients who were administered flexible doses of the aforementioned drugs. The authors observed that relatively low doses of antipsychotic drugs lead to significant symptomatic improvement in most patients with a first psychotic episode. AT long-term, risperidone prevented relapse in a greater number of patients and for a longer peiod of time and, also, caused less abnormal movements than haloperidol.

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Later, McEvoy et al. conducted a study to assess the effectiveness of olanzapine, quetiapine and risperidone in patients in an early phase of psychosis.[122] Patients were randomly assigned to one of the following pharmacological treatment conditions: 1) olanzapine, 2) quetiapine and 3) risperidone. The authors studied the rates of treatment interruption over a period longer than 52 weeks and determined that olanzapine, quetiapine and risperidone showed comparable efficacy in patients with incipient psychotic disorder, as was evidenced by similar treatment interruption rates in the different study conditions.

Schooler conducted a systematic review of the literature published between 1975 and 2006 on the short- and long-term efficacy of conventional and atypical antipsychotic drugs in patients with a first episode of schizophrenia with the aim of determining strategies to improve treatment adherence in this population.[123] A total of 17 studies that met the established inclusion criteria were selected, and after review, the author concluded that atypical antipsychotic drugs present advantages in the long-term management of a first episode of schizophrenia. Futhermore, it was emphasized that long-term use of atypical antipsychotics could be considered a new strategy in patients with a first episode of schizophrenia.

More recently, Opjordem et al. elaborated a naturalistic study with the aim of comparing treatment interruption rates with first generation antipsychotic versus second generation antipsychotics in patients with a first psychotic episode.[124] To do so, they considered the prescription of these drugs in 301 patients with a first psychotic episode from four recruitment areas. During the first year of study, the first pharmacological option was low-dose first generation antipsychotics. At the second year, second generation antipsychotics were considered the first option. A switch of treatment was allowed when any of the drugs were deemed to be ineffective or triggered significant side effects. This switch was more frequent in the group treated with low-dose first generation antipsychotics than in the group treated with second generation antipsychotics. The lack of therapeutic effect and the presence of side effects were the most common reasons for a switch of treatment in the group of patients who received first generation antipsychotics. Furthermore, this group of patients reported the presence of akathisia, Parkinsonism, dyskinesia, dystonia and dysphoria more frequently. On the other hand, patients who received second generation antipsychotics reported weight gain and sedation as the most frequent side effects. Results point to better adherence and tolerability of second generation antipsychotics versus low-dose first generation antipsychotics.

In conclusion, decision-making regarding the use of antipsychotic drugs seems to be conditioned by three main factors. Firstly, the similarities of both antipsychotic groups' therapeutic effects on positive symptoms, which are the ones that usually lead to the initiation of pharmacological treatment. Secondly, the different profiles of side effects that they can produce, and which are deemed to be the main cause of poor adherence to treatment. And finally, the patient's preference towards one specific drug or presentation. Hence, it can be concluded that antipsychotic treatment should be individualized.

On these grounds, the following section presents a series of recommendations on pharmacological interventions with antipsychotics, accompanied by a Pharmacological Intervention Algorithm (annex 2).

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## General aspects

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| **A** | Whenever possible, antipsychotic medication should be prescribed in a non-coercitive manner in combination with psychosocial interventions that include adherence-promoting strategies.[1] |
| **A** | Antipsychotic medications are indicated in nearly all patients who experience an acute relapse; the choice of medication should be guided by the individual characteristics of each patient.[2] |
| **C** | Weight and body mass index should be measured at the beginning of treatment, then every month for six months, and after that every three months. Consultation with a dietitian is advisable, as well as encouraging regular physical exercise. It may also be necessary to consider a drug with a smaller risk of weight gain if weight does not change or is significant. Pros and cons should be assessed with the patient, and he/she should be provided with psychosocial support.[1] |
| **C** | Fasting plasma glycaemia and lipid profiles should be measured at baseline and at regular intervals over its course.[1] |
| **C** | An optimum initial assessment should include magnetic resonance imaging, neurocognitive assessment, neurological exam of neurological and motor disorders, an electrocardiogram, height and weight measurement (body mass index), illegal substance detection tests, lipid profiles and fasting plasma glycaemia (and/or HbA1c).[1] |

## Prescription of antipsychotics and side effects

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| **A** | Pharmacological treatments should be prescribed with extreme caution in patients who have not undergone prior treatment, under the basic principle of producing the least harm possible, while obtaining the maximum benefit. This means a gradual introduction, after careful explanation, of low doses of antipsychotic medication together with antimania or antidepressant drugs when these syndromes are present.[1] |
| **A** | In patients who initiate treatment for the first time, second-generation antipsychotic medication is recommended given that it is justified due to its better tolerance and lower risk of tardive dyskinesia.[1] |
| **A** | The use of oral second-generation medication such as risperidone, olanzapine, quetiapine, amisulpride and aripiprazole is recommended as the first and second line of treatment in the first episode of psychosis. Initial doses should be low and then be gradually increased little by little at spaced out intervals only if response is low or incomplete. Secondary discomfort, insomnia and restlessness should be initially treated with benzodiazepines. Other symptoms such as mania and severe depression require specific treatment with mood stabilisers and antidepressants.[1] |

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| **C** | These doses probably will not have an early effect (during the first days) on discomfort, insomnia and behavioural disorders secondary to psychosis. Hence, a safe, supportive context, and regular and sufficient dose of benzodiazepines will provisionally represent essential components in the management of specialised nursing care.[1] |
| **C** | If the risk-benefit relationship changes in certain patients due to, for example, weight gain, impaired glucose tolerance or sexual side effects associated with the development of second generation agents, an alternative first or second generation antipsychotic drug should be reconsidered.[1] |
| **C** | In emergency situations it is recommended to avoid the first choice use of drugs that tend to undermine the future adherence to treatment due to the production of undesirable side effects that generate an aversive subjective effect. First generation drugs should be used only as a last resort in these circumstances, particularly haloperidol, given that they produce more rigidity than sedation.[1] |
| **C** | If in the first episode of non-affective psychosis there are side effects, such as weight gain or metabolic syndrome, the use of a conventional antipsychotic is recommended. If response is insufficient, other causes should be assessed. If there are no side effects, doses should be increased. If adherence is poor, analyse the reasons, optimize the doses and provide therapeutic compliance therapy.[1] |

## Technical aspects of prescription

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| **A** | Maintenance of pharmacotherapy is recommended for the prevention of relapse in stable and stabilisation phases, with doses that are always within the recommended treatment range for first and second generation antipsychotics.[2] |
| **B** | Antipsychotic medication for the treatment of a first episode of psychosis should be maintained for at least two years after the first recovery from symptoms.[2] |
| **B** | In a first episode of psychosis, dosage should be initiated in the lower half of the treatment range; second generation antipsychotics are indicated due to the lower short and long term risk of extrapyramidal side effects.[2] |
| **B** | The use of clozapine is recommended in cases of persistent aggressiveness.[2] |
| **B** | The administration of multiple antipsychotic drugs, such as the combination of first and second generation drugs, should not be used except during the transition phases of switching medication.[1] |
| **C** | Antipsychotic drugs, whether second or first generation, should not be prescribed simultaneously, except for brief periods of time during a transition phase.[3] |

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| **C** | The combination of two antipsychotics is not recommended, given that it could increase the risk of side effects and pharmacokinetic interactions.[3] |
| **C** | The recommendation to combine an antipsychotic drug, a mood stabiliser and a benzodiazepine or antidepressant could be totally justified by the characteristics of comorbid symptoms, which are extremely common in psychotic disorders.[1] |
| **C** | If parenteral treatment is deemed necessary, intramuscular administration is preferable to intravenous, from the point of view of safety. Intravenous administration should only be used in specific circumstances.[3] |
| **C** | Vital signs should be monitored after parenteral administration of treatment. Blood pressure, pulse rate, body temperature and respiratory rate should be recorded at regular intervals, established by the multidisciplinary team, until the patient is active again. If he/she is asleep or seems to be so, more intensive monitoring is required.[3] |
| **C** | Depot drugs should be reserved for two groups. Firstly, for those who clearly and voluntarily choose this administration route. Second generation injectable drugs are preferable due to their better tolerability and lower risk of tardive dyskinesia. Secondly, for those who, despite a series of comprehensive psychosocial interventions aimed at promoting adaptation and adherence, repeatedly fail to adhere to the necessary medication and present frequent relapses. This is even more pressing when the consequences of relapses are severe and entail substantial risk both for the patient and for others.[1] |

## Resistance to antipsychotic treatment

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| **A** | Patients who are taking first generation antipsychotic drugs and who still present persistent positive or negative symptoms, or who experience uncomfortable side effects, should switch to oral second generation antipsychotic medication under close surveillance of a specialist.[1] |
| **A** | If the risk of suicide is high or persistent despite treatment for depression, if antidepressant treatment is ineffective, or if depression is not severe, the immediate use of clozapine should be considered.[1] |
| **A** | Second generation medication is recommended for patients who relapse in spite of good adherence to first generation antipsychotic medication, although other reversible causes of relapse should be taken into account.[1] |
| **A** | If the patient is resistant to treatment, clozapine should be introduced with safety guarantees on the very first administration.[1] |
| **A** | When there is no response to treatment with adequate administration of two different antipsychotics, the use of clozapine is recommended.[2] |

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| **B** | Depot antipsychotic drugs should be considered for those patients who present poor adherence to medication.[2] |
| **C** | If schizophrenia symptoms do not respond to first generation antipsychotics, the use of a second generation antipsychotic should be considered before diagnosing treatment-resistant schizophrenia and introducing clozapine. In these cases, the introduction of olanzapine or risperidone can be assessed. It is recommended to inform the patients.[3] |
| **C** | The addition of a second antipsychotic to clozapine could be considered in people resistant to treatment in whom clozapine alone has not been proven to be sufficiently effective.[3] |

### Comorbidity and coadjuvant medications

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| **B** | It is possible to introduce antidepressants as complementary treatment to antipsychotics when depressive symptoms fulfil the syndromic criteria of major depression or are severe, causing significant discomfort or interfering with the patient's functionality.[4] |
| **B** | An episode of major depression in the stable phase of schizophrenia is an indication for treatment with an antidepressant drug.[2] |

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## 6.2. Electroconvulsive therapy

Electroconvulsive therapy (ECT) is always a second choice treatment in schizophrenia,[47] indicated after the failure of antipsychotics; the most frequent indications are: catatonic schizophrenia, severe cases that present intense agitation and/or confusion, cases where antipsychotics are contraindicated (due to the possibility of causing neuroleptic malignant syndrome), secondary depression and resistant schizoaffective disorders.[125]

Unilateral ECT has been proven to be as effective as bilateral ECT, and seems to cause less cognitive impairment.

The efficacy of ECT as maintenance treatment has not been properly studied. However, this option should be considered in patients who respond to ECT and in whom pharmacological prophylaxis alone has been ineffective or poorly tolerated.[47]

Three systematic reviews on the effectiveness of ECT suggest that it can be considered a therapeutic option combined with antipsychotic drugs, particularly when the aim is to achieve a quick reduction of symptoms and overall improvement.[126-128] However, Thayran believes that this improvement could only be a short-term effect, the evidence to refute its use being unclear.[126] After more than five decades of clinical use, there are still many unanswered question on its role in the management of patients with schizophrenia.

In one of the guidelines selected, ECT occupies a residual place in the management of schizophrenia and two recommendations for its use are established:[1]

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| **C** | ECT may be indicated in refractory or medication-intolerant patients. It may also be occasionally useful when there is an evident psychotic episode and the disorder is characterized by catatonic or affective symptoms.[1] |

It is unlikely that patients with persistent, chronic or neuroleptic-resistant schizophrenia respond to ECT. However, there is evidence indicating that ECT coupled with antipsychotics may be beneficial for at least some of these patients (**level of scientific evidence IV**).[1]

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| **C** | Some patients with persistent, chronic or neuroleptic-resistant schizophrenia could benefit from ECT.[1] |

The assessment prior to ECT should include psychiatric clinical history and a psychiatric examination to verify the initiation of treatment, a general medical exam to identify possible risk factors (clinical history and physical exploration, assessment of vital signs, haemogram, blood electrolytes values and electroencephalogram), anaesthetic assessment to evaluate the type and degree of anaesthetic risk, obtention of the informed consent and an assessment that summarizes treatment indications and risks and that suggests if other additional evaluation techniques, treatment modification or changes in the ECT technique are indicated.[47]

Recent myocardial infarction, some cardiac arrhythmias and lesions that occupy intracranial space should be a call for caution given that ECT causes temporary increases in heart rate, cardiac work load, blood pressure, intracranial pressure and permeability of the blood-brain barrier.

The main side effects of ECT are cognitive, relating to a transient postictal confusional state and a longer period of anterograde and retrograde memory impairment, which is usually resolved in a few weeks after cessation of ECT.

## 6.3. Psychosocial interventions

Psychosocial interventions encompass a series of measures aimed at minimizing the patient's vulnerability to stressful situations, facilitating recovery processes, boosting adaptation and family, social and educational-occupational functioning, as well as increasing the patient's resources to cope with conflicts, problems and interpersonal or biographical tensions. These interventions can also favour the analysis or modification of perception styles or defence mechanisms and affect areas such as relapse prevention, acquisition of social skills and social and occupational functioning.

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The care framework that is offered to patients should fulfil a therapeutic function; it should be aimed at promoting change in mental, behavioural and relational functioning, with the aim of promoting the capacity to live a healthier life.[129]

Over the past few years, a new approach has been developed to understand the treatment and course of severe mental disorders such as schizophrenia, represented in the concept of Recovery. It is the disease recovery process, understood in terms of the recovery of autonomous functioning and community integration, and not only as stabilization of symptoms. On the other hand, the concept of recovery also refers to boosting the patient's capacity to manage the disease and, therefore, the patient's role in the entire process (empowerment). This requires reworking care systems and making efforts to eliminate discriminatory barriers.

Many patients with schizophrenia are not receiving proper care because, despite the fact that there is scientific evidence available on effective psychotherapeutic treatments and psychosocial interventions, the care they receive is not tailored to their particular needs. At present, psychosocial treatments with proven efficacy are being notably underused.[130]

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| **C** | The choice of a specific approach will be determined by the patient, his/her clinical situation, needs, capacities and preferences, as well as by available resources at that time.[5] |
| **C** | It is recommended that psychosocial interventions are carried out by professionals with specific training, sufficient experience, qualifications (backed by supervision and technical expertise), as well as availability and constancy in order to maintain a long term relationship.[6] |

The spectrum of psychosocial interventions is very broad and encompasses several types of interventions that are often integrated in a care continuum, making their delimitation difficult. In order to describe them more clearly, psychosocial interventions have been classified in the following sections:

1. Cognitive-behavioural therapy
2. Supportive therapy
3. Psychodynamic psychotherapy
4. Psychoeducations
5. Family interventions
6. Cognitive rehabilitation
7. Social skills training
8. Training in Activities of daily living
9. Expressive activities (art therapy, music therapy, etc.)
10. Occupational insertion support

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11. Housing resources

The first three sections correspond to specific psychotherapeutic treatments. Psychoeducation and family interventions can be developed as specific treatments or be considered within the framework of other interventions. Section 6 to 11 addresses several rehabilitation interventions and support resources for social integration.

Psychotherapeutic treatments share the fact that they stem from several specific psychological techniques, recognized by the scientific and professional communities. Based on mental, physical or interpersonal manifestations, the fundamental aim of these treatments is to reduce suffering, mainly relating to mental disorders, and to promote healthy changes. The aspects that have been taken into account in all therapeutic modalities are:

- Relationship with the patient.
- Therapist's active role.
- Need to establish clear limits in the approach in order to avoid premature treatment interruption and lack of impulse control.
- Therapist's flexible attitude.
- Therapist's capacity to create warm and empathetic surroundings, as well to manage his/her own feelings.[129]

Psychotherapy stems from the basic premise of the existence of a human relationship based on trust, the acknowledgement of mental suffering, deep understanding and attentive presence. Whenever psychotherapy is indicated, is should be carried out within a wider therapeutic approach integrating other psychosocial and psychopharmacological interventions.[47]

The general objectives of psychotherapy and psychosocial interventions in general are to minimize vulnerability and stress and to maximize adaptation capacities and functioning, while favouring social support.[4]

Psychotherapy should be based, in the first place, on the patient's needs and preferences, but it is not possible to ignore the importance of respecting his/her system of values in the selection of objectives to achieve. Optimum psychotherapy uses several strategies and facilitates the consolidation of an ongoing interpersonal relationship based on understanding and empathy between the patient and psychotherapist.

Likewise, psychotherapy encompasses a series of interventions that may be useful for the treatment of schizophrenia and early phases of psychosis. The most commonly described forms are supportive, cognitive-behavioural and dynamic. In practice, many psychotherapists employ a combination or synthesis of different approaches and strategies. This combination is individually determined and adjusted for each patient based on his/her specific clinical state, coping capacities and preferences.

Fenton reviewed randomized clinical trials on psychotherapy spanning from the 60s up until the mid-90s[131]. This review highlights the important role exercised especially by researchers from

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the United States and Great Britain in the study of psychotherapy in schizophrenia. The studies reviewed are framed within the historical context of research and treatment of the disease, indicating that progress in this respect has not been unencumbered by ideological battles. The conclusions of this review, pertaining to the period between 1985 and 1995, are listed below and should be situated in the context of the advances in biological therapeutics, family interventions and community support techniques:

a. Treatment should be based on an alliance that provides continuity of care and that integrates the different modalities of treatment based on the phenomenological understanding of the patient's needs. Given the heterogeneity of the disease, treatment should be based on the individual needs of the patient.

b. The core aspect is a trust-based alliance and intrusive interventions are not advised, advocating a supportive role and an active agent role in the management of the disease.

c. The most appropriate focus in psychotherapy should be: helping the patient in the management of the disease, addressing daily problems, eclectic approach that includes education, crisis intervention, empowerment and support for existential anxieties, practical advice and insight.

d. The stress vulnerability model is considered adequate to guide psychotherapeutic efforts.

e. The psychodynamic concept of counter transference is reviewed to help clinicians avoid power struggles and other undesirable reactions in the course of treatment of patients with schizophrenia.

In terms of psychosocial rehabilitation, its aim is to facilitate recovery processes and prevent deterioration of social, occupational, educational and family function, as well as to promote these capacities as much as possible.[47] According to the Spanish Association of Neuropsychiatry, psychosocial rehabilitation strives for the following objectives:[132]

- To favour and enable the acquisition or recovery of a series of skills, abilities and competences necessary for the functioning in community in the best normalization and quality of life conditions possible.

- To promote social integration within the community, supporting and encouraging the most autonomous, integrated and independent functioning possible, as well as the occupation of valuable and normalized social roles.

- To provide the follow-up, support and social help required by each person in order to ensure his/her maintenance in the community in the most autonomous and normalized manner possible in each case.

- To prevent or reduce the risk of psychosocial deterioration, marginality and/or institutionalization.

- To advise and support the families of patients with schizophrenia to favour their competence in the management of the problems they face and positively impact the

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rehabilitation process and social adjustment of their relatives with psychiatric problems.

Psychotherapeutic treatments and rehabilitation interventions can be developed individually or in a group setting. This choice will depend on the patient's characteristics and state, preferences and resources available to professionals and teams. Group-based approaches offer patients a sharing space which facilitates free oral expression and favours their ability to understand their own suffering and the suffering of other participants. It enables multifocal identification and transference relationships with the group therapists, which are shared with other group members.

Group-based psychosocial therapies and interventions hold a very important role in schizophrenia management programs: they provide a specific and realistic reference setting, promote the alliance and the therapeutic relationship and provide, aside from improved self-knowledge, a better understanding of other group members, thus improving interpersonal relationships and the capacity to cope with psychotic symptoms.

Kanas describes three main theory approaches in group-based interventions: educational, psychodynamic (aimed at insight) and interpersonal (aimed at interaction).[133]

- Educational: aims to help patients manage their most pressing problems and symptoms, using advice and educational techniques. Information regarding the disease, medication and social skills applied to interpersonal relationships are usually the most covered topics.
- Psychodynamic: aims to improve the patient's self-knowledge by means of the clarification and interpretation techniques.
- Interpersonal: aims to improve the capacity of its members to relate better with others, by means of the here and now of the interaction with other group members and/or the discussion of their interpersonal problems and possible solutions.

Group-based treatment can be included throughout the patient's management process, requiring a different intervention modality depending on the phase of the disease and the degree of impairment and clinical stability.

Scientific evidence endorsing the efficacy of group therapy in schizophrenia is not robust. Some well controlled studies in stable patients indicate modest scientific evidence supporting the effectiveness of group therapy at improving social adaptation and coping capacity. For hospitalized patients in acute phases, there is no scientific evidence in favour of group psychotherapy aimed at insight and there is evidence pointing to the possibility that it may even be harmful. However, self-help groups may be useful for helping patients cope with their symptoms, practice with others in a controlled environment, and develop a therapeutic alliance with the treatment team (**level of scientific evidence IV**).[4]

Despite its specificity, we have chosen not to address group-based approaches independently, but to consider that the group-based modality can be present in each of the different psychosocial interventions.

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## 6.3.1. Cognitive-behavioural therapy

It is a specific psychological intervention that stimulates the patient to establish relationships between his/her thoughts, feelings or actions in relation to current or past symptoms.

It enables recipients to reassess their perception, beliefs or reasoning linked to the target objective. It entails at least one of the following actions: a) monitoring of thoughts, feelings or behaviours in relation to symptoms; b) promotion of alternative symptom coping routes; c) stress reduction.[3]

Over the past decade there has been a growing interest in applying cognitive-behavioural therapy (CBT) techniques to people with schizophrenia, especially those who present psychotic symptoms despite receiving adequate pharmacological treatment (**level of scientific evidence 1a**).[3] The main objectives of CBT in medication-resistant psychosis are to reduce the intensity of delusions and hallucinations, as well as to stimulate the patient's active collaboration to reduce the risk of relapse and social impairment levels.[3]

In terms of the patient acceptability of CBT, there is limited scientific evidence, based on the number of subjects who dropped out of the studies that suggests that CBT is more acceptable for patients than standard treatment by the end of treatment or at follow-up (**level of scientific evidence 1a**). When CBT is used to treat a first episode of psychosis, there is some scientific evidence suggesting that CBT is more acceptable than standard treatment (**level of scientific evidence 1b**).[3]

There is scientific evidence on how CBT duration and/or number of sessions can influence treatment efficacy. Hence, some studies indicate that in the treatment of people with schizophrenia, CBT comprised of less than ten sessions or which lasts under three months slightly improves depressive symptoms compared to standard treatment, but there is not an improvement of psychotic symptoms (**level of scientific evidence 1a**). In this respect, there is some scientific evidence suggesting that CBT which lasts over 6 months and which includes more than ten sessions manages to improve the mental state when compared to other interventions (**level of scientific evidence 1b**).[3]

The objectives of the SRSE of CBT for schizophrenia, conducted by the Cochrane collaboration,[7] were to review the effectiveness of CBT in people with schizophrenia when compared with standard care, specific medication, other interventions and no intervention. 10 randomized clinical trials are included (**level of scientific evidence 1a**):

a) In the comparison of CBT with standard care, the results of the meta-analysis are:

- There are no significant differences between both approaches in terms of the reduction of relapse rate and number of re-hospitalizations.
- There are statistically significant differences in favour of CBT in terms of the reduction of hospital stay length.

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- There is a difference in favor of CBT for general psychological and psychiatric functioning measure with the Global Assessment Scale (GAS)[d] at short- and mid-term. There is no long-term maintenance of this effect.
- There are statistically significant differences in favour of CBT in terms of improvement of the mental state. At one year, differences are not statistically significant.

There is insufficient evidence to determine the overall effect of CBT with standardized scales for the clinical course of schizophrenia (BPRS[e], CPRS[f], PANSS[g]). In terms of the groups of specific symptoms, CBT has a significant long-term effect superior to standard care on hallucinations.

- Patients who receive CBT should a greater degree of insight than those who only receive standard care, both at short- and mid-term. No significant differences are observed at long-term.
- There are no differences in terms of quality of life.
- In regards to social functioning, only one significant effect that favours CBT is observed in prosocial behaviours.

b) When comparing CBT to standard care and supportive therapy, meta-analysis results do not show effects in relapse rate or in improvement of the mental state.

c) When comparing CBT in combination with psychosocial interventions and educational interventions, CBT is shown to contribute to the reduction of the number of people who drop out of treatment.

Gaudiano conducted a review of 12 randomized clinical trials that compare CBT with normal care, psychoeducation and supportive therapy.[134] The data analysed verify improved symptoms when CBT is added to standard care. It is also suggested that CBT is particularly effective in the treatment of positive symptoms (**level of scientific evidence IIb**).

Zimmerman and collaborators published a meta-analysis of 14 studies on the scientific evidence of the effect of CBT on positive symptoms in schizophrenia .[135] Results indicate that the effect of CBT, no matter how slight, is significantly positive (level of scientific evidence 1a). The authors attribute this slight improvement to the severity of the disorder.

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[d] The Global Assessment Scale (GAS) is a measurement scale that assesses the general functioning of the psychiatric patient. The GAF scale, Global Assessment of Functioning, is the new version of this scale.

[e] BPRS: Brief Psychiatric Rating Scale.

[f] CPRS: Comprehensive Psychiatric Scale.

[g] PANSS: Positive and Negative Sympton Scale.

Terrier and Wykes performed a review of 20 randomized clinical trials searching for evidence of the efficacy of CBT, and, when positive, they attempted to understand why it was efficient and to determine what apparent benefits could be owed to other potential causes, with a view to improve the assessment of treatments. The trials included compare CBT with standard care and support group. The review's main conclusion is that CBT is effective in the treatment of schizophrenia (**level of scientific evidence 1a**).[8] Slightly improved positive symptoms are reported when compared to standard care. Additionally, it is suggested that the efficacy of pharmacological treatment can hide the efficacy of other treatments. There is also some scientific evidence that CBT provides protection from future relapse for the following 18 months. In this respect, patients who only receive medication present more residual symptoms. CBT demonstrates more benefits than standard care in the prevention of the evolution of psychosis in early intervention, preventing the prescription of antipsychotic medication and reducing symptoms. Finally the authors determined that many important aspects of CBT are not quantified and they recommend the identification and assessment of these aspects in larger trials.

In the case of patients in acute phases, there is some scientific evidence indicating that CBT produces an effect faster than standard treatmen, but this does not occur when compared to supportive interventions.[8] However, there is scientific evidence in this phase that CBT couple with standard care can accelerate recovery and hospital discharge (**level of scientific evidence 1b**).[1]

Cognitive improvements ensure the interest of future research, despite the fact that the scientific evidence found up until now is vague.[1]

In a RCT of first schizophrenia episode, CBt versus standard treatment presented significant improvements in post-traumatic stress at 12 months and in positive symptomatology at 6 months. These effects are not maintained beyond 12 months.[136]

One of the difficulties in the recommendation of specific interventions in the phases of early psychosis is that many of the research studies that have been developed compare early intervention teams (with a "package" of psychological interventions amongst others) with standard care teams. In these studies some use CBT as part of their therapeutic offer, obtaining the following results at 18 months: improved social, vocational and quality of life functioning, and increased patient satisfaction and adherence to medication (level **of scientific evidence 1b**).[137]

However, when early intervention teams plus CBT is compared to early intervention teams, differences are not significant, neither in suicidal tendencies nor in treatment dropout (**level of scientific evidence 1b)**[138] nor are benefits added to those of early intervention teams, nor are there differences in hospital admittances (level of scientific evidence IIa).[139]

In Pfammatter's meta-analysis, a beneficial effect of CBT on positive symptoms in schizophrenia is reported, although the stability of these effects over time and the element responsible for this improvement remain unclear (**levels of scientific evidence 1a**).[140] Together with its efficacy on positive symptoms, CBT should be considered in the treatment of stress,

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anxiety and depression in patients with schizophrenia, and therefore some adaptations to the techniques employed in other people may be required.[2]

Crawford-Walker and collaborators carried out a review of distraction techniques used in the treatment of schizophrenia. These are specific techniques to cope with auditive hallucinations that can be divided into three categories:[141]

- Cognitive, for example tasks such as Reading a book, counting objects, thought stopping techniques, answering the voices.
- Behavioural, such as social activities, in which active efforts are made to distract oneself from the voices, for example reading or going for a walk.
- Physiological such as relaxation, exercise, listening to music.

This review has included all randomized controlled studies in patients with schizophrenia and other psychotic disorders in which these techniques are used. There is no evidence that they provide benefits over standard treatment (**level of scientific evidence 1a**).[141]

The conclusions on the efficacy of CBT for incipient psychosis are limited due to the different types of results assessed and the reduced number of subjects in the majority of studies. Despite this, overall results for CBT are promising, as are some significant benefits that appear at long-term. Furthermore, research on CBT for incipient psychosis is clearly justified given the results of CBT efficacy in resistant schizophrenia. However, its clinical use should be limited to people in prolonged recovery or secondary comorbidity such as depression, until there is more literature on CBT that provides a CPG for this area.[41]

A SRSE on psychosocial treatment in the first episodes of psychosis describes studies which suggest that CBT and psychological support reduce symptoms more than standard intervention does, and can have long-term (18 months) beneficial effects on them (level of scientific evidence 1b). Likewise, they suggest that CBT obtains better results than standard intervention in the reduction of suicidal risk, hospitalization and symptoms, and improvement in adaptation to the disease and quality of life (**level of scientific evidence 1b**).[142]

Lawrence and collaborators reviewed controlled studies on group-based CBT. They selected a total of five randomized controlled studies that included 214 patients with schizophrenia, and compared group CBT with other types of interventions. The intervention was proven to be effective at reducing social anxiety and depression when compared to standard treatment. Results regarding auditive hallucinations were inconsistent. In terms of relapses, rehospitalizations and general symptomatology, they were shown to improve to the same degree as the control group that received psychoeducation. The conclusion is that gorup-based CBT is more effective than standard treatment, but does not provide benefits when compared to group-based psychoeducational interventions. Available data and scientific evidence do not make it possible to formulate practical recommendations on this type of intervention.[143]

Beyond the results provided by specific techniques, recent research such as Grawe's shows how the integration of several CBT interventions, both at a family level to improve communication, problem solving and coping with crises in the home, and at an individual level for the management of residual symptoms and impairment, in an approach that also includes

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pharmacological treatment and case management yields better outcomes.[144] These results are measured in terms of decreased negative symptoms, non-persistence of positive symptoms and lower number of hospitalization days. Patients who present recent onset psychosis obtain better results (**level of scientific evidence 1b**).

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| **A** | Cognitive-behavioural therapy (CBT) is recommended for the treatment of psychotic symptoms that are persistent despite receiving adequate pharmacological treatment.[3] |
| **A** | CBT should be indicated for the treatment of positive symptoms of schizophrenia, especially hallucinations.[7] |
| **A** | CBT is recommended as a treatment option to aid in the development of insight and to increase adherence to treatment.[7] |
| **A** | CBT is recommended to prevent the evolution to psychosis in early intervention.[8] |
| **A** | CBT is recommended as a treatment option to prevent the prescription of drugs and reduce symptomatology in the management of incipient psychosis.[8] |
| **A** | CBT, together with standard care, is recommended in the acute phase to accelerate recovery and hospital discharge.[1] |
| **B** | CBT should be considered for the treatment of stress, anxiety and depression in patients with schizophrenia and consequently the techniques employed should be adapted to other populations accordingly.[2] |

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## 6.3.2. Supportive psychotherapy

It is not easy to find a widely accepted definition of supportive psychotherapy and this is due mainly to the extensive variety of interventions encompasses within this concept, which range from support and counselling in a non-directive and non-structured framework, to interviews in which the therapist follows the guidelines of active and empathetic listening (understanding what the patient is saying and the accompanying feeling), cooperation attitude and crisis management. Support and counselling are the specific components of this type of therapy, but suggestions, explanations and clarifications are also frequent strategies.[145]

It has been observed that many professional interventions aimed at people with schizophrenia contain support elements and that these elements are present in all psychotherapy modalities. In fact, it is one of the most common practices and embodies an essential pillar of psychotherapeutic activity. Supportive psychotherapy is considered an intervention modality that is especially adequate for people with schizophrenia due to the important role of professionals' emotional support attitudes in the treatment of these patients.[146] A support-based therapeutic alliance favours the expression of feelings and the reaffirmation of the patient's

abilities and contributes to the creation of an appropriate setting for the contention of the patient's anxiety.[9]

In relation to the findings of scientific evidence pointing to the beneficial effects of supportive psychotherapy, due to the variety of therapeutic strategies that the concept encompasses and to the frequency with which these type of interventions are performed in mental health services, supportive psychotherapy is often used as follow-up therapy in research aimed at examining the results of other psychological and social treatments. This approach makes it more likely to find studies in which supportive psychotherapy serves as comparative treatment for other therapies than to locate correctly designed research projects in which the benefits of supportive psychotherapy as main treatment are assessed. In this respect, the review performed on 21 randomized clinical trials, most of which were designed to analyze specific psychological therapies such as cognitive-behavioural psychotherapy, should be mentioned.[147] Supportive therapy is the comparative therapy with which the advantages of other therapies are determined or the reference therapy used to analyze differences with standard care; it is not the main focus of interest of researchers. Review results show that patients who receive any other psychological or social therapy present better overall functioning than those receiving supportive therapy, and in no case are better results obtained with this therapy than with the treatments with which it is compared. Despite this, the authors do not recommend the establishment of firm conclusions based on this review given that the data on which it is based are limited (**level of scientific evidence 1a**). [147]

As a result, the limited availability of other proven efficacy interventions and patient preferences should be taken into account when making recommendations. On the other hand, supportive relationships, the empathy between a patient with schizophrenia and professionals, and understanding listening exercise a very important role in the development of the therapeutic alliance and are an essential part of good clinical practice. In fact, it is one of the most common practices, and supportive elements can be found in all types of psychotherapy (**level of scientific evidence IV**).[9]

| | |
|---|---|
| **C** | It is recommended to develop the therapeutic alliance by providing emotional support and cooperation, given that this alliance plays an important role in the treatment of patients with schizophrenia.[9] |
| **C** | Supportive therapy is not recommended as a specific intervention in the normal management of patients with schizophrenia if other interventions whose efficacy has been proven are indicated and available. In spite of this, patient preferences should be acknowledged, especially if other more effective psychological treatments are not available.[9] |

## 6.3.3. Psychodynamic psychotherapy

Psychodynamic treatment is an intervention that can be classified as a conversation therapy, in which the relationship between the person seeking treatment and the therapist constitutes the

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main component of therapy.[148] It is structured in regular individual therapy sessions with an experienced therapist or a supervised therapist. Therapy sessions should be based on the psychodynamic or psychoanalytical model, using a wide range of strategies that include exploratory activity aimed at insight or supportive or directive activity, applied with flexibility, working with transference, but with therapists that use a much lesser strict technique than the one used in psychoanalysis.[3]

Malmberg and Fenton's SRSE for schizophrenia included three randomized controlled studies. The objective was to review the effects of psychodynamic therapy and/or psychoanalysis in people with schizophrenia or severe mental disorder. Most patients were inpatients and, over time, were managed at an outpatient level. The therapists' degree of loyalty to the psychoanalytical model is not clear in the reviewed studies. On the other hand, randomized clinical trials on psychoanalytical approaches were not identified. Data were limited for all comparisons relating to psychodynamic approaches and there was no scientific evidence of any positive effect of psychodynamic therapy. Likewise, there was insufficient scientific evidence to suggest that, by the end of treatment, psychodynamic psychotherapy influences an improved level of health when compared to standard care, even though it does seem to contribute to the non-administration of additional drugs after hospital discharge. There is also insufficient evidence to determine if, by the end of treatment, psychodynamic therapy reduces the risk of self-injury or suicide when compared to isolated pharmacological treatment (**level of scientific evidence 1b**). However, it is suggested that patients treated with psychodynamic therapy, when compared to those receiving cognitive therapy for adaptation to reality, have a higher chance of staying in touch with their therapists (**level of scientific evidence 1b**).[148]

On the other hand, Gottdiener and Haslam reviewed 37 studies published on individual psychotherapeutic interventions in patients with schizophrenia: psychodynamic, cognitive-behavioural and non-psychodynamic supportive psychotherapy. Although this meta-analaysis acknowledges significant methodological deficits due to the characteristics of the studies included (small samples, no randomized studies, etc.), it contributes interesting results that corroborate the impressions of many clinicians. All forms of psychotherapy included in the study were associated with improved functioning of patients, but the best results were obtained with psychodynamic and cognitive-behavioural psychotherapy (**level of scientific evidence 1a**). On the other hand, the number of patients who improved exclusively with psychotherapy was similar to those who improved with combined psychotherapy and psychoactive drugs.[149]

New systematic reviews on this topic have not been found. However, renowned authors such as Gobbard, Gunderson and Fonagy insist on the need to perform a greater number of randomized studies in order to confirm the impression, endorsed by international experiences (Finland, Norway, Sweden, Australia and the United States), that psychodynamic psychotherapy may be useful in the treatment of patients with severe mental disorders,[150] as well as in helping professionals to understand patients' experiences and their interpersonal relationships (**level of scientific evidence IV**).[3]

Over the years several scales such as the Working Alliance Inventory (WAI) and the Active Engagement Scale (AES) have been developed, with the objective of trying to predict the continuity of the patient in psychotherapeutic treatment. Within the framework of the Danish project, the APPP (Assessment of Psychotic Patients for Dynamic Psychotherapy) scale has

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been developed, which, unlike prior ones, can be used in the first interviews, before agreeing to initiate treatment or not.[151]

In a study on first episodes of psychosis patients were distributed into three groups based on the assigned modalities of treatment. Group 1: received supportive psychodynamic psychotherapy; Group 2: received integrated treatment (ACT plus multifamily group); Group 3: received standard care. Groups 1 and 2 obtained the best results in the Global Assessment of Functioning (GAF) scale at one year of treatment. Hospitalization duration was lower for groups 2 and 3. The differences between the three groups were not statistically significant in any case (**level of scientific evidence IIa**).[152]

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| **C** | Psychoanalytical and psychodynamic principles may be useful to help professionals understand the experience and interpersonal relationships of people with schizophrenia.[3] |

## 6.3.4. Psychoeducation

It is a therapeutic approach which is not identified with one sole theory model. It provides patients and relatives with specific information regarding the disease and training in techniques aimed at coping with the problems derived from this disease. Its objective is to improve patient and carer quality of life by creating environments with a low level of stress, decreasing the chances of relapse and burden on the family, and providing information on the disorder.

Although the concept of psychoeducation was used for the first time in the medical literature in an article by John E. Donley, «*Psychotherapy and re-education*», in 1911, the dissemination and development of the term in its current form, in the context of schizophrenia treatment, is attributed to Anderson. His aim was to provide families with education on the symptoms and course of schizophrenia and to improve family members' management of the disease. His approach included stress management techniques.

Psychoeducation has been proven to be effective at improving therapeutic compliance. Despite the development of effective drugs in the treatment of schizophrenia symptoms, non-adherence to treatment occurs in over 50% of cases. Psychoeducation can improve knowledge of the disorder but findings are vague in regards to the increase of treatment adherence if it is not also accompanied by motivational and behavioural strategies to follow prescription correctly (**level of scientific evidence 1b**).[2]

Pekkala and Merinder performed a SRSE to assess the efficacy of psychoeducational interventions as a means to help people with severe mental disease when they entered "standard" care, in comparison to the efficacy of "standard" care. This review included 10 randomized controlled trials focused on psychoeducation for schizophrenia or severe mental disorders. Psychoeducational interventions were defined as individual or group-based programs that treat the disease from a multidimensional point of view that includes family, social, biological and pharmacological perspectives. Patients were provided with support, information

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and treatment strategies. Programs were considered "brief" if they consisted of 10 or fewer sessions, and "standard" if they comprised 11 or more sessions. Interventions that included elements of behavioural training such as social skills or training in daily life activities and peer-taught education were excluded. The authors concluded that (**level of scientific evidence 1a**):[10]

- Psychoeducational interventions can reduce relapse and hospital readmission rates after 9 to 18 months of follow-up.
- These programs should be part of the treatment plan.
- These interventions are brief and not too costly, characteristics which should facilitate their implementation in services.

Pitschel et al. carried out a randomized controlled study on 194 patients distributed according to two treatment modalities. In one group, patients and their families received psychoeducation over a period longer than four or five months (separate psychoeducational program which consisted of eight sessions). The other group of patients received "standard" care. Results were assessed at 12 and 24 months after finalizing the intervention, and suggest that a relatively brief 8 session psychoeducation intervention with systematic family involvement in simultaneous groups can considerably improve the treatment of schizophrenia. Psychoeducation should be offered to all patients and family members as part of standard treatments (**level of scientific evidence 1b**).[153]

The diagnosis of schizophrenia is often difficult to accept by the patient and his/her family, especially at the onset of the disease, when diagnosis may be uncertain. By providing information on the causes and effects of the disorder, as well as on the possibilities of recovery, the active role of the patients and his/her environment is facilitated, favouring the therapeutic alliance and involvement in the therapeutic process.

Although information is the patient's and family's right, it should be provided in accordance with their needs and the phase of the disorder.[h] Over the past few years an increasing number of systematic group programs have been developed, with the aim of making knowledge more accessible to patients and their families.

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| **A** | The routine implementation of psychoeducational interventions for patients and family members in treatment plans is recommended.[10] |
| **C** | It is recommended to transmit information gradually depending on the needs and uncertainties of the patient and his/her family and the phase of the disorder the patient is in.[3] |

[h] *Law* 14/1986, dated April 25, Health Authority. Madrid: Official State Gazette; number 102, of 29/04/1986. p. 15207-15224; *Law* 21/2000, dated December 29, on the information rights concerning health and patient autonomy and to clinical documentation. Barcelona: Generalitat de Catalunya Official Gazette; number 3303, of 11/01/2001. p. 464; *Law* 41/2002, dated November 14, basic law regulating patient autonomy and rights and obligations regarding information and clinical documentation. Madrid: Official State Gazette; number. 274,of 15-11-2002. p. 40126-40132.

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## 6.3.5. Family intervention

At present the impact of schizophrenia on family life and the importance of the family's collaboration to properly address the disease are undeniable. The influence on family functioning is obvious, given that family members must deal with crisis situations and live with a person suffering from a disorder which may become chronic and require prolonged treatments, even for life. Hence, all schizophrenia treatment programs should provide attention to families based on their needs as the carers of these patients, and on the key role of their collaboration in the management of the patient's symptoms and rehabilitation.

The first approaches to family intervention (FI) in psychosis are based on theories that emerged during the 1950s within the systemic model, mainly studies on human communication and the double bind theory. These theories had in common the fact that they stemmed from a parentogenic conceptualization of schizophrenia, they emphasized negative, lacking and deficitary aspects of the family and were speculative in nature, lacking solid empirical research that justified their application. The fundamental problem of these interventions was the excessive blaming that was placed on the family, which was considered responsible for the disease. This triggered the understandable rejection on the part of families and family associations with the subsequent marginalization of these types of interventions.

As an alternative, in later years the idea of "family-based" interventions was born, based especially on studies conducted by Brown, which analysed the factors that were involved in relapses. These new perspectives share the fact that they broke away from any etiological approach, they are integrated in global treatment and are based on research that highlights the role of the surrounding environment's characteristics on the course of the disease, mainly life events (acute stress) and high expression of emotions (chronic stress).

The term expressed emotion (EE) refers to a series of attitudes the family has towards the patient (hostility, criticism and overprotection) which are associated with relapse rate. This term was used to develop a series of psychoeducational FI programs aimed at reducing EE, improving therapeutic compliance and providing the family with emotional support. At present EE is considered valid and modifiable, and a strong predictor of relapse and poor evolution in schizophrenia and other pathologies.[13] It seems it would have more predictive influence the longer the duration of the disease, acting independently from other prognostic factors.[13]

FI objectives are:

- To build an alliance with family members
- To provide information on the disorder
- To provide guidance on behavioural problems and relational conflicts
- To provide counselling on family stress management
- To reduce negative family climate
- To improve communication in the family

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- To boost the capacity of family members to anticipate and resolve problems
- To reduce anxiety and guilt within the family
- To maintain reasonable expectations of the patient's functioning
- To help family members maintain proper boundaries, as well as an adequate distance when necessary
- To achieve desired changes in the behaviour of family members and in their belief system

Most studies published on the utility of FI programs in schizophrenia[11,11-14,16,140,155] show the efficacy of this type of interventions in the reduction of relapse and hospitalization rates (**level of scientific evidence 1a**). The reduction of relapses is significant during the first 4 months after treatment; however, these differences disappear after this time. Furthermore, when compared to other treatments, FI reduces the possibility of relapses in patients with persistent symptoms after 12 months of treatment. Improved overall adjustment after 12 months of treatment improved treatment adherence and reduced family burden have also been reported. However, there is no scientific evidence indicating improved negative symptoms and social functioning (**level of scientific evidence 1a**).[155]

Amongst more recent works, a SRSE that reviewed 43 studies (4,124 patients) which included all controlled and randomized or quasi-randomized trials stands out. The studies compared FI (any psychosocial intervention with family members of schizophrenic patients which required more than 5 sessions), with standard care. Results indicated that FI reduced the number of relapses and hospital admittances, and improved treatment compliance. It was not proven that it influenced treatment dropouts or suicide rates. The effect on social impairment was also unclear (**level of scientific evidence 1b**).[155]

Likewise, a meta-analysis included 31 randomized controlled trials. Results indicated that psychoeducational family interventions considerably reduced EE, improved social adjustment, decreased hospitalizations, and produced a reduction of psychopathology at follow-up (**level of scientific evidence 1b**).[140]

In regards to the type of FI, no specific model has been shown to be more effective, although the majority of programs use psychoeducational interventions. The psychoeducational programs that have been suggested include different therapeutic strategies; mainly stress coping techniques, problem resolution training and information on the disease. Some research suggests that these programs, more than just conveying information, are useful at conditioning a change in the relationship between the patient and his/her family, and entail an alliance between family members and therapists.

It seems that more than the type of intervention, the duration of this intervention is what matters the most. Brief interventions have not been proven to be effective at preventing relapses; hence, programs which last at least six months are recommended (**level of scientific evidence 1a**).[3,11,12] The patient's participation in FI is also an important factor given that his/her inclusion significantly reduces relapse rate (**level of scientific evidence 1a**),[3] whereas if there is no such

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participation, the scientific evidence available is insufficient to determine if relapses decrease (**level of scientific evidence Ib**).[3]

Another element which has been studied is the performance of therapy on multifamily groups or single families. There is enough evidence to determine that the efficacy of the intervention is similar if it is performed on single families or in a group-based manner (**level of scientific evidence Ia**),[3] although certain works claim that multifamily groups could be more effective than a single family (**level of scientific evidence 1b)**.[1] Other studies maintain that during the first episode multifamily groups are more effective.[156] However, there is scientific evidence that group-based interventions lead to earlier dropouts than single-family interventions **(level of scientific evidence Ia**).[3]

In studies of first episodes of non-affective psychoses comparing treatment carried out by early intervention teams (which integrate assertive community treatment, multifamily groups and social skills training) with standard care, results favoured early intervention teams in terms of decreased family burden and improved treatment satisfaction.[157] Family selection based on EE leads to effective reduction of relapses at 4-15 months follow-up after treatment. In this respect, the patient's inclusion in the type of intervention effectively decreases relapses (**level of scientific evidence 1a)**.[3]

On the other hand, support groups are effective for the family (**level of scientific evidence III)**.[1] A randomized study compared a group of family members of schizophrenic patients who were in a family self-help program with a group of family members who were on a waiting list. The patients linked to the group presented reduced depressive symptoms, improved emotional functioning and a less negative view of their schizophrenic family members **(level of scientific evidence Ib).**[158]

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|---|---|
| **A** | Family Intervention (FI) programs are recommended to reduce the burden on the family, improve social functioning of the patient and reduce economic cost.[11,12] |
| **A** | The application of FI therapy is recommended in patients who are moderately or severely impaired and, especially, in those with long evolution of the disorder. In patients with recent onset of the disease, each situation will have to be individually assessed.[11,12] |
| **A** | FI should be offered to families who live together or who are in contact with patients with schizophrenia, especially those who have relapsed or present relapse risk, and also in cases of persistent symptomatology.[3] |
| **A** | Psychoeducational FI, based on the management of expressed emotion, is recommended to avoid relapses and improve the prognosis of the disease (its effects are maintained at 24 months).[11-16] |
| **A** | Programs should be applied in groups comprised of family members of similar patients, taking expressed emotion into account and should include the patient to the greatest possible extent. These programs should be added to standard treatment and should never last under six months in order for them to be effective.[11,12] |

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| **A** | Patients should be included, whenever possible, in FI sessions given that it significantly reduces relapses.[3] |
| **A** | Prolonged FI (over six months) is recommended to reduce relapses.[3] |
| **A** | Patients and their families usually prefer single family interventions rather than multifamily group interventions.[3] |
| **A** | Programs should always include information for the families regarding the disease along with different strategies, such as stress coping strategies or problem-solving training.[17,18] |
| **B** | Referrals to patient and carer social networks is recommended.[1] |
| **B** | FI programs should last more than nine months and include characteristics of commitment to attend the program, support and development of skills and should not simply provide information or shared knowledge.[2] |
| **C** | It is recommended to transmit information gradually depending on the needs and uncertainties of the patient and his/her family and the phase of the disorder the patient is in.[3] |

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## 6.3.6. Cognitive rehabilitation

People with schizophrenia present different degrees of cognitive difficulties that affect their information processing capacities, attention, memory, executive function and planning. Cognitive deficits are often related to negative symptomatology and seem to have implications on daily functioning, and also reduce the proper use of psychosocial therapeutic resources.[2]

Cognitive dysfunctions are present from the onset of the disease.[159] Available scientific evidence suggests that cognitive impairment constitutes a fundamental characteristic of schizophrenia, which would justify its inclusion in the diagnostic criteria of this disease (**level of scientific evidence IV**).[160]

Cognitive rehabilitation treatment is defined as an intervention focused on the most basic levels of cognitive functions (attention, memory and executive functions), which aims to improve the performance of these functions. It is an instrument that improves deficitary cognitive functioning, reduces brain hypofunctionalism, increases personal autonomy and psychosocial functioning of patients with schizophrenia with better prognosis.[159]

There are different types of interventions for cognitive rehabilitation that can be carried out individually and/or on a group-based manner and which generally entail one or several of the three following strategies:[2]

- Restoration strategies, which aim to reduce underlying cognitive deficit.

- Compensation strategy, which aims to help the patient compensate for the cognitive deficit.

- Environmental strategies, which consist of using strategies in the patient's social environment, such as external reminders (post-its, objects or electronic instruments), which alert or remind the patient of actions required in a certain social activity of daily life[20] with the aim of reducing the impact of cognitive impairment.

The efficacy of cognitive rehabilitation in patients with schizophrenia has been studied in several meta-analyses. One of them identified three randomized clinical trials, two of which compared it to placebo and the other with occupational therapy.[161] In total they included 117 patients but no effect was proven in terms of mental state, social adaptation or cognitive function (**level of scientific evidence 1a**)**.** In the clinical trial which compared cognitive rehabilitation with occupational therapy, a statistically significant improvement was reported in self-esteem with cognitive rehabilitation (**level of scientific evidence Ib**).

Other studies also report improved mood of patients treated with cognitive rehabilitation[19] and improved daily life functioning, at least during training (**level of scientific evidence Ia**).[162]

26 randomized controlled studies which included 1,151 patients were reviewed. These studies assessed the effects of cognitive rehabilitation on cognitive performance, symptoms and psychosocial functioning in schizophrenia. Results indicated that cognitive rehabilitation strengthens and improves cognitive functioning in a variety of cognitive rehabilitation programs and patient conditions. Effect size in cognitive executica indicates improvement after cognitive rehabilitation, which is maintained over mean eight months after finalizing treatment. Additionally, it was observed that cognitive rehabilitation also has an important effect on psychosocial functioning, even though it is slightly lower than the effect on cognitive execution. It should be noted that the improvement of psychosocial functioning is greater in studies that offer psychiatric rehabilitation and in cognitive rehabilitation programs that include training in strategies, instruction and practice[19] **(level of scientific evidence Ia**).

In regards to characteristic symptoms of the disease, the overall effect size of cognitive rehabilitation on symptom improvement was important but smaller than the effect on cognitive execution and psychosocial functioning.[19] Negative symptoms are related to areas of daily functioning; however, there is no scientific evidence of the relationship of positive symptoms with functional level[163] **(level of scientific evidence III).** On the other hand, the relationship between symptoms and executive function, reviewed in some studies, poses that both positive and negative symptoms are correlated with the level of executive function.[164] However, other variables, such as duration of the disease or number of hospitalizations, do not seem to influence this level.

Some studies have been conducted which address the rehabilitation of specific cognitive functions (executive functions, attention and memory):

- In terms of executive functions, assessed using the Wisconsin Card Sorting Test (WCST), it has been demonstrated that it can improve variables such as perseverance errors, number of categories achieved and conceptual level responses (**level of scientific evidence Ib).** It has also

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been reported that disorganization symptoms significantly correlate with perseverance in the WCST; on the other hand, there is significant correlation of negative symptomatology with worse performance of the WCST.[166]

- The same results have been obtained in terms of sustained attention: the more negative symptomatology, the worse performance of the Continuous Performance Test (CPT).[166] there is also evidence of improvement in the performance of basic attention exercises versus sustained attention. Attention training can improve function in this area in some short term measures, but no consistent mid- and long-term results have been demonstrated (**level of scientific evidence Ib**).[167]

- In terms of memory, different studies[165] show that semantic and affective encoding strategies increase memorization of verbal learning in schizophrenia (**level of scientific evidence II)**.

Roder's integrated psychological therapy (IPT) has shown efficacy in cognitive rehabilitation.[168] In the light of the history of evidence-based treatments for schizophrenia, the authors defend the current importance of implementing specific cognitive and behavioural interventions in the standard care of these patients. This is reflected in their study, which aims to assess the efficacy of IPT under changing treatment conditions and research in academic and non-academic settings. Firstly, a meta-analysis of 30 studies on IPT which included a total of 1,393 patients was performed. The highest quality studies were subsequently selected and analysed to confirm the results of the previous meta-analysis. It was observed that IPT was superior to placebo and to standard care in terms of symptomatology, psychosocial functioning and neurocognition. Additionally, the superiority of IPT continued to grow throughout an 8.1 month follow-up period and in the different dimensions of results, assessment formats, contexts and treatment phases. The analysis showed that IPT is an effective approach in the rehabilitation of schizophrenia and in a wide range of patients with treatment conditions.

From a general point of view, cognitive rehabilitation based only on traditional methods has not been proven to have a clear effect on mental state, cognitive function or social adaptation (**level of scientific evidence** 1a).[161] However, cognitive rehabilitation applied in the patient's social environment has been proven to be effective in social adaptation and relapse prevention (**level of scientific evidence Ib**).[20]

Regarding environmental strategies, there is only one RCT that assesses the efficacy of this intervention at improving functional adaptation and relapse prevention.[20] The 45 patients included in this study were randomly assigned to three intervention groups: 1) medication and standard follow-up, 2) medication and standard follow-up plus cognitive rehabilitation in the setting, 3) medication and standard follow-up plus regular visits like the previous group offering objects for their environmental adaptation, but having no relation with cognitive rehabilitation. Results at nine months of therapy showed statistically significant improvements in social adaptation. In terms of relapse reduction, there were also statistically significant differences: there as a 13% relapse rate in the cognitive rehabilitation group versus 33% in the group using medication and standard follow-up and 69% in the third group (**level of scientific evidence 1b**).

Most studies have been developed on patients with chronic schizophrenia. However, recent research points to the importance of differentiating the different areas affected in first episode

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patients, given that motor and executive function seem to be less impaired than memory and attention in this patient profile.[169] There are indications that significant recovery in problem solving and executive function is possible with one year of treatment.[170] Therefore, results point to the possibility that cognitive rehabilitation is effective in this phase of the disease, even though the objective of rehabilitation should not be only specific deficits, but also related functional deficits (**level of scientific evidence IV**).[169]

All relevant studies suggest the importance of increasing methodologically correct research in this area, given that the scientific evidence available is insufficient to determine if, by the end of treatment, cognitive rehabilitation improves the mental condition **(level of scientific evidence Ib**).[3] It is necessary to clarify aspects such as the association that exists between psychiatric symptoms and cognitive execution and functional measures, the generalization of results in cognitive rehabilitation to situations different from training conditions and the evolution of impairment in relation to the phases of the disease.

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| **A** | The application of cognitive rehabilitation therapy, in all its modalities, is recommended as a technique that improves cognitive functioning in a wide range of clinical conditions of the patient with schizophrenia.[19] |
| **A** | The application of cognitive rehabilitation therapy in the daily environment of the patient with schizophrenia is recommended.[20] |

## 6.3.7. Social skills training

Social skills are defined as behaviours that are effective in social interaction. They include aspects such as verbal and non-verbal communication, self-awareness of internal feelings and attitudes, context perception, capacity for adaptive responses and social reinforcement.

The intervention, which requires a behavioural assessment of interpersonal skills, can be group-based or individual and aims to reduce stress and difficulties in social relationships and to increase coping strategies for social interaction situations. In order to carry out these interventions, behavioural or learning techniques are used that enable patients to acquire some instrumental skills necessary for relating with others and coping strategies to address community living problems.

Different effects associated with social skills training have been described: it improves skills for an independent life; when associated with longer group psychotherapy it reduces symptoms; it improves skills for proper management of medication and symptoms.[106]

Based on Bellack and Mueser's model,[171] which has been referenced by Bustillo and collaborators,[15] there are three different modalities of social skills training:

- **Basic model** *(motor skills model)*, in which complex social behaviours are divided into much more simple steps which can be learned through role playing.

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- **Social problem solving model**, which is focused on areas that should change, including management of medication, symptoms, free time, basic conversation levels and self-care. Each area is pedagogically approached as part of a module with the aim of correcting impaired receptive, processing and expressive capacities.

- **Cognitive resolution model**, which consists of a group-based intervention where the corrective learning process is initially focused on the more basic cognitive disturbances, such as attention and planning.

It has been determined that social skills training leads to better results in social interaction and also in symptomatology, social functioning and quality of life, compared to standard care or occupational therapy.[2] Marder and collaborators, in an RCT performed over a period of 24 months, reported that in patients with early onset schizophrenia better results are obtained with social skills techniques than supportive techniques. In patients without cognitive impairment, the differences in terms of skills acquisition are levelled off over time (**level of scientific evidence 1b**).[21]

According to a SRSE of six controlled prospective studies with sample sizes ranging from 28 to 103 patients and six month duration at two years, the efficacy of the **basic model** –in terms of certain improved social skills- in people with schizophrenia has been demonstrated (**level of scientific evidence IIa**).[172] However, efficacy in reducing relapses has not been demonstrated in any of these six studies. Efficacy in terms of improved symptoms or social adaptation is not clear either. Out of the six studies included in this review, only in two were improved symptoms reported versus the control group, but it should be noted that in the studies in which there was no improvement, the control group's therapy was another psychosocial treatment. As far as social adaptation, this variable was measured in four studies; in two of them social adaptation improved in the social skills training group versus the control group, and did not improve in the other two.

The **social problem solving model** has also been demonstrated to have a favourable effect on the improvement of social skills according to a SRSE.[15] The long term effect of this model has been studied in two randomized clinical trials (**level of scientific evidence 1b**). Both studies showed statistically significant improvements by the end of treatment; in the first study, in terms of a greater number of material goods, greater cooking skills and improved economic management[173] and, in the second group, in two social adaptation scales out of a total of six .[21] Social skills training, according the problem solving model, is effective in relation to social adaptation and its effects are maintained after two years (**level of scientific evidence 1b)** .[21]

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| **A** | The application of social skills training (based on the problem-solving model) is recommended for severely or moderately impaired patients.[21] |
| **B** | Social skills training should be available to patients with difficulties and/or stress and anxiety related to social interaction.[2] |

In terms of the **cognitive resolution model**, a statistically significant effect is yet to be demonstrated in terms of improving social skills.[15] However, it seems that in severely impaired

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patients the cognitive resolution approach could boost the response to social skills training by means of the problem solving model (**level of scientific evidence IIb**).[174]

## 6.3.8. Training in activities of daily living

In occupational therapy, the fundamental pillar of people's functionality is occupation, which includes the different activities that people carry out throughout a lifetime, in order to prepare themselves and exercise their corresponding roles. There are some comprehensive models that are used in occupational therapy to assess, organize and carry out the intervention, such as Gary Kielhofner's model of human occupation, Reed and Sanderon's model of adaptation through occupation and Anne Mosey's model of adaptive skills.

Activities of daily living (ADLs) are part of these areas of human occupation. They include two modalities:

- Basic ADLs (aimed at bodily self-care: personal hygiene, dressing and undressing, eating, functional mobility, use of technical aids, rest and sleep)
- Instrumental ADLs (aimed at interaction with the environment: care of other people or animals, use of communication devices, community mobility, financial management, health management and maintenance, house maintenance and cleaning, food preparation, grocery shopping, safety procedures and emergency responses)

A high percentage of people diagnosed with schizophrenia lose functionality, interfering with their ability to meet the demands of their corresponding roles. In order to tackle these deficits, training in activities of daily living techniques is applied. These techniques are aimed at acquiring or improving skills related with practical aspects of ADLs, with the aim of boosting autonomous living and functional improvement.

There are studies that report that training in activities of daily living leads to better results than standard care in terms of social functioning and quality of life. However, given that the results of recent meta-analysis do not demonstrate a level of scientific evidence indicating that daily living skills programs are useful or harmful for people with schizophrenia (**level of scientific evidence 1a**)[175], large, well-designed, guided and informed studies that demonstrate the efficacy of this type of treatments should be performed.

A consensus document specifies that psychosocial rehabilitation services should include training in social skills and basic and instrumental ADLs to improve behaviour areas associated with self-care, personal competence, economic planning, eating habits and general health care, with the aim of increasing Independence and autonomy is aspects considered basic and standard.[27]

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| **B** | Training in ADLs, based on scientific evidence, should be available to patients who have difficulties handling daily functioning tasks.[2] |

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## 6.3.9. Expressive techniques

These techniques are a set of therapeutic techniques developed by specifically qualified professionals, based on the use of symbolization, communication and expression mechanisms via verbal or non-verbal routes (artistic, musical or body expression). They are different from occupational activities in terms of their objectives and methodology employed. They include therapeutic modalities such as art therapy, music therapy and bodily expression techniques.

The application of these expressive techniques in patients with severe mental disorders is mentioned in a consensus document[27] and it is supported by a long tradition of implementation in hospitalization and rehabilitation services.

The efficacy of expressive techniques in patients with schizophrenia has been studied in several meta-analyses. The results of the study on art therapy are not conclusive enough to determine if its use in people with severe mental disorder would be beneficial (**level of scientific evidence 1a**).[176] The study on music therapy determines that, as complementary treatment to standard care, it may help patients with schizophrenia improve their mental, general and functional state, but it depends to a large degree on the number of sessions applied (**level of scientific evidence 1a)**.[177] Both studies throw light on the need to perform more research assessing the effect of these therapies.

More recent research supports recommending the application of expressive techniques (regardless of the modality used: art therapy, music therapy, etc.) performed by professionals with accredited specialised training in patients with negative symptomatology.[178]

## 6.3.10. Occupational insertion support

The person with schizophrenia may be faced with difficulties when trying to find employment. In most cases, these people wish to find a job; however, there is high unemployment rate in this population sector due in great part to the social stigma linked to mental disorder.[27] Occupational rehabilitation programs are aimed at patients who live in a community, who are not institutionalized, and who present a satisfactory level of psychopathological stability, in order to provide them with support in the development of occupational insertion itineraries. It should be noted that this modality of psychosocial rehabilitation depends to a large degree on available occupational insertion resources and services and employment in a certain setting.

It is important to mention that being involved in an occupational rehabilitation process seems to have positive psychosocial consequences for the patient and, indirectly, for the family, given that it reduces rehospitalizations, and improves insight.[1] It is therefore necessary to assess the need to work at a family, individual and group-based level simultaneously, in order for everyone to understand and support the occupational rehabilitation process.

On the negative side, when finding a job it is possible to lose public financial aid and/or disability payments, which in some cases causes insecurity and doubts in patients and their families regarding the convenience of continuing the occupational insertion process. In any case, the patient should be assured that he/she will have a regular source of income, that it is a

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basic condition for autonomous living in the community, even when many daily needs are covered by different institutional supports. The most integrating and normalizing route for it is paid employment, but when it is not possible the patient should be advised to request the financial aid he/she is entitled to.[179] Activities which enable significant occupation in cases where occupational insertion is not possible should also be offered.[178]

Most studies on occupational rehabilitation are not specific to schizophrenia, but instead refer to severe mental disorders in general. A further aspect that should be noted is that higher scientific evidence level studies have been developed in Anglo-Saxon social and economic settings, which is why application to other settings cannot be automatic and requires specific studies.

The common elements of occupational rehabilitation programs are, amongst others,[15] the fact of finding a normal and stable job, the learning of the skills necessary for the job selection process, unlimited support over time and acknowledgement of the patient's preferences in the selection and obtention of the job position.

Occupational insertion support has two basic modalities in terms of the patient's initial capacities:

- **Pre-employment training:** it is the most traditional approach and consists of the rehabilitation of basic general capacities and competences prior to employment, as well as the development of motivation and orientation in job seeking. This approach can include pre-employment rehabilitation services to protected employment.

- **Supported employment:** it is a more recent approach that consists of immediately incorporating the patient to normalized employment and providing him/her with support in the maintenance of the job. This support can be initiated in the job search and can be general (for example, for personal hygiene, transportation or social relationships) or specific to the particular job (tasks that are required by that job position).[15,25]

Reviews of scientific literature suggest that occupational support should be continued and integrated within a psychosocial rehabilitation program where patients can benefit from the support of a multidisciplinary team [47,180] Several SRSEs have demonstrated the efficacy of occupational support in terms of finding a normalized job in moderately or slightly impaired patients who are in the stable or maintenance phase.[24,25]

A SRSE identified 18 randomized controlled trials of reasonable quality. The main finding refers to the primary result (number of subjects under competitive employment). Supported employment was significantly more effective than pre-employment training in people with severe mental disorders. For example, at 18 months, 35% of people with supported employment had a job, while only 12% of those with pre-employment training were employed. Patients in the supported employment program also obtained better pay and worked more hours monthly than those in pre-employment training (**level of scientific evidence 1a**).[181]

A recent SRSE of the scientific evidence on occupational rehabilitation programs in patients with severe mental disorders identified 11 studies that showed better results in supported employment programs versus other occupational rehabilitation programs (**level of scientific**

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**evidence 1a)**.[23] 61% of participants managed to find a job over the course of the study versus 32% of patients receiving control therapies (other types of occupational or psychosocial rehabilitation programs). In this review the authors recommended performing future research which focused on studying predictive variables of occupational insertion success (modifiable predictors versus non-modifiable predictors), as well as conducting studies with older psychotic populations presenting certain characteristics (for example, female gender).

In a further SRSE of eight longitudinal studies with people presenting severe mental disorders who participated in some occupational rehabilitation program (psychosocial rehabilitation, transitional employment, supported employment, pre-employment training), the **personal variables** that were most closely related with success in the obtention and maintenance of a job were identified.[182] Results obtained show that the most significant variable for predicting success is occupational performance, specifically, the better the patient's occupational performance is at the beginning of the occupational rehabilitation program, the greater his/her success is at obtaining and maintaining the job. Other personal variables that predict successful obtention and maintenance of employment are:

- Patient's degree of self-perceived efficacy in the work place (the more self-perceived efficacy, that is, more positive expectations, the greater insertion success).
- Social functioning during the participation in the occupational rehabilitation program.
- A longer training period.

This SRSE's conclusions are, therefore, that occupational performance and social functioning assessed during occupational rehabilitation are better predictors of occupational outcome than prior employment history and prior occupational functioning (**level of scientific evidence IIb**).[182]

In regards to the implementation of assisted employment (supported employment), in adult patients with severe mental disorders, the following components are identified as factors which, integrated into professional practice, forecast better employment outcomes for these patients (**level of scientific evidence 1b**):[183]

- Focusing on paid employment as an objective that can be achieved by people with mental disorders.
- Prioritizing a fast employment search approach instead of long evaluation, training and pre-employment counselling processes.
- Guiding the employment search in a personalized manner in accordance with the user's preferences, abilities and work experience.
- Follow-up maintained over an indefinite period of time.
- The supported employment program should work in coordination with the mental health treatment team.

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Supported employment has been shown to be the most adequate and effective intervention method for enabling people with severe mental disorders to find normalized employment (**level of scientific evidence Ib**):[183]

Regarding the use of supported employment programs in groups of patients with first episodes, the review of two studies has been conducted. The first study determines that the supported employment model is effective in these patients (40 of them with first psychotic crisis) and that the same importance should be granted to education, meaning that the professional dedicated to occupational rehabilitation should help the patient find educational training or employment, as well as maintain this educational training and/or employment (**level of scientific evidence III**).[184]

The second study, identified via a recent review, is a RCT that also used the supported employment program, randomly assigning 51 patients to the supported employment/educational training modality or to the control situation (more traditional occupational rehabilitation program)[22]. Follow-up was carried out over 18 months (6 months intervention and 12 months follow-up). Results were superior in the experimental group (supported employment or studies), given that 93% of patients in this group resumed studying or working during the 6 months of intervention, versus 50% of patients in the control group. In the follow-up period, 93% continued studying or working versus 55% of the control group (**level of scientific evidence Ib**).

In this same review, a further study which compared, amongst other topics, supported employment with other types of occupational or psychosocial rehabilitation interventions, was described. This study reiterated that supported employment is the best possible type of intervention for finding normalized employment and achieving successful occupational insertion (**level of scientific evidence Ia**).[22]

Supported employment program should be offered to patients with schizophrenia who wish to work or find employment. However, employment-related activities are not the only type of activities that should be offered, especially when the individual is unable to work or cannot find employment.

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| **A** | It is recommended to encourage people with schizophrenia to find employment. Mental health specialists should actively facilitate it and specific programs that incorporate this intervention should be widely established.[1] |
| **A** | Supported employment programs are recommended for the occupational insertion of patients with schizophrenia, given that better outcomes are obtained when compared to other occupational rehabilitation interventions.[22,23] |
| **A** | It is recommended to provide occupational support to moderately or mildly disabled patients and who are in the stable or maintenance phase.[24,25] |
| **C** | Mental health services, in collaboration with social and health care staff and other |

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| | relevant local groups, should facilitate access to employment opportunities, including an array of support modalities adapted to the different needs and abilities of people with schizophrenia.[3] |

## 6.3.11. Housing resources

In our social model, three basic aspects are recognized to affirm that a person is completely integrated: housing, employment and leisure. Within this triple base, housing is:

- The starting point of integration given that the patient feels like he/she belongs and identifies with the community where he/she lives.
- Safeguards privacy
- For people with schizophrenia, it is the platform from which they develop their psychosocial rehabilitation objectives.

Different resources are available to address the need of housing for people with schizophrenia. This diversity should be adapted to the different stages and support needs of the patient, acknowledging socioeconomic conditions, capacities and level of autonomy in performing ADLs:[27]

- **Autonomous housing:**
  It is the most autonomous modality possible in which a person, alone or with others, lives in a rental property or other modality in complete autonomy and only with individualized follow-up from external resources, benefiting from certain economic aids or support provided by community-based social care teams. This modality requires that the patients be in advanced stages of social integration, and with sufficiently normalized use of the community space.

- **Home-based help:**
  Intervention in the home and environment of the patient who lives alone or with his/her family, by a professional team that provides support to home organization, basic care of health and body image, and improvement of adaption to the community. This intervention has three main functions: educational, preventive and health care delivery.

- **Supervised housing/protected apartment/tutored apartment:**
  Housing located in the community for four to six occupants, with staff providing support and supervision in domestic functioning, daily cohabitation and integration in the community environment. In regards to internal organization of the apartment, the group's self-management is promoted, with the aim of creating a family environment that is as normalized as possible.

- **Residence:**
  This type of housing can hold a variable number of residents (15 to 40), providing a flexible residential setting of different durations and an array of different responses to

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people with severe mental disorders (it can be a place to live, a place for rehabilitation or support in certain specific situations). A multidisciplinary team is available to provide 24 hour assistance and support, including an ADL management program, eating services, laundry and free-time organization; with the objectives of social integration, normalization and development of autonomy. This type of housing is different from supervised residence modalities, with more continued health care support.

In any case, it is important to prioritize permanence in the home, based on the patient's possibilities, guaranteeing the necessary support services, over more restrictive housing resources.[4]

In terms of patient preference, people who present a severe mental disorder prefer to live as autonomously as possible in independent housing, given that sharing housing with other residents who also have a mental disorder is too similar to living in a psychiatric hospital.[4] The study performed by the Andalusian Foundation for the Social Integration of the Mentally Ill (FAISEM) shows that people with severe mental disorders in the residential program prefer to live in their homes and/or with their families, but positively value their current home, especially when they live in smaller spaces (and therefore, with fewer people) with more autonomy, which more closely resemble their own home.[185]

Independent housing is associated with improved quality of life, in terms of living conditions and better social relationships, as well as availability and adequacy of affective relationships (**level of scientific evidence IV**).[4]

A SRSE of the scientific literature which assessed the efficacy of supported housing resources reviewed 139 articles which aimed to study the effects of supervised apartments and government sponsored pensions for people with severe mental disorders. In this review no intervention was proven to be more effective than others, even though it was not possible to include any of these articles due to their poor methodological quality .[186]

Another study reports that living in congregate housing with other people with mental disorders favours the improvement of the quality of life of residents with more clinical stability, reducing the number of hospitalizations, hospital stay length and improving the level of linkage with community resources (**level of scientific evidence IIb**).[26]

Several studies evidence the relative insufficiency of housing resources to respond to the complexity of patient profiles managed and their different levels of need (capacity to perform ADLs, social functioning, psychopathological instability, specialised management of general health problems).[26,187]

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| **B** | It is recommended that housing resources focus on the interaction between the patient and his/her environment, activating the individual's personal resources and community resources with the aim of achieving as much autonomy as possible. [26] |
| | If possible, patient preferences in terms of housing and resource selection should be |

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| **C** | favoured, acknowledging the right of the patient to live in an environment that is as normalized as possible, articulating the necessary training programs and providing proper support so that the patient can access and remain in the aforementioned setting.[27] |

# 6.4. Modalities of care and intensive follow-up in the community

Beginning in the 1970s and as a result of psychiatric reform processes, the management of people with severe mental disorders was moved from old psychiatric hospitals to the community with the aim of achieving equal civil rights and social inclusion of these patients.

This change has resulted in the development of different modalities of community-based care in the last 40 years[i], spanning from community mental health teams to other modalities of care and more specific intensive follow-up in the community, such as case management (CM) and assertive community treatment (ACT) analyzed by Burns in the *Community mental health teams*.[188]

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| **A** | It is recommended that patients be treated in the least restrictive setting possible, while ensuring safety and enabling effective treatment.[*] |

## 6.4.1. Community mental health teams

Community mental health teams have been the basic model for the development of other more specialized teams. They consist of multidisciplinary teams comprised of nurses, social workers, psychologists and psychiatrists, and are located in community mental health centres. The size of these teams usually ranges from 10 to 12 people up to 20, depending on whether they include early intervention programs, crisis intervention, home care, etc. These teams present large differences in terms of the health care organization of the context where they intervene, even though they are consistent at an international level in terms of their function and objectives.

Mental disorders constitute the paradigm of multifactorial disorders given that they respond to biological, psychological and social rupture factors. Hence, their assessment and management require care and response in all areas. Good quality mental health care is characterized by a detailed and broad assessment of patient problems and needs.

[i] Initially *case management* referred to a general intensive intervention model in the community that encompassed other subtypes; as these have been gradually defined, *case management* has been used for the modality performed by a *case manager* and ACT for intervention conducted by a team.

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In this respect, since 1990 the United Kingdom has been developing a care program, the Care Programme Approach (CPA), designed so that people with special needs or complex management have a formalized care plan.[189] The coordinator of the program or key worker is responsible for developing this care plan and its review, which includes identified needs, proposed responses, as well as the identification of the person in charge of carrying them out.

In our setting, severe mental disorder management programs performed in community care centres are in charge of performing a comprehensive assessment of the patient's needs and periodic review of the care plan in order to provide a complete, adequate response, as well as continued care follow-up and support.

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| **C** | Outpatient management in a community mental health centre that provides pharmacological treatment, individual, group-based and/or family therapy, psychoeducational measures and different intensities of individualized treatment is recommended for stable patients with relatively mild disability.[28] |

Tyrer et al. conducted a meta-analysis in which the effectiveness of community mental health teams in the treatment of any severe mental disorder was assessed.[29] The meta-analysis included four randomized clinical trials in which community mental health team treatment was compared with conventional care. Results indicated that treatment with these teams could be associated with fewer deaths by suicide or with a lower number of people dissatisfied with the care received and, therefore, with reduced treatment dropouts (**level of scientific evidence 1a**).

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| **A** | Outpatient management in a community mental health centre is recommended for patients with severe mental disorder given that it decreases deaths by suicide, dissatisfaction with care delivery and treatment dropout.[29] |

Malm and collaborators performed a RCT which compared the efficacy of two community care programs in Sweden for patients with severe mental disorder. The first offered standard care and the second an integrated care plan. The main difference between both was the patient's inclusion in decision-making and the emphasis on his/her ability to recover. The second program demonstrated superiority in the social recovery of patients and the degree of satisfaction (**level of scientific evidence 1b**).[30]

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| **A** | Community management with a comprehensive care plan for patients with severe mental disorder is recommended. The patient should be included in decision-making, emphasising his/her ability to improve his/her degree of satisfaction and social recovery.[30] |

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## 6.4.2. Case management and assertive community treatment

There is a type of patients with severe mental disorder characterized by its severity, persistence and impairment who cannot receive adequate psychiatric care due to the difficulty in accessing or remaining in community-based teams.

CM or ACT, which are designed for this type of patients, are not treatments in themselves but models employed to get to know the patient and manage the resources required by this patient. Both models differ mainly in the fact that CM is carried out a by a professional: the case manager; whereas ACT is performed by a specific team.

Initially, CM had an administrative function *(brokerage case management)* which consisted of connecting the patient with the services required and coordinating different providers, i.e., assessment, planning, contact with services, follow-up and safeguarding of patient rights. It soon evolved towards clinical case management, which combines health care with management and coordination of services and provides services in four areas:

- In the initial phase, commitment, assessment and planning.
- Interventions aimed at patient's setting: contact with community resources, with the patient's social network including family and other social support, collaboration with doctors and hospitals, patient advocacy.
- Interventions aimed at the patient: intermittent individual psychotherapy, training in independent lifestyles, psychoeducation.
- Interventions aimed at the patient and his/her setting, crisis intervention, and follow-up.

Within CM, there are some differences depending on whether emphasis is placed on personal capacities and the relationship with the case manager, on rehabilitation aspects, etc.:

- Personal strengths model.
- Rehabilitation model.
- Intensive case management.
- ACT.

A country's culture influences the incorporation of the CM service and the research approach that should be applied. It is necessary to know what interventions this service should have, its main components and the manner in which culture influences CM outcomes in each area.[190]

ACT is the most established model of specialized teams in the United Kingdom, the United States and Australia. Its history began with the development of case management in the United States as a way to address deinstitutionalization.

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ACT is offered by a multidisciplinary team with a low staff-to-recipient ratio, providing individualized treatment that is focused on the patient and his/her natural living setting and direct delivery of services, including support for daily life.

ACT is a clearly defined model:[188]

- Assertive follow-up
- Low caseload (10-15 cases per team)
- Increased frequency of contact (daily to weekly)
- Carried out in the patient's setting
- Emphasis on medication
- Support to family members and carers
- Provision of all types of services
- Coordination with other services when necessary
- Crisis stabilization interventions and availability 24 hours a day, 7 days a week

Both care modalities, CM and ACT, are aimed at patient profile with severe mental illness who present deficitary or negative symptomatology,[191] linkage difficulties, repeated hospitalizations,[192] poor treatment compliance and often additional problems (marginalization, drugs, legal problems).[193]

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| **A** | CM and ACT programs are recommended for high risk patients with a history of rehospitalizations, difficult linkage to normal services or who are homeless.[40] |

Marshall and Lockwood analyzed the effectiveness of ACT as an alternative to standard care in the community, traditional rehabilitation in the hospital and CM. 17 randomized clinical trials which compared ACT with other care modalities in patients with severe mental disorder aged 18 to 65 years were included. Conclusions indicated that ACT is a clinically effective approach for the management of people with severe mental illness in the community. If correctly aimed at people who require frequent inpatient care, it can substantially reduce hospital costs, improving patient outcome and satisfaction (**level of scientific evidence Ia**).[194]

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| **A** | ACT is recommended for people with severe mental disorder aged 18 to 65 years, who require frequent inpatient care to substantially reduce hospital costs, improving patient outcomes and satisfaction.[194] |
| **A** | ACT is recommended for patients with a high risk of rehospitalisation and who cannot continue with conventional community-based treatment.[4] |

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Marshall et al. analyzed 11 randomized clinical trials which aimed to determine the efficacy of CM for community-based management of severe mental disorders. CM was compared to standard care using four indicators: 1) cases connected to services; 2) length of hospital stays; 3) clinical and social outcome, and 4) costs. Conclusions indicated that CM increased linkage to services, doubled inpatient care and increased hospital stay lengths, improved therapeutic compliance but did not present significant improvement of clinical condition, social functioning or quality of life (**level of scientific evidence Ia**).[31]

| | |
|---|---|
| **A** | CM is recommended for community-based management of patients with severe mental disorder with the aim of increasing linkage to services and improving therapeutic compliance.[31] |

Mueser et al. analyzed the results of 75 studies on community-based management of people with severe mental illness in which schizophrenia accounted for 66% of cases. 44 ACT programs and 16 intensive case management programs were included. Controlled studies of both models indicate that they both reduce length of hospital stay and increase stability in the home, especially in patients who are frequent users of services. They seem to have a moderate effect on the improvement of symptomatology and quality of life. Some studies suggest a limited effect on social and occupational functioning, arrests and length of imprisonment (**level of scientific evidence IIa**).[32]

| | |
|---|---|
| **B** | ACT and intensive case management programs are recommended for patients with schizophrenia who are frequent users of services.[32] |

Different studies on the efficacy of CM or ACT to reduce inpatient care or the length of hospital stay often show contradictory results. A SRSE performed by Burns showed that when consumption of hospital services by patients with severe mental disorder is high, intensive case management may reduce it, but is less effective when this consumption is low (**level of scientific evidence Ia**).[33]

| | |
|---|---|
| **A** | Intensive case management is recommended in patients with severe mental disorder when they use hospital services with the aim of reducing this consumption.[33] |

There are no comparative studies indicating if CM is superior to ACT or vice versa; their function and objectives are the same, given that the implementation of one model or another is conditioned primarily by the healthcare organization of the place where they are implemented.[188] The presence of a psychiatric care network equipped with good community teams and specific programs makes it advisable to have case management which enables the linkage of services that are already offered by the network and continuity of care, while its absence forces specific teams such as the ACT to provide comprehensive care.

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In a RCT of 251 patients with severe mental disorder in north London, which compared the results of ACT teams and community mental health teams, no statistically significant differences were found between both groups in terms of the use of inpatient care or in clinical or social outcomes, even though the group treated with ACT obtained better results in linkage and patient satisfaction. The study's author questions the implementation of ACT services in places that are well-equipped with community teams and presents what assertive community treatment elements could be incorporated to these teams to improve linkage and patient satisfaction (**level of scientific evidence Ib**).[192]

Studies on the effectiveness of these models at an international level often offer contradictory results and throw light on the methodological difficulties of the design of these studies:

- Lack of specification of the interventions used.
- Poor characterization of the patient population.
- Inadequate outcome measures.
- Inadequate length of the program.
- Lack of specification of the community context.

In spite of this, there is consensus on its utility, enabling a more widespread use. In our setting, there is increasing experience on the implementation of the CM model, the Individualized Services Program[195] coordinated by the current psychiatric network with health delivery and resource management functions, even though there is still a lack of studies on its effectiveness. Likewise, there are several experiences on ACT implementation in predominantly rural settings and care delivery to homeless patients.

In a RCT standard care was compared to ACT in a sample of 20 patients with schizophrenia and mood disorders. Results show that ACT is superior in terms of quality of life, overall functioning and reduction of the level of unknown needs (**level of scientific evidence Ib**).[196]

Another RCT compares ACT with standard care in a sample of 235 patients with schizophrenia who are on parole, and determines that ACT is especially effective in people with drug and alcohol problems, in whom a reduction of criminal activities is observed (**level of scientific evidence Ib**).[197]

Finally, a cohort study analyzes the efficacy of ACT in 66 patients from minority ethnic groups with a diagnosis of severe mental disorder and language and cultural barriers to access services. Results show higher effectiveness of ACT in this type of patients (**level of scientific evidence III**).[198]

Likewise, indications are established for these models, which are deemed especially useful for patients with schizophrenia and other additional problems such as drug use and/or legal problems, or for patients who belong to minority groups.[198] New indications in early onset schizophrenia are also assessed.

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The American Academy of Child and Adolescent Psychiatry CPG considers that treatment of early onset schizophrenia prior to 18 years of age requires a continuum of providers of services and treatments. Aside from the administration of psychoactive drugs and psychotherapy, some of these young patients require intensive case management and community-based support services (**level of scientific evidence IV**).[34]

| | |
|---|---|
| **C** | Intensive case management and community-based supportive services, coupled with the administration of psychoactive drugs and psychotherapy, is recommended in patients who present early onset schizophrenia (prior to 18 years of age).[34] |

# 6.5. Monitoring of the health state and somatic comorbidity

Having a schizophrenic disorder is associated with a higher risk of having other diseases and increased mortality.

People with schizophrenia have a higher degree of physical comorbidity. It is estimated that nearly half of these patients present a medical disorder, half of which are not detected by the physician treating them. However, recent studies such as Carney's et al. have found these values to be much higher, suggesting that 70% of people with schizophrenia have at least one other medical disorder, and that 33% have three or more health disorders, the most common being hypertension, COPD and diabetes. Hence, premature mortality is five times higher in this population.[199]

Lambert describes the most common health problems (diabetes, hyperlipidemia, cardiovascular disorder, obesity, malignant neoplasm, AIDS, hepatitis C, osteoporosis, hyperprolactinemia, and other physical disorders) detected in patients with mental disorders, associating them with their psychiatric condition, medication and lifestyle (table 9).[199]

**Table 9. Common health problems in patients with mental illness and relationship between physical disease and psychiatric condition, medication and lifestyle factors**

**Diabetes**

- Increased risk, in patients with schizophrenia, of developing anomalies in glucose regulation, insulin resistance and type 2 diabetes mellitus.
- Lifestyle factors, such as poor diet and sedentarism, which aggravate the problem.
- All antipsychotic drugs (some second generation drugs more than first generation drugs) increase the risk of developing diabetes.

**Hyperlipidemia**

- Antipsychotic mediations have been associated with the development of hyperlipidemia (both

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related with, and independent from, weight gain).

- Some atypical antipsychotics (e.g. haloperidol) do not have an effect on lipids; phenotiazines (e.g. chlorpromazine) tend to increase triglyceride levels and reduce high density lipoprotein levels.

- Second generation antipsychotics derived from dibenzodiazepines (e.g. clozapine, olanzapine) are associated with increased levels of fasting glucose and lipids, when compared to risperidone.

**Cardiovascular diseases (hypertension, arrhythmias)**

- People with mental illness have a higher chance of presenting cardiovascular and respiratory disorders than the rest of the population.

- Antipsychotic drugs contribute to metabolic syndrome X (hypertension, hyperlipidemias, hyperglycaemia, insulin resistance and obesity).

- Lifestyle factors (smoking, alcoholism, poor diet, and lack of exercise) contribute to an increased risk of cardiac problems.

- Mortality due to ischemic cardiopathies, cardiac arrhythmias and myocardial infarctions is higher in people with mental illness.

**Obesity**

- 40-62% of people with schizophrenia are obese or overweight.

- First and second generation antipsychotics can result in weight gain. Second generation drugs derived from dibenzodiazepines (e.g. clozapine, olanzapine) produce fast short-term weight gain. Long-term differences between both types of drugs are unclear.

- Lifestyle factors and poor capacity to modify them also affect obesity.

**Malignant neoplasms**

- In general people with schizophrenia do not have a higher risk of developing cancer, but if they do develop this disease they have a 50% lesser chance of overcoming it.

- There are differences in terms of site-specific cancers in people with mental disorders (e.g. increased risk of breast cancer in women, reduced risk of lung cancer in men).

**AIDS**

- The incidence of AIDS in people with schizophrenia (approximately 4-23%) is higher than in the rest of the population. Associated factors include engaging in unprotected sex and use of injectable and non-injectable drugs.

**Hepatitis C**

- Increased prevalence in people with schizophrenia when compared to the rest of the population.

**Osteoporosis**

- Accelerated osteoporosis rates in people with schizophrenia are attributed to the tendency of antipsychotics to decrease estrogens and testosterone, reduce calcium due to tobacco consumption and alcoholism, and favour polydipsia.

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**Hyperprolactinemia**

- High doses of first and second generation antipsychotics, such as risperidone and amisulpride, increase prolactin levels causing galactorrhea, amenorrhea, oligomenorrhea, sexual dysfunctions and reduced bone mineral density, contributing to the development of cardiovascular diseases.

**Other diseases**

- The incidence of irritable bowel syndrome in people with schizophrenia is 19% (versus 2.5% in the rest of the population).
- The prevalence of *helicobacter pylori* infection is significantly higher in people with schizophrenia (*Odds ratio:* 3.0).

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The elements that contribute to the generation of these types of associated physical disorders stem from different areas, such as lifestyles, which incorporate health risk factors, for example inadequate eating habits, sedentarism, and the use and abuse of substances such as tobacco and alcohol. On the other hand, side effects of pharmacological treatments also contribute to the aggravation of health risks, either as a result of neurological extrapyramidal effects and tardive dyskinesia, or the symptomatology associated with the metabolic syndrome. Lastly, difficulties in access to continued medical care that responds to the needs of these patients can also be considered a risk factor, be it due to the subject him/herself or the healthcare system. All these factors should possible be considered, as well as their interaction, as the basis of worse general health state in the population suffering from a schizophrenic disorder.

Marder et al. suggest, as a result of the consensus among psychiatrists and other medical experts, the monitoring of schizophrenic patients' physical health, particularly those receiving antipsychotic treatment. To do so the following issues were examined: 1) weight gain and obesity; 2) diabetes; 3) hyperlipidemia; 4) prolonged QT interval in the ECG; 5) increased prolactin and associated sexual side effects; 6) extrapyramidal side effects, akathisia and tardive dyskinesia; 7) cataracts; and 8) myocarditis. For each one of them a review of available scientific evidence was performed and the corresponding recommendations were developed.[101]

In this respect, participants agreed to recommend that psychiatrists and other mental health professionals should exercise an active role in the monitoring of the general health state and also proposed specific formulas to carry it out by means of interventions that could be performed in routine therapeutic meetings. Hence, they suggest monitoring BMI, glycaemia and lipidemia, performing an ECG, inquiring on symptoms associated with increased prolactin and its values, as well as the incorporation of basic neurological and vision exams (**level of scientific evidence IV**).

Kelly et al. examined these problems, concluding that most excess mortality seems to be caused by cardiovascular complications, especially coronary cardiopathy.[200] The risk of developing coronary cardiopathy at 10 years is significantly higher both in men and women with schizophrenia, than in the general population (9.4 versus 7% and 6.3 versus 4.2% respectively). In this respect, they suggest monitoring physical health and performing the following

interventions: 1) smoking cessation; 2) weight loss; 3) diabetes management; 4) hyperlipemia management; and 5) hypertension management.

In the last decade there has been increasing interest in the surveillance of health in people with schizophrenia, and, as a result, schizophrenia CPGs have included some references on this topic. Furthermore, the American Diabetes Association, together with the APA and the North American Association for the Study of Obesity, have reached consensus on antipsychotic drugs and obesity and diabetes .[201] The Mount Sinai conference, which took place in New York throughout 2002, has also reached consensus on the aforementioned monitoring.[101]

As a result of all this we can determine the need to incorporate follow-up formulas, health promotion and prevention of disorders in the psychiatric management of schizophrenia by means of the collaboration between primary care, specialized mental health care and the health care system as a whole.

# 6.6. Stigma and discrimination

Stigma is the prejudice that leads to negative attitudes towards the mentally ill. It entails a series of incorrect beliefs, social rejection attitudes, fear and excluding actions which hinder recovery processes and increase the risk of social exclusion and discrimination. This attitude also appears in family members (who are also victims of it), professionals and the patients themselves (self-stigma). The tendency to deny having a mental illness can lead to the refusal to seek professional help, and, in consequence, delay detection, diagnosis and treatment initiation.

The most frequent stereotypes are: danger and association with violent acts, responsibility for the disease, incompetence and inability to perform basic tasks of daily living, unpredictable reactions and lack of control. Stigma is maintained due to poor knowledge and beliefs and prejudices that are very rooted in the population, resulting in strong resistance to logical argumentation. Mass media can contribute greatly to its maintenance or to counteract the problem's dimension.[202]

People with mental illness experience a lot of rejection, especially in the area of employment, from friends and family: 44% reports having experienced discrimination in the area of employment, 43% in relationships with friends and 32% with neighbours. 37% of these patients have experienced discrimination within their own families.[203] The perception of stigma is increased when it is associated with other variables such as race or sex.[204] Reports of verbal abuse are more frequent amongst people with mental illness (41%) than amongst the general population (15%).[205]

There is data indicating that educational campaigns at a local level, campaigns with audience segmentation and campaigns that increase contact with people with schizophrenia, are effective at reducing stigma, given that personal understanding of mental illness leads to increased tolerance.[203] However, no studies have been found on initiatives aimed at reducing mental disorder-related stigma and discrimination which enable the development of well-founded recommendations. Many interventions present very local characteristics and hence it is not easy to generalize their use or outcomes. Based on the consensus document of the Spanish Society

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of Neuropsychiatry, the recommendation is to establish, in accordance with available tests, the most effective interventions to promote integration and reduce the stigma of people with mental illness. These interventions should be aimed at healthcare, communication, education and school professionals, business people and social agents, local police and other law enforcement forces, associations of people with mental illness and their families, with corresponding training formats for each of these groups.

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# 7. Treatment in different phases of the disorder and specific situations

In the first version of this CPG schizophrenia phases were divided into acute phase, stabilization phase and stable phase, and a special section was created for schizophrenia in childhood and adolescence. Additionally, a section on first episodes was introduced, which described new research lines in early phases of psychosis. Subsequently, this research has been widely developed and has promoted the implementation of numerous specific programs in different parts of the world: Australia and New Zealand, Canada, Great Britain, Nordic Countries, Holland, Germany and Spain. This has favoured the appearance of increasing scientific evidence of the potential benefits of early intervention in psychosis. Hence, the phase encompassing the period prior to the onset of the first psychotic episode and the first five years of evolution of the disorder is currently known as early phases of psychosis or incipient psychosis phase, and it has been determined that it can contribute to:[206]

- Avoid biological, social and psychological impairment which, generally speaking, can occur in the years following the onset of the psychotic disorder.[207]
- Decrease comorbidity.
- Favor faster recovery.
- Improve prognosis.
- Help maintain psychosocial skills.
- Maintain family and social support.
- Decrease the need of inpatient care.

Given the importance of early intervention to avoid or minimize the development of the disorder, this section has been reorganized in the following structure:

7.1. Early phases of psychosis:
- 7.1.1. High risk mental state phase
- 7.1.2. First psychotic episode phase
- 7.1.3. Recovery phase and critical period

7.2. Schizophrenia phases:
- 7.2.1. Acute phase
- 7.2.2. Stabilization phase
- 7.2.3. Stable phase

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# 7.1. Early phases of psychosis: incipient psychosis

The evolution of the disorder in these phases and the delay in treatment can lead to disturbance in life circumstances, such as academic and employment failure, self-aggression, changes in interpersonal relationships, interfamily conflicts, etc. These disturbances can produce what is known as "psychological toxicity", the effects of which can limit the subsequent level of recovery from the disorder even if later, at the onset of the first psychotic episode, it is treated effectively.[208,209]

Hence, intervention in this phase should be aimed at detecting the disorder as early as possible and applying the most appropriate treatment for each situation.

## 7.1.1. High risk mental state phase

This phase, also known as the phase with high risk of developing psychosis or the initial prodromal phase, is characterized by a disturbance in emotional, cognitive, behavioural or social functioning and by the presence of unspecific prodromes.

Previously, the concept of prodrome was used as a precursor and predictive factor of psychosis. Yung and collaborators posed a conceptual change, replacing the notion of prodrome with high risk mental state (HRMS).[210] In this perspective, the initial prodrome of psychosis shifts from being seen as an attenuated form of psychosis to being considered a risk factor for its development, especially if combined with other risk factors (e.g., family history), which does not irrevocably lead to psychosis. This would explain the normal changes that take place in the symptomatology of this phase, which contribute to its characteristic diagnostic instability.

As is described in section 4, the group of researchers from Melbourne (Yung, McGorry and collaborators) have established three high risk mental state subtypes: 1. Presence of attenuated psychotic symptoms (subthreshold); 2. History of brief and limited psychotic symptoms (Brief Limited Intermittent Psychotic Symptoms), and 3. Family history of psychosis and persistent reduction of prior functional level.[211]

The concept of prepsychotic intervention is controversial given that it can consider any symptoms present prodromal when they may not actually lead to the development of a psychotic disorder, a phenomenon called "false positive". However, many people will need treatment for their attenuated, disabilitating or disturbing symptoms, regardless of long-term diagnosis. Duration of Untreated Illness (DUI) refers to the untreated period of the disorder, prior to the onset of a psychotic episode. A significant part of psychotic disorder-related impairment is established and accumulated in this phase, which can last between two and five years .[212]

In this phase, the objective of treatment is to prevent, delay or minimize the risk of transition to psychosis. Interventions are usually aimed, on the one hand, at treating present symptoms, and, on the other, at attempting to reduce the risk of aggravating their severity or evolution to a first psychotic episode.

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To do so, different types of treatment have been applied: combined psychological (cognitive-behavioural, supportive and psychodynamic therapies) and pharmacological (antipsychotics, antidepressants, anti-anxiety drugs) treatments in the context of traditional services or specific early intervention programs and services. The types of studies perform present several methodologies: prospective, controlled, randomized studies, amongst others.

It seems that offering people who meet high risk criteria at least one initial psychosocial treatment that includes the nine cognitive therapies, aimed at alleviating the anxiety and impairment of young people, and symptomatic pharmacological treatment, with antidepressants or ant anxiety-drugs, is justified. The information regarding the level of risk of developing future psychosis that should be shared with the patient and family has been discussed. An open approach characterized by exploration and guided by the patient and family's need to know, works well, especially when many of these patients and relatives are aware and concerned about the risk. Overall, a firm and optimistic attitude towards treatment and the possibility of recovery in schizophrenia and psychosis should be adopted (**level of scientific evidence IV**).[213] However, one must not forget that only approximately 33 to 58% of this population will develop psychosis[214] and that the intensity, timeframe and length of the intervention have not been well-established. Therefore, no intervention should be aimed at interpreting symptoms as prodromes, but at indicating that there is a risk of psychosis. Treatment should be aimed at current suffering and symptoms (for example, depression, anxiety and insomnia, amongst others) and close follow-up of the course of the disease will be carried out. Stress factors that may be exacerbating symptoms will be addressed in an attempt to prevent or modify them, changing the threatening perception of these factors and decreasing the corresponding physiological reactions. Specific treatment for psychosis (e.g., antipsychotic medication, education on psychosis) should be initiated only at the onset of true psychosis.[215] There is still an ethical debate on the convenience or lack thereof of applying treatment in patients in whom psychosis has not been established.

The primary results derived from studies regarding this phase are:

- There are individuals at increased risk of developing psychosis (**level of scientific evidence Ib**;[216,217] **levels of scientific evidence III**[218,219]).

- The review of available scientific evidence shows that pharmacological and psychological treatment are superior to placebo or mere surveillance in delaying the transition to psychosis (**level of scientific evidence Ia**;[8] **level of scientific evidence Ib.**[216])

- Additionally, specific early intervention programs obtained better results than unspecific treatments: decreasing or delaying the transition to psychosis, improving prepsychotic symptomatology and preventing social decline and stagnation (**level of scientific evidence Ib;**[216,217,220,221] **level of scientific evidence III.**[218])

| | |
|---|---|
| **A** | Specific early intervention programs are recommended given that they can reduce and/or delay the transition to psychosis.[8,216] |
| **B** | Specific early intervention programs are recommended to improve prepsychotic symptomatology and prevent social decline or stagnation.[216-218,220,221] |

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| | |
|---|---|
| **C** | It is recommended to carefully approach current symptomatology and suffering, both with the patient and with the family, with an empathetic and hopeful attitude.[213] |
| **C** | It is recommended to develop early intervention programs with comprehensive pharmacological (depending on symptomatology) and psychosocial (psychological treatment, family interventions and recovery support) interventions.[222] |
| **C** | Antipsychotic medication should not be prescribed as standard procedure unless there is accelerated deterioration, a high risk of suicide, if treatment with any other antidepressant has not been effective or if increasing aggression and hostility endanger other people.[42] |

## 7.1.2. First psychotic episode phase

The onset of a first psychotic episode can be sudden or insidious, but most patients present some type of prodromal phase which is characterized by a slow and gradual development of several signs and symptoms (social withdrawal, loss of interest in school or work, deteriorated personal hygiene and self-care, unusual behaviour, sudden episodes of anger, etc.), after which an affective or non-affective symptom may appear, a key feature of the active phase, enabling the diagnosis of first psychotic episode. This prodromal phase can last several day or weeks, but may sometimes persist for several months. The characteristics of this period usually reappear in new relapses.

It was observed that the time elapsed from the onset of the psychotic disorder and its diagnosis and therapeutic intervention was very long, a period that was called duration of untreated psychosis (DUP).[212]

The objectives of treatment in this phase are:[213,222]

- To provide a supportive therapeutic relationship.
- To transmit hope to patients and families.
- To introduce the idea of disorder.
- To help patients accept medication.
- To request the family's support and provide them with support too.
- To prevent the patient from harming him/herself or others.
- To reduce psychotic and associated symptomatology.
- To manage disordered behaviour.
- To attempt to restore prior functional level.

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- To offer treatment in the least coercitive and restrictive setting possible.

The primary interventions in the acute phase of a first episode are aimed at providing support and psychoeducation, and are focused on addressing immediate problems at the beginning of treatment instead of focusing on the patient's past traumas or family dysfunction. Support requires conveying hope, respect and empathy that is recognized by the patient. The first step of treatment is to build a therapeutic alliance. Once this has been achieved, supportive therapy is based on a synchronized psychoeducational approach that is tailored to the patient's level of comprehension. These approaches give the patient hope and a feeling of greater control over the disorder.[213]

The main outcomes of the primary studies in this phase were:

- It is important to treat the disorder to reduce DUP, given that available scientific evidence provides better results. In this respect, delayed treatment initiation is associated with the non-recognition of prodromal or primitive symptoms of psychosis (**level of scientific evidence III**)[223] and insufficient accessibility to treatment teams (**level of scientific evidence IIb**).[224]

- Shorter DUP has been associated with (**level of scientific evidence IIb**):[225]

  Improved response to antipsychotics

  Improved overall functioning (measured using GAF or GAS)

  Improved social and vocational functioning

  Higher probability of reaching response criteria

  Improved quality of life

- A longer DUP has been correlated with higher severity of negative symptoms and decreased grey matter as has been determined in a study with volumetric NMR imaging. No correlations have been found with relapse risk and neurocognitive disturbances (**level of scientific evidence IIb**).[225]

- CBT shows more benefits than standard care in preventing the evolution of psychosis in early intervention, decreasing prescription of antipsychotic medication and reducing symptoms (**level of scientific evidence Ia**).[8]

- A study on patients presenting a first psychotic episode reported that supportive psychodynamic psychotherapy or an integrated intervention with assertive community treatment and multifamily group treatment yields better outcomes at one year of treatment, measured using the GAF scale, than standard care, but differences are not statistically significant (**level of scientific evidence IIa**).[152]

- In studies on first episodes of psychosis (non-affective), treatment with early intervention teams, which integrate assertive community treatment, multifamily groups and social skills training, obtains better outcomes in terms of reduced family burden and increased satisfaction, when compared to standard care (**level of scientific evidence Ib**).[152]

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- Another RCT study which compared early intervention teams and standard care, better outcomes were obtained by the intervention group in terms of social and vocational functioning, satisfaction, quality of life and adherence to medication (**level of scientific evidence Ib**).[137]

- Similarly, a review of studies on first psychotic episodes which compare multi-element programs (which include CBT or supportive therapy in addition to pharmacological treatment) with standard care, better outcomes are obtained with the former in terms of symptom reduction, fewer inpatient care days, better adaptation to the disease, decreased suicide risk and improved subjective assessment of quality of life (**level of scientific evidence Ib**).[142]

- It is recommended to provide outpatient care to people in early phases of psychosis using service strategies that are as least restrictive and coercitive as possible: developing strategies to minimize the use of treatments against the will of the patient in early psychosis (e.g. home intervention, alternative residential setting), hospital services focused on young people and routinely divided into "classes", day programs for young people, residential facilities aimed at young people with psychosis so that they can live independently (**level of scientific evidence IV**).[222]

## *Pharmacological intervention in a first psychotic episode*

The current state of research on pharmacological intervention in the first psychotic episode does not yield sufficient scientific evidence to administer first or second generation antipsychotics. However, some studies seem to show that second generation antipsychotics lead to better adherence, whereas first generation ones have a higher dropout rate.[112,121,122,124,226]

| | |
|---|---|
| **A** | If there is no response to treatment or low adherence or persistent suicide risk, the use of clozapine is recommended.[1] |
| **A** | Initiate the administration of low dose second generation antipsychotics.[1] |
| **C** | A 24 to 48 hour antipsychotic-free observation period is recommended, but benzodiazepines may be used for anxiety and sleep disorders.[1] |
| **C** | If there is response to treatment, maintain treatment over a period of 12 months, and if there is symptom remission gradually reduce dose over a few months with close follow-up.[1] |
| **C** | If there is no response to treatment, assess the causes. If there is poor adherence, analyze the reasons, optimize the doses and provide help to improve compliance.[1] |
| **C** | If there is no response to treatment, switch to another second generation antipsychotic and assess outcomes over a period of six to eight weeks.[1] |
| **C** | If second generation antipsychotics are being used and there are side effects, the switch to a first generation drug could be considered.[1] |

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*Psychosocial intervention in a first psychotic episode*

| | |
|---|---|
| **A** | CBT is recommended for the prevention of psychosis progression in early intervention, reducing prescription of drugs and symptomatology.[8] |
| **A** | Treatments in early intervention teams or multi-element programs are recommended in first psychotic episodes (non-affective).[137,142,157] |
| **C** | Informative campaigns are recommended to help recognize prodromal symptoms in the general population, general practitioners and professionals involved with the population at risk.[222] |
| **C** | Very accessible detection teams are recommended to reduce DUP and its corresponding outcomes.[42] |
| **C** | Care should be provided in the least restrictive and coercitive settings possible, while ensuring the safety of the patient and family.[222] |
| **C** | Supportive family interventions are recommended in accordance with their needs.[138] |
| **C** | Intensive case management and community-based support services, coupled with psychoactive drugs and psychotherapy, are recommended for some patients with early onset schizophrenia.[34] |

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## 7.1.3. Recovery phase after the first episode

It is a high vulnerability phase that encompasses the period between the third to fifth year after having had a psychotic episode, comprising the so-called critical period.[207]

An optimum and continued treatment is indicated in this critical period in which vulnerability reaches its peak and in which personal, social and biological factors influence the future balance between disorder and wellbeing. Relapses are very common during the first few years following the onset of a psychotic disorder and vulnerability to relapses persists in about 80% of patients. The restoration phase of the first episode and the stabilization phase are included here.

Psychological and psychosocial treatment should be the central elements in the critical period and should be used to help in the resolution of persistent positive and negative symptoms, secondary morbidity management and promotion of recovery and positive mental health. Recovery efforts should emphasize the need to find sense in psychotic experience and develop a certain degree of "control" over the situation.[206]

The highest degree of disability occurs during the first few years, but after this time it tends to stabilize, so the level of functioning achieved two years after diagnosis is a good indicator of what the level of functioning will be fifteen years later.

However, services usually offer less intense treatment during the periods between acute phases, constituting an inadequate model to address the needs of patients who are in the critical period.

The objectives of treatment in this phase are:

- To achieve realistic academic or employment objectives.
- To develop social relationships and normal sexual development.
- To provide support to achieve an independent life.
- To promote the establishment of personal values and identity.
- To provide adequate age-adjusted support to minimize the effects of the disorder in the patient's life and empower him/her to successfully cope with challenges that favour development.
- To limit suffering and negative consequences of psychotic behaviour.
- To provide support for families.
- To be sensitive to factors that may hinder adequate follow-up of treatment, such as the negative effects generated by an assessment or procedures that cause rejection, side effects of medications, stigma or other obstacles to a collaborative relationship.
- To offer treatment for associated problems such as suicidal tendencies, depression, aggression, substance abuse, cognitive impairment, anxiety disorders, instead of simply assuming that they are secondary phenomena.
- To reinforce the concept of biological illness.
- To emphasize the need of drug and alcohol abstinence.
- To obtain the commitment of the patient and his/her family to a cooperation process.
- To provide continued support to treatment adherence.
- To provide comprehensive psychoeducation focused on positive and negative symptoms.
- To teach coping strategies.
- To facilitate opportunities to reduce social withdrawal by means of group-based treatment.
- To help rebuild self-esteem.
- To provide social skills training.

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Several studies support the scientific evidence indicating that early intervention programs in psychosis versus traditional approaches offer better outcomes in several areas:

- In these studies, some use CBT as part of their therapeutic offer obtaining the following outcomes at 18 months: improved social, vocational functioning and quality of life, and increased patient satisfaction and adherence to medication, but there are no differences in symptom improvement (**level of scientific evidence Ib**).[137]

- In a study which compared a specialized team versus standard treatment, it was reported that comprehensive treatment significantly improved the situation of employment and studying. However, two more years were needed to obtain this type of benefit. The study recommended more research in this respect. Additionally, an improved overall condition was observed at two years (measured using GAF) and also greater continuity and adherence to treatment (**level of scientific evidence Ib**).[138]

- In another study which assessed early intervention with the combination of different types of treatment, no statistically significant differences were reported in the improvement of the symptoms measured in the PANSS scale and the Calgary Depression Rating Scale (**level of scientific evidence Ib**).[137]

- The need to promote research studies on the benefits of treatment with early intervention teams is evidenced. Some authors recommend using a fidelity scale to make studies comparable, as well as to assess the results of specific interventions.[138]

Furthermore, these is scientific evidence indicating that psychosocial treatments improve outcomes in the treatment of the first psychotic episode in several areas and may aid symptomatic and functional recovery:

- Early implementation of CBT and supportive therapy boosts faster recovery and reduces symptoms more than standard intervention, and may have long-term (18 months) benefits on these symptoms (**level of scientific evidence Ib**).[142]

- CBT obtains better outcomes than standard intervention in suicidal risk, hospitalization, symptom reduction, adaptation to the disease and quality of life (**level of scientific evidence Ib**).[142]

- When comparing CBT with supportive therapy and standard treatment, CBT offers protection from future relapses in the next 18 months (**level of scientific evidence Ib**).[227]

- Patients who receive CBT present fewer residual symptoms than patients who only received standard treatment (**level of scientific evidence Ib**).[8]

- FI seems to prevent re-hospitalizations[138,142] and relapses[142] and promotes better adherence to medication[138] (**level of scientific evidence Ib**).

- Family members and carers exercise a crucial role in the access to care of patients with a first psychotic episode (**level of scientific evidence III**).[223]

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- Psychodynamic, cognitive-behavioural and non-psychodynamic supportive psychotherapy, combined with pharmacological treatment, improve the overall functioning of patients more than pharmacological treatment alone or in combination with other psychosocial interventions. The best outcomes are obtained with dynamic psychotherapy and cognitive-behavioural therapy (**level of scientific evidence Ia**).[149]

In the specific area of cognitive rehabilitation, in which most of the scientific evidence established up until now is based on patients with chronic schizophrenia, recent research points to the importance of differentiating the different impaired areas in first episode patients, given that motor and executive functions seem to be less impaired than memory and attention in this profile. There are indications that it may be possible to achieve significant recovery and resolution of problems and executive functions within one year of treatment (**level of scientific evidence IV**).[169]

In the area of occupational insertion of people with first episodes there is scientific evidence indicating that supported employment is the most effective method, with maintenance of outcomes over longer periods of time. In this approach, the educational and training settings should be granted the same importance (**level of scientific evidence IIb**).[184]

The professional dedicated to occupational rehabilitation should help the patient search for training or employment, as well as maintain them when found (**level of scientific evidence IIb;**[184] **level of scientific evidence Ib**)[22].

## *Pharmacological intervention in the recovery from a first psychotic episode*

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| **A** | If there are relapses, identify their causes, differentiating whether they are due to poor adherence or in spite of satisfactory adherence. If it is due to poor adherence, restore treatment.[1] |
| **A** | If resistance to treatment is evident and two antipsychotic drugs have been used, and at least one of them is a second generation drug, switch to clozapine.[1] |
| **B** | If there are tolerance problems with second generation medication, especially weight gain or metabolic syndrome, offer the possibility of switching to a different second or first generation antipsychotic.[1] |
| **C** | If a first generation antipsychotic is being use, switch to a second generation one if response is not adequate or if there are tolerance problems.[1] |
| **C** | If the patient has relapsed despite good adherence to a first generation antipsychotic, switch to a second generation one. If the patient presents symptom remission, good quality of life, and has not presented tolerance problems to conventional medication, maintain its use.[1] |
| **C** | As a last resort the switch to a first generation depot medication can be considered. However, long acting second generation injectable drugs may be considered an alternative to clozapine when there is low or uncertain adherence, especially if the |

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| | patient prefers this option.[1] |
| **C** | If there is no response to treatment or low adherence with frequent relapses, low dose first generation depot antipsychotics should be tried for a period of 3 to 6 months.[1] |

*Psychosocial interventions in the recovery from a first psychotic episode*

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| **A** | Early intervention programs for psychosis are recommended over traditional approaches.[137,138] |
| **A** | Psychosocial interventions are recommended in the treatment of first episodes.[8,138,142] |
| **B** | Supported employment is recommended as the most effective method to promote occupational insertion of people with first episodes.[184] |
| **C** | Cognitive rehabilitation is recommended in patients with specific deficits, even though the objective should also include related functional deficits.[169] |
| **C** | It is recommended to provide high quality intensive biopsychosocial care in a continued and active manner during the critical years following the onset of psychosis, preferably from specialized early intervention programs which also include pharmacotherapy, psychoeducation, stress management, relapse prevention, problem solving, reduction of harm due to substance use, supportive counselling and social and occupational rehabilitation, as well as family intervention and cognitive therapy.[42] |

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# 7.2. Phases of schizophrenia

The following section presents the general guidelines to follow for the treatment of schizophrenia according to the phases described in chapter 4.2 of the CPG.[4,47]

## 7.2.1. Acute phase (or crisis)

The acute phase is characterized by an acute psychotic episode. The corresponding objectives are as follows:

- To prevent the patient from suffering injuries.
- To control disordered behaviour.
- To decrease the severity of psychosis and associated symptoms.
- To identify and resolve the factors that triggered the onset of the acute episode.
- To quickly restore an optimum level of functioning.

- To establish an alliance with the patient and his/her family.
- To formulate short- and long-term treatment plans.
- To put the patient in touch with an adequate post-hospital care service.

An initial comprehensive diagnostic study should be performed on each patient, including psychiatric and general medical clinical history, physical exploration and mental health examination. Systematic interviews can be conducted with family members and other people who know the patient well, given that many patients are unable to provide reliable accounts of their clinical history during the first interview. For more information on diagnosis and assessment, refer to chapter 5.1 of this CPG.

The factors which trigger symptom relapse should be considered, such as compliance of antipsychotic treatment, substance abuse and stressful life events. One must not forget that relapses are frequent in the natural course of the illness, even when there is good adherence to treatment. When poor therapeutic compliance is suspected, it is recommended to analyze the reasons and taken them into account in the treatment plan.

In this phase it is important to pay special attention to the existence of suicidal potential. Prior suicide attempts, depressed mood, and suicidal ideation may be prognostic factors of a subsequent suicide attempt (**level of scientific evidence IB**). It is recommended to perform similar assessments in terms of the possibility of dangerous and aggressive behaviour towards others.[4]

## *Pharmacological intervention in the acute phase*

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| **B** | Pharmacological treatment should be initiated immediately, unless it interferes with diagnostic assessment, given that acute psychotic aggravation is associated with emotional discomfort, disturbances in the patient's life and considerable risk of behaviours that may endanger the life of the patient and others.[4] |
| **C** | Patients and family members should be completely informed on the benefits and risks of pharmacological therapy and advised when choosing antipsychotic medication; the services of interpreters or cultural mediators should be used when necessary. In the case of not being able to openly discuss treatment options with the patient, as occurs in the case of some acute episodes, oral second generation medication should be the treatment of choice due to the lower risk of extrapyramidal symptoms.[1] |
| **C** | When choosing a certain antipsychotic medication, the patient's prior response to treatment, the side effects profile, preferences for a certain drug based on prior experience and the foreseen administration route should be taken into account.[228] The recommended doses of antipsychotics have been described in the corresponding tables of this CPG. |
| **C** | The key principle is to avoid the first choice use of drugs that tend to weaken future adherence due to the development of side effects. The immediate objective is not only |

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| | the reduction of aggression, agitation and risk but also to make the patient feel subjectively better and calmer with good tolerability.[1] |
| **C** | The first step of clinical management of resistant schizophrenia is to establish that antipsychotic medications have been adequately used in terms of dose, duration and adherence. Other causes of poor response should be considered in clinical assessments, such as the incorrect use of comorbid substances, poor adherence to treatment, simultaneous use of other prescribed drugs and physical disease.[3] |
| **C** | If schizophrenia symptoms do not respond to first generation antipsychotics, the mental health professional and patients should consider the use of a second generation antipsychotic prior to the diagnosis of treatment-resistant schizophrenia or a trial with clozapine.[3] |

Frequently other psychoactive drugs are added to antipsychotic drugs when patients continue to present active psychotic symptoms: lithium, carbamazepine, valproic acid and benzodiazepines; however, the efficacy of these coadjuvant treatments has not been proven in randomized clinical trials.[47]

Furthermore, coadjuvant medications can be used to boost the response in patients who present insufficient response (especially with affective symptoms), to reduce violent behaviour, or in disorders associated with schizophrenia: antidepressants if there are persistent depressive symptoms, benzodiazepines if there is anxiety or agitations (lorazepam or clonazepam).

Drugs for the treatment of extrapyramidal symptoms or other side effects are also used. Their use depends on the severity or intensity of symptoms and on the consideration of other possible strategies such as the reduction of antipsychotic dose or switching of antipsychotic. In terms of the prophylaptic use of antiparkinson medication, the following factors should be taken into account: the tendency of antipsychotic medication to cause extrapyramidal side effects, the patient's preferences, history of extrapyramidal side effects, other risk factors (dystonia), and risk factors and possible consequences of anticholinergic side effects.

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| **C** | It is recommended that the use of medications such as lithium, carbamazepine, valproic acid or benzodiazepines be reserved for cases where clozapine is not appropriate in treatment-resistant patients due to poor efficacy, side effects, patient preference or likely lack of compliance of the surveillance program.[25] |

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## *Use of ECT in the acute phase*

ECT is always a second choice treatment in schizophrenia,[47] indicated after the failure of antipsychotics; the most frequent indications are: catatonic schizophrenia, severe cases that present intense agitation and/or confusion, contraindications to antipsychotics (due to the

possibility of causing neuroleptic malignant syndrome), resistant secondary depression and resistant schizoaffective disorders.[125]

Available data suggest that antipsychotic treatment should be maintained during and after ECT.

## *Psychosocial interventions in the acute phase*

Psychosocial interventions in this phase are aimed at reducing relationships, environments or episodes in life which are too overstimulating or stressful and to promote relaxation by means of simple, clear and coherent communications and expectations in a structured and predictable environment, with low functional demands and supportive, tolerant, non-demanding relationships with all the professionals who are involved in the management of this phase of the disorder.

The patient should be encouraged to collaborate with the psychiatrist in the choice and adjustment of medication and other treatments. The psychiatric should initiate a relationship with family members, who are usually concerned about the patient's disorder, his/her disability, prognosis and hospitalization. Training meetings that teach the family how to cope with schizophrenia are recommended, as well as referral to patient and family associations.

Scientific evidence in patients in acute phases indicates that CBT produces a faster effect than standard treatment, but not when compared with supportive.[8] However, there is scientific evidence in this phase determining that CBT coupled with standard care can accelerate recovery and hospital discharge (**level of scientific evidence Ib**).[1]

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| **A** | CBT is recommended in the acute phase, coupled with standard care, to accelerate recovery and hospital discharge.[1] |

Additionally, the following aspects should be considered in this phase:[47,70]

- Outpatient treatment, if the patient's symptomatology can be tackled on an outpatient basis, the patient has a contained environment and both he/she and the family prefer it.

- Inpatient treatment if several factors are present: intensity of psychopathology, assessable risk of self- or hetero-aggression, general medical pathology for which outpatient management is not suited, psychosocial or family factors.

- The possibility of admittance into an inpatient or day care unit (day hospital), depending on the assessment of the patient's state, the need for specific treatments, family function, social support, patient and family preferences, and therapeutic resources available in the community.

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## 7.2.2. Stabilization phase (or postcrisis)

The stabilization phase or postcrisis corresponds to the 6-12 months following an acute episode. During this phase the patient is recovering functionality and adjusting to an increasingly more demanding environment.

The objectives of treatment in this phase are:

- To reduce the stress experienced by the patient as much as possible.
- To decrease the probability of relapse and symptoms.
- To continually reduce symptoms and consolidate their remission.
- To favour the recovery process.

If the patient has required inpatient care, once he/she has been discharged gaps in the continuity of treatment should be avoided. A prior appointment should be made with the corresponding mental health centre and the patient should be aided in establishing realistic objectives to prevent stress or an increased risk of relapse, avoiding inadequate pressure to reach an excessive degree of occupational and/or social function.

### *Pharmacological treatment in the stabilization phase*

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| **C** | Due to the risk of fast relapse in the postcrisis phase, the discontinuation or reduction of antipsychotic pharmacological treatment initiated in the acute phase should be avoided. The continuation of treatment over a period of one or two years after a crisis should be discussed, when appropriate, with the patient and family.[3] |
| **C** | If possible, in patients with complete remission antipsychotic medication should be administered over a period of at least 12 months and a subsequent attempt should be made to gradually discontinue medication over a period of at least several weeks. Close monitoring should be followed by specialist follow-up over the next 12 months and any relapse should be promptly identified and treated. Patients should not be referred to primary care exclusively, as shared health care is the best option in all these phases.[1] |

### *Psychosocial interventions in the stabilization phase*

In this phase, supportive psychosocial interventions should be less structured and guided than in the previous phase. Furthermore, education on the course and consequence of the disease should be initiated for patients and maintained for family members.

According to reviewed scientific literature, the recommendations for psychosocial interventions in this phase can be summarized as follows (see chapter on Psychosocial Interventions):

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| **A** | Health education programs are recommended in this phase given that they have been proven effective at teaching self-management of medication (maintenance antipsychotic treatment, side effects, etc.), self-management of symptoms (identification of the first signs of a relapse, their prevention, and refusal to consume drugs and alcohol), and basic social skills.[229-231] |
| **A** | The application of CBT is recommended for the treatment of positive and negative symptoms that are resistant to antipsychotics.[232] |
| **A** | CBT is recommended for the treatment of positive symptoms in schizophrenia,[134] especially hallucinations.[7] |
| **A** | CBT is recommended as a treatment option to aid in the development of insight.[7] |
| **A** | CBT is recommended as a treatment option to increase adherence to treatment.[7] |
| **A** | Patient psychoeducation is recommended given that it reduces relapse risk, probably by improving adherence, improves the patient's satisfaction with treatment and improves knowledge.[1] |
| **A** | FI therapy is recommended in patients who are moderately or severely disabled and especially in patients with long evolution of the disease. In patients with recent onset of the disorder each situation should be individually assessed.[11,12] |
| **A** | FI should be offered to families who live or are in contact with patients with schizophrenia, especially those who have relapsed or present relapse risk and also in those cases with persistent symptomatology.[3] |
| **A** | FI programs should include family members of patients with homogeneous diagnosis, enable the patient's participation and ensure that he/she is well-informed. FI should take place over a period of at least six months.[12] |
| **A** | FI programs are recommended to reduce family burden, improve the patient's social functioning and decrease economic cost.[11,12] |
| **A** | Psychoeducational FI, based on the management of expressed emotion, is recommended to prevent relapses and improve disease prognosis(its effects are maintained at 24 months).[11-16] |
| **A** | Programs should always include information for families regarding the disease and different strategies such as stress coping techniques or problem solving training.[17,18] |
| **A** | The application of social skills training (based on the problem-solving model) is recommended in patients who are severely or moderately disabled, given that it is effective in terms of social adaptation and its effects are maintained after two years.[21] |
| **B** | Referral to patient and carer social networks is recommended given that support |

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| | groups are effective at providing support to the family.[1] |
| **C** | It is recommended to develop a therapeutic alliance based on emotional support and cooperation, given that it plays an important role in the treatment of people with schizophrenia.[9] |
| **C** | Supportive therapy is not recommended as a specific intervention in the normal care of people with schizophrenia if other interventions with proven efficacy are indicated and available or if the patient expresses his/her preferences for this type of psychotherapy.[9] |
| **C** | Supportive psychotherapy focused on reality, with realistic objectives, is recommended for patients who are moderately disabled and stable or intermittently stable.[28] |

The continuity of care services is important for the prevention of relapses. In the case of inpatients, it is recommended to have a consultation with a psychiatrist prior to initiating outpatient treatment. If the patient must live in an out-hospital residence, the consultation should be made before hospital discharge.[4]

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| **B** | Adaptation to the community can be facilitated by establishing realistic objectives and avoiding excessive pressure on the patient to achieve high employment and social performance.[4] |

At an out-hospital level, it is very important to maintain a certain level of activity to improve social functioning and to convey feelings of hope and progress to the patient and family.[4]

## 7.2.3. Stable phase (or maintenance phase)

During this phase patients may not have any symptoms at all or present symptoms such as tension, irritability, depression, negative symptoms and cognitive deterioration. Some patients may still present positive symptoms, but to a lesser degree than in the acute phase (the patient may present hallucinations, delusions or disordered behaviour).

The therapeutic objectives in this phase are:

- To maintain symptom remission or management.
- To preserve or improve functionality and quality of life.
- To effectively treat increasing symptoms and relapses.
- To carry out continued follow-up of treatment side effects.

In this phase the administration of antipsychotics should take the following aspects into account:[47]

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- To establish a long-term treatment plan to reduce side effects and relapse risk to a minimum.
- In patients with a history of poor compliance, long acting depot drugs are an option given that these drugs tend to result in improved long-term evolution of these patients.
- The significant reduction or discontinuation of antipsychotics can cause almost immediate aggravation.
- In other patients with minimal psychotic symptoms medication can have a prophylaptic effect.
- The dose of maintenance medication should be established acknowledging that excessively high doses can produce extrapyramidal side effects (akinesia or akathisia) that may hinder adaptation to the community and reduce treatment compliance.
- During chronic treatment, subtle akinesia may develop in the form of decreased spontaneous movement, reduced conversation, apathy and difficulties initiating any activity. It is hard to differentiate from negative deterioration of schizophrenia and depression symptoms.
- Very low doses of antipsychotics may be associated with increased compliance, improved subjective state, and improved adaptation to the community, but the higher risk of relapse and exacerbation of the most characteristic symptoms of schizophrenia should be acknowledged.

On the other hand, during this period psychosocial interventions are effective complementary treatment to pharmacological treatment. Specific psychosocial instructions such as re-education in terms of basic daily life skills, social skills training, cognitive rehabilitation and the initiation of occupational rehabilitation can be introduced. It is also important to provide health education aimed at the patient and his/her family to increase knowledge on the first signs of relapse.

In the patient agrees, it is useful to maintain contact with people closest to the patient given that they have more possibilities of detecting the appearance of symptoms, stressful factors and events which could increase relapses or interfere with functional restoration.[4]

## *Pharmacological intervention in the stable phase*

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| **A** | Coadjuvant medication is frequently prescribed for comorbidity in patients with schizophrenia who are in the stable phase. Major depression and obsessive-compulsive disorder may respond to antidepressants.[4] |
| **C** | Withdrawal of antipsychotic medication should be carried out gradually while performing regular monitoring of signs and symptoms that may indicate potential relapses.[3] |
| **C** | A complete physical examination, including weight, blood pressure, lipid profile, ECG and blood fasting glucose should ideally be performed in collaboration with the primary care physician at least once a year. Routine screening of cervical and breast cancer should be carried out in women. In patients over the age of 40, it is important |

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| | to consider new symptoms and perform screening tests for the common types of cancer. If there are no guarantees that primary care will carry out this type of monitoring, it should be placed in the hands of the psychiatrist.[1] |

## *Psychosocial interventions in the stable phase*

As was presented throughout the CPG, psychosocial interventions that are effective in the stabilization phase are also effective in the stable or maintenance phase (see chapter on Psychosocial interventions). The following interventions can also be considered:

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| **A** | Supportive psychotherapy for problem solving is recommended given that it significantly reduces relapses and boosts social and occupational function when added to medication in patients treated on an outpatient basis (**level of scientific evidence Ia**).[233-235] |
| **A** | Cognitive rehabilitation is recommended in the patient's social environment given that it has been shown to be effective (in contrast to traditional cognitive rehabilitation) in the prevention of relapses and social adaptation.[20] |
| **A** | It is recommended to provide occupational support to patients who are moderately or mildly disabled, given that it has been shown to be effective in the obtention of normalized employment.[24,25] |
| **A** | In patients with early onset schizophrenia social skills techniques are recommended, given that they result in better outcomes than supportive techniques.[21] |
| **A** | The application of cognitive rehabilitation, in all its modalities, is recommended as a technique that improves cognitive functioning in a wide range of clinical conditions of the patient with schizophrenia.[19] |
| **A** | Patients with schizophrenia should be encouraged to find employment. Mental health specialists should actively facilitate this process and specific programs incorporating this intervention should be widely established. [1] |
| **A** | The best outcomes in occupational insertion of people with schizophrenia are obtained with supported employment programs, when compared to other occupational rehabilitation interventions.[22,23,181] |
| **B** | The strategies to tackle social stigma and discrimination of the mentally ill are more effective when education includes contact with schizophrenic people who share their story.[2] |
| **B** | An evidence-based format of training in abilities for daily living should be available to patients who have difficulties in daily functioning.[2] |

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| C | If possible, patient preferences in terms of housing and resource selection should be favoured, acknowledging the right of the patient to live in an environment that is as normalized as possible, articulating the necessary training programs and providing proper support so that the patient can access and remain in the aforementioned setting.[27] |

# 7.3. Specific situations

This chapter addresses some specific situations that may be related with schizophrenia, such as substance abuse, suicide, violent behaviour, depressive symptoms, or homeless patients. In order to guarantee an adequate intervention it is necessary to treat not only specific symptoms of schizophrenia but also to carefully assess the conditions described.[4,47]

## 7.3.1. Substance use-related disorders

Substance use-related disorders are an important morbidity factor when they develop in combination with schizophrenia. It is estimated that up to 40% of people with schizophrenia engage in substance abuse or present dependence, long-term incidence increasing throughout life (60% in some studies). Substance use-related disorders are associated with more frequent and prolonged inpatient care, and with other negative outcomes, such as homelessness, violence, imprisonment, suicide and HIV.

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| C | It is recommended that treatment objectives in patients with this associated pathology mirror the objectives of treatment of schizophrenia with no associated pathology, but adding the objectives relating to substance use problems, such as harm reduction, abstinence, relapse prevention and rehabilitation.[47] |

The presence of substance use-related disorders is frequently undetected or underestimated in individuals with schizophrenia, especially if the patient is examined during an acute psychotic episode. Spontaneous information is frequently unreliable, hence making it necessary to find confirmation from other sources, such as family members and other therapists who have been involved in the management of the patient.

Lab tests and substance detection studies may be useful to detect or suggest consumption of alcohol or other substances. Many patients with schizophrenia do not present a physiological dependence syndrome associated with alcohol or other substance dependence. Therefore, psychiatrists are advised to stay alert to other possible signs of substance abuse in this population, such as marginality, violence, lack of treatment compliance, frequent symptomatic exacerbations and family and economic conflicts.

The effects of substance use in schizophrenic symptoms are diverse, making it difficult to differentiate substance use-related symptoms from symptoms due to psychosis or to both.

The key issue for the application of treatment in this population is to develop an approach that integrates treatment of substance use-related disorders and schizophrenia. At present, there are

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many programs that provide this integration by means of interdisciplinary teams with experience in the treatment of schizophrenia and substance use-related disorders. Antipsychotic drugs can be used at normal doses, but patients should be informed that the combined use of antipsychotic medication and alcohol or other substances can increase sedation and lack of coordination. When prescribing drugs, the psychiatrist should take into account the possibility that the convulsive threshold may decrease when using antipsychotic drugs, as well as the possibility that patients may engage in benzodiazepine and anti-Parkinsons drug abuse. Rarely, antipsychotic drugs may trigger convulsive crises during alcohol or benzodiazepine abstinence.

Disulphiram may entail a certain risk for patients with schizophrenia who engage in alcohol abuse, given that it can trigger a psychotic episode. Given that this drug has harmful negative effects when taken with alcohol, it should only be used in patients with reasonably good judgement, who adhere to treatment and have adequate contact with reality.

Naltrexone is a drug that seems to reduce alcohol craving and is used to treat opiate dependence, but it has not been studied in depth in patients with schizophrenia. New studies are necessary to assess the use of naltrexone on this population.

The therapeutic approach should be integrated and take into account the patient's cognitive deficits and limited tolerance to stress. Overall, groups should be supportive and psychoeducational. The length and frequency of group sessions should be regulated in terms of the patients' attention periods and tolerance. Therapists should actively maintain the group structure and limit the degree of stress, avoiding direct confrontation of patients, which is common in programs aimed at substance abuse.

Patients should understand that they have two complex chronic disorders that, together, lead to worse prognosis than each would have by itself.

Some studies indicate that support and acceptance programs for these patients yield better outcomes than confrontation programs aimed at patients who only present addictive pathology (**level of scientific evidence Ib**).[47]

Even if the patient has not achieved complete abstinence, he/she should not be excluded from interventions recommended for patients with schizophrenia or for patients with disorders due to substance use.

## 7.3.2. Schizophrenia and suicide

Suicide is the leading cause of premature death amongst patients with schizophrenia. In contrast to the general population, the probability that people with schizophrenia will die from suicide is nine times higher. Up to 30% of patients with schizophrenia attempt suicide, and between 4 and 10% die after the attempt. The estimated percentage of suicidal behaviour in people with schizophrenia ranges from 20 to 40%.

Knowledge on suicide risk factors associated with schizophrenia is limited. Some of these risk factors are shared by the general population: male gender, Caucasian race, being single, social

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isolation, depression or hopelessness, unemployment, substance dependence, recent losses, and a personal and/or family history of suicide attempts.

Other specific risk factors are, on the one hand, youth, with mean age 33 years, whereas in the general population the highest risk corresponds to ages over 65; and on the other hand, the period encompassing the first six years after the first hospitalization, having high IQ, chronic course and progressive deterioration with exacerbations, or perceived loss of functional capacities. Other additional risk factors are the presence of suicidal ideas, auditive hallucinations and recent hospital discharge.

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| **C** | It is recommended to increase the frequency of outpatient visits in patients who have recently been discharged from the hospital, given that it is a vulnerable period for the patient.[47] |

It is possible that the increased suicide risk in schizophrenia occurs in the remission phase. Associated depressive symptomatology is characterized more by hopelessness, cognitive impairment and deterioration, than by symptoms that can be diagnosed as major depression.

Many patients present one or several of these risk factors, but do not commit suicide or attempt to commit suicide, whereas others may do it unexpectedly without prior signs of significant risk. It is not possible to predict if a specific patient will commit suicide.

Overall, early suicides coincide with clear awareness of disabling disease and after remission of acute symptomatology. Later suicides coincide with impairment that is especially social; overall they are premeditated suicides even though they may have been triggered by a stressful event.

A significant percentage of the suicides committed by patients with schizophrenia take place during a remission period after five to ten years of illness. It seems to be a reflection of perceived hopelessness in terms of their own pathology, which can reappear without any warning signs. Family members should be aware of this possibility. Even with the best of care, it is likely that a percentage of patients with schizophrenia will die from suicide.

However, it is essential to assess the risk of suicide initially and on a regular basis as part of the psychiatric evaluation of the patient. Suicide ideas or threats should be assessed in the context of the patient's clinical history provided by him/herself and family members and the current therapist, if possible.

Some data indicate that both first and second generation antipsychotic decrease the risk of suicide. However, clozapine is the drug that has been most studied, and it has been reported that it reduces suicide rates and persistent suicidal behaviour (**level of scientific evidence Ib**).[4]

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| **C** | During inpatient care it is essential to adopt precautions to avoid suicide and closely monitor suicidal patients.[4] |

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| **C** | Patients who have been deemed to have high suicidal risk should be put into inpatient care, and the necessary measure to avoid suicide should be applied. It is important to optimize pharmacological treatment of psychosis and depression, and to address the suicidal inclination of the patient directly, with an empathetic and supportive approach. Close surveillance should be carried out on vulnerable patients during periods of personal crisis, environment changes or periods of hardship or depression over the course of the disease.[47] |

A meta-analysis of four randomized clinical trials, already mentioned in the section on Modalities of care and intensive follow-up in the community of this CPG, assessed the effectiveness of community mental health teams versus conventional care in the treatment of any type of severe mental illness. One of the outcomes analyzed was suicide. Results indicated that treatment with community teams is superior in terms of better acceptance of treatment, reduced hospitalizations and prevention of deaths by suicide (**level of scientific evidence Ia**).[29]

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| **A** | Treatment by community mental health teams is recommended in severe mental disorders to reduce deaths by suicide.[29] |
| **C** | When discharged, the patient and his/her family members should be advised to stay alert to warning signs and initiate prevention measures if suicidal ideas reappear.[4] |
| **C** | When a patient has been recently discharged, it is recommended that he/she undergoes more frequent outpatient management. The number of visits should be increased in times of personal crisis, significant changes in the patient's surroundings, increased discomfort or depression that is accentuated over the course of the disease.[4] |

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## 7.3.3. Violent behaviour

Violent behaviour can appear in patients with schizophrenia and its incidence varies in terms of the more or less acute or severe nature of the patient's psychosis. General risk factors are: a history of prior arrests, substance use, presence of hallucinations, delusions or strange behaviours, neurological deterioration, male gender, low socioeconomic class, limited studies and being single.

The identification of risk factors of violence and violent ideas is part of the standard psychiatric assessment. The assessment of a patient who may be violent requires the application of safety measures (additional staff). If a patient represents a serious threat to others, the psychiatrist should use his/her own judgement, in accordance with legal regulations, to protect those people from foreseeable harm. In patients who present an imminent risk of violent behaviour,

assessment should be carried out for possible inpatient care and, if indicated, apply precautionary measures at the moment of hospital admittance.

Treatment of aggression can often be performed using behavioural and maintenance therapy in a restricted setting. Antipsychotic medication is the core of treatment, but the use of anticonvulsants, lithium and propanolol at high doses has also been described, together with the possible favourable effect of clozapine.

Emergency treatment of violence in schizophrenia may include sedation (using benzodiazepines such as diazepam in intramuscular doses of 10-20 mg,[236] or in combination with 5 mg of intramuscular haloperidol), and a restricted setting. The use of a restricted setting should be an emergency measure applicable when other less restrictive measures have failed, and the patient should be seen with the frequency required to adequately monitor changes in the physical or mental state. Restrictions should be gradually removed as the risk of self- or hetero-aggressiveness decreases.

Ethical regulations[j] stipulate that restrictive measures can only be applied if they stem from a therapeutic plan and the following criteria are met:

- A clinical indication that is individualized and limited to a certain period of time.
- A prior explicit medical order need. In an emergency situation and should any nursing action be taken, it should promptly be reported to the referral physician for final approval.
- It should be applied in exceptional situations and with an exclusively therapeutic objective which is based on the principle of the patient's benefit.
- The previous measure should be reasonably effective and clearly yield more benefits than risks.
- There are no other less restrictive means in order to offer the patient the treatment he or she requires.
- In no case shall this measure be applied as punishment or a form of control.
- In no case shall this measure respond to extra clinical motives, such as to compensate for insufficient staff.
- Actions should be carried out by health care staff with adequate level of knowledge and training in the care of these patients.

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[j] *White Paper on the protection of the human rights and dignity of people suffering from mental disorder, especially those placed as involuntary patients in a psychiatric establishment. CM (2000)23 Addendum, 10.2.2000. Committee of Ministers. Council of Europe.*

- The patient should be provided with adequate prior information and, if possible, his/her consent should be sought. The family will also be informed and encouraged to collaborate in the treatment process.

- Actions will be performed with the utmost dignity and respect towards the patient, safeguarding and upholding his/her constitutional rights.

- Restriction should always be based on the patient's decreased mental competence due to his/her psychopathological state. The idea that it is being done "for the patient's own good" is not acceptable if the patient acts responsibly and competently.

- The restrictive measures indicated shall always appear in medical orders of the clinical history.

## 7.3.4. Depressive symptoms

Depressive symptoms frequently develop in the psychopathology of schizophrenia and may occur in all of its phases. When they occur in the acute phase of the disorder a differential diagnosis with schizoaffective disorder should be performed. The differential diagnosis should take into account the influence of side effects of antipsychotic medications, personal attitudes or substance use. The addition of an antidepressant during the acute phase should be performed with caution given that it may exacerbate psychotic symptoms. Treatment should be performed sequentially.

Depressive symptoms that persist or appear after the remission of psychotic symptoms are called "residual" or "secondary" (postpsychotic) depressive symptoms and they have been shown to respond to antidepressant treatment.

As with negative symptoms of a deficitary state, secondary depression should be differentiated from other possible causal disorders:[47]

- General medical disorders.

- Substance-induced disorders.

- Extrapyramidal side effects of antipsychotics: akathisia and akinesia. This "depression" may disappear by decreasing the antipsychotic dose or adding an anticholinergic drug.

- Demoralization due to the effect of the illness and "situational" reactions of personal crises or changes in the surroundings which require more surveillance of the patient and an empathetic and supportive approach.

Some data suggest that depressive symptoms are reduced with the use of antipsychotic treatment. Some comparative trials have reported that second generation antipsychotics could be more effective at treating depression than first generation drugs (**level of scientific evidence Ib**). However, some scientific evidence also suggests that this apparent antidepressant effect

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could be related with the low probability of neurological side effects of second generation antipsychotics (**level of scientific evidence IV**).[4]

| | |
|---|---|
| **A** | Second generation antipsychotics are recommended for the treatment of depressive symptoms.[4] |
| **B** | A major depression episode during the stable phase of schizophrenia is an indication for treatment with an antidepressant drug.[2] |
| **B** | It is possible to add antidepressants as complementary treatment to antipsychotics when depressive symptoms meet the syndromic criteria of major depression or are severe, causing significant discomfort or interfering with the patient's functionality.[4] |

## 7.3.5. Homeless patients

Different studies and settings present a prevalence of schizophrenia in homeless patients ranging from 2 to 43%; in Spain it ranges from 18 to 26%.[237]

In patients with schizophrenia the risk factors for becoming homeless after hospital discharge are, according to a longitudinal study: comorbidity with a substance use-related disorder, persistent psychiatric symptoms –for example, BPRS > 40- and decreased overall function –for example, GAS < 43- (**level of scientific evidence III**).[238]

It would not be reasonable to assume that the problems of homeless patients with schizophrenia could be resolved exclusively by mental health services. However, mental health professionals can detect patients with an increased risk of becoming homeless and act preventively by tackling known risk factors.

| | |
|---|---|
| **B** | Follow-up of patients after hospital discharge is recommended. Professionals should remain alert to comorbidity due to patient's substance use, psychiatric symptoms and overall function to prevent the risk of patients becoming homeless.[47] |

In regards to the clinical assistance to homeless patients, this CPG includes what has been reported by previous studies given that there is insufficient evidence that assesses the efficacy of these interventions and whilst the pertinent studies are awaited.[47]

| | |
|---|---|
| **C** | Treatment and support in transition to housing are recommended for homeless schizophrenic patients.[47] |

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# 8. Healthcare network for the management of patients with schizophrenia, action directives, programs and services

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As was stated in the introduction, the objective of this CPG is to offer recommendations on diagnostic, therapeutic and rehabilitation interventions for people who have schizophrenia or incipient psychotic disorder which are applicable via action directives of the National Health System.

Hence, applicability conditions should be examined in terms of the general healthcare system and the characteristics and development achieved by public use mental health networks in particular.

Our healthcare setting offers favourable conditions for the management of people with a schizophrenic disorder. In the first place, it is a system that guarantees universal access to healthcare services. Secondly, it offers a sectorized and scalonating healthcare system. And, thirdly, it offers healthcare networks specialized in mental health care.

However, the different level of general evolution of the healthcare system and psychiatric reform in particular, the different degrees of integration of psychiatric care in the general system and the uneven development of social resources greatly condition the accessibility, utilization and coordination of these resources.

The first level of the general healthcare network offers primary care, which is the starting point of care for early detection and referral to specialized services, and also constitutes the ideal setting for continued care of the patient's general state and support to families. It would be advisable for primary and specialized care levels to agree upon certain referral, interconsultation and coordination criteria. This would also gradually enable increasing integration of mental health care and corresponsibility of management of patients.

Established public use mental health networks tend to be inspired by the ideas and principles of community psychiatry, and present a series of action directives for addressing the different phases and circumstances experienced by people with schizophrenia or incipient psychotic disorder.

Overall, a great number of services differ in their outpatient vs in-hospital characteristics in offering total or partial care, in being aimed at child-adolescent and adult populations, and in the amount of time and hours it takes per day to provide such services. They also differ in the accessibility, intensity and continuity of care they provide.

These networks tend to include outpatient or in-hospital treatment services in the form of mental health centres, inpatient care for acute and sub acute patients, therapeutic community care, mid-

and long-term inpatient care or hospital rehabilitation, partial hospitalization units such as day hospitals, emergency services and psychosocial rehabilitation services, psychiatric residences and assisted living apartments. These services also present differences when they accommodate child and adolescent, adult or elderly populations.

The formulation of ideal conditions for mental health services should acknowledge the interrelationship between the different phases of evolution and the current characteristics of the disorder, the therapeutic objectives of each phase, different available action directives and the services these directives can facilitate.

The main scopes of specialized intervention aimed at patients with incipient psychotic disorder or schizophrenia encompass the following services:

- **Mental Health Centres (MHC)**: They embody the standard setting for treatment of patients with incipient psychotic disorders or schizophrenia in the community in all phases and moments of the disorder. To provide proper care, it is necessary for MHCs to have the resources needed to develop programs and interventions adapted to each situation. It is also necessary for these centres to identify the individual therapeutic plan of each patient and articulate and coordinate interventions with other professionals and services involved in the management of patients, in a concomitant and successive manner.

- **Inpatient care (Acute and subacute patients unit, therapeutic community)**: it is usually indicated for patients who present serious risk of harming themselves or others, or such intense disorganization or extreme delusions or hallucinations that they are unable to take care of themselves and require constant supervision. Voluntary hospitalization of these patients should be sought. If they refuse, they may be hospitalized against their will if their state meets the criteria established for involuntary admittance according to current legal regulations.

  Other indications for inpatient care are general medical or psychiatric problems and comorbidities in which outpatient management would not be safe or effective.

  Based on the phase of evolution, clinical assessment, detectable risk and therapeutic plan, the most adequate hospitalization scheme should be selected.

- **Partial hospitalization (Day hospital**): it can be used as an immediate alternative to inpatient care for patients with incipient psychotic disorder or acute phases who do not present a risk of harming themselves or others and who may favourably respond to intensive outpatient management. It can also be indicated in the recovery phase of the first episode or in the stabilization phase after an acute episode, as a relapse prevention measure or during the beginning of treatment processes in patients with high outpatient care needs.

- **Community Rehabilitation Services:** Community Rehabilitation Services, psychosocial services and day centres are indicated for patients who require rehabilitation interventions that facilitate psychosocial integration into the community, adapted to each phase of the disorder. These interventions should be integrated within

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one same individualized therapeutic plan and carried out in coordination with other professionals and services.

- **Modalities of care and intensive follow-up in the community:** these more intensive interventions, case management and assertive community treatment, are indicated for patients who are not connected to healthcare services or who present significant difficulties doing so or maintaining a continuity of care. These intervention modalities have been less developed in our system in spite of the evidence recommending their use. This is likely due to the difficulties of creating a new array of services adapted to our healthcare setting. However, basic aspects of the philosophy of case management and assertive community treatment have been incorporated into community-based programs aimed at incipient psychosis and schizophrenia in mental health centres, be it with the design of care continuity programs with a pronounced assertive approach or the incorporation of professionals who carry out case management tasks.

The following tables summarize the mental health objectives, services and interventions indicated in each phase of incipient psychotic disorder and schizophrenia.

**Table 10. Mental health provision in the different early phases of psychosis: therapeutic objectives, services and interventions**

| PHASE | OBJECTIVES | SERVICES | INTERVENTIONS |
|---|---|---|---|
| HRMS | To avoid, delay or minimize the risk of transition to psychosis<br>To treat current symptoms and dysfunctions | Mental health centers: program for the specific care of incipient psychotic disorder | Diagnosis, assessment and therapeutic plan<br>Symptomatic pharmacological treatment (non-antipsychotic)<br>Individual and family psychosocial interventions and recovery support |
| First psychotic episode | To reduce psychotic and associated symptomatology<br>To prevent harm<br>To achieve functional recovery<br>To introduce the idea of disorder<br>To transmit hope<br>To provide the therapeutic relationship | Mental health centres: program for the specific care of incipient psychotic disorder<br>Day hospital<br>Inpatient care for acute patients<br>Emergency services<br>Rehabilitation service | Diagnosis, assessment and therapeutic plan<br>Pharmacological treatment<br>Individual and family psychosocial interventions and recovery support<br>Health education and psychoeducation |
| Recovery from the first episode | To support adherence to treatment<br>To achieve functional recovery and insertion<br>To treat associated problems | Mental health centres: program for the specific care of incipient psychotic disorder<br>Day hospital<br>Rehabilitation service | Continued assessment and adaptation of the therapeutic plan<br>Pharmacological treatment<br>Individual and family psychosocial interventions and recovery support |

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| | | | |
|---|---|---|---|
| | | | Health education and psychoeducation<br>Rehabilitation and insertion: social skills, cognitive and occupational rehabilitation, community insertion support |

**Table 11. Mental health provision in the different phases of schizophrenia: therapeutic objectives, services and interventions**

| PHASE | OBJECTIVES | SERVICES | INTERVENTIONS |
|---|---|---|---|
| ACUTE | To reduce/eliminate acute symptoms<br>To prevent harm<br>To achieve functional recovery | Mental health centres<br>Inpatient care for subacute patients<br>Day hospital<br>Emergency services | Diagnosis, assessment and therapeutic plan<br>Pharmacological treatment<br>Individual and family psychosocial interventions and recovery support |
| STABILIZATION | To achieve continued reduction of symptoms<br>To improve community adaptation<br>To provide support for the reduction of stress<br>To consolidate remission and reduce the chance of relapse | Mental health centres<br>Day hospital<br>Therapeutic community<br>Inpatient care for subacute patients<br>Mid- and long-term hospital stay/rehabilitation hospital units<br>Rehabilitation services | Diagnosis, assessment and therapeutic plan<br>Pharmacological treatment<br>Individual and family psychosocial interventions and recovery support<br>Health education and psychoeducation |
| STABLE | To maintain symptomatic reduction<br>To reduce the risk of relapse and early detection<br>To support functional and community adaptation<br>To improve quality of life | Mental health centres<br>Rehabilitation service<br>Social clubs<br>Occupational insertion services<br>Assisted living apartments<br>Psychiatric residences | Continued assessment and adaptation of the therapeutic plan<br>Pharmacological treatment<br>Individual and family psychosocial interventions and stability support<br>Health education and psychoeducation<br>Social skills<br>Cognitive rehabilitation<br>Occupational rehabilitation<br>Community insertion support<br>Home-based support<br>Housing support |

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The existence of two large phases in incipient psychotic disorder and schizophrenia and the diversity of action directives, programs and services that take part in the diagnosis/assessment, treatment and rehabilitation/insertion of these disorders present us with the problem of continuity of care and articulation and coordination of different healthcare resources.

A line of response to this problem is the design of longitudinal programs for coordination of action directives and services, as well as the implementation of cross-sectional programs that organize healthcare provision. In both cases the objective is to guarantee minimum healthcare quality in the treatment of people with incipient psychotic disorder and schizophrenia and to ensure continuity of care and articulation of interventions.

Longitudinal programs should ensure continuity of care between services, and especially between outpatient and in-hospital settings, with the aim of avoiding treatment interruption and the disconnection of patients from the healthcare network. They should also ensure the transmission of relevant diagnostic, clinical and therapeutic information.

On the other hand, cross-sectional programs should be aimed at adequately integrating different services that overlap at a given time and the patient and family's adherence to the care provided.

Some of the programs that try to reach these objectives acknowledge different evolution phases such as, for example, early phases of psychosis or more advanced phases of schizophrenia. There are also programs that stem from the specific difficulties of linkage with services or greater clinical severity of outpatient conditions, mirroring assertive community treatment or case management.

Finally, it is important for these interventions and programs to acknowledge deontological and legal regulations relating to healthcare practice and which should preside in the relationship between healthcare teams and people with incipient psychotic disorder or schizophrenia and their families. This is especially important when the intention is to incorporate patients as active participants in decision-making and in the entire healthcare process.

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# 9. Dissemination and implementation

## 9.1. Dissemination

As in the previous edition, the CPG will be distributed by post to interested professionals, and will be communicated at congresses and presented officially in public events. It will be necessary to contact mental health services of different autonomous communities and the corresponding scientific societies.

The dissemination strategy includes the following actions:

- Ellaboration of press releases sent to the media, both scientific and general media.
- Individual delivery to potential professional users of the CPG. A shorter format of the guideline and the most important annexes with algorithms and figures are also sent to these users.
- Presentation to scientific societies and professional groups that are considered to be an objective sector of the public.
- Indivualised distribution to opinion leaders and experts in accordance with criteria such as publication volume in scientific journals, presidency of scientific societies, members of the expert committees of biomedical journals, members of the scientific committees of congresses, etc.
- Distribution of the guideline aimed at people with schizophrenia, and their families, friends or people they have a relationship with.
- Use of the CPC in adademic activities related to the methododlogy and development of CPGs.
- Diffusion of the CPG in electronic format in the websites of the CAHTA and scientific societies.
- Presentation of the CPG in scientific activities (conferences, congresses, meetings).
- Publication of the CPG in medical journals.

## 9.2. Determination of implementation indicators

The objectives of implementing the CPG are:

- To provide a comprehensive approach for the management of patients with incipient psychosis or schizophrenia which includes pharmacological treatment; individual, group-based and family psychotherapy; and rehabilitation.
- To provide an adequate idiosyncratic combination of treatments of patients with incipient psychosis and schizophrenia.

The indicator designed to measure its scope is the percentage of patients with schizophrenia or incipient psychosis attended who have been offered pharmacological treatment; psychosocial intervention and rehabilitation, in accordance with the recommendations suggested in this CPG.

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# 10. Recommendations for future research

- Conclusions on the efficacy of **cognitive-behavioural therapy** for incipient psychosis are limited due to the different types of outcomes assessed and the small number of subjects in the majority of studies, thus confirming the need for more research in this respect.

- Conclusions on the efficacy of **psychodynamic therapy** are controversial. It is necessary to perform more studies with improved methodological rigour.

- It is necessary to increase research with improved methodological quality, mainly in areas such as **cognitive rehabilitation**, given that scientific evidence is insufficient.

- It is necessary to perform more research assessing the effect of **expressive techniques**, in any of its modalities (art therapy or music therapy), and the adequate duration of these techniques.

- In regards to **occupational insertion support**, it is recommended to carry out more research focused on analyzing variables that predict successful occupational insertion (modifiable predictors versus non-modifiable predictors), as well as studies with older psychotic populations presenting certain characteristics (e.g., female gender). It is also necessary to conduct research in social-occupational settings, given that it is a factor that can have a significant effect on the efficacy of both clinical and economic interventions.

- The need to promote research regarding the benefits of treatment with **early intervention teams**, where the intervention modalities employed are more clearly defined is also established.

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# ANNEXES

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# Annex 1. Tables of levels of scientific evidence and grades of recommendation

The definitions of levels of scientific evidence (table 1) used in this CPG are the ones used by the US Agency for Health Care Policy and Research (now called, the US Agency for Healthcare Research and Quality),[239] and the grades of recommendation are those used in the classification system proposed by the Scottish Intercollegiate Guidelines Network (SIGN), which was based on previous levels (table 2).[240]

**Table 1. Levels of scientific evidence**

| Level | Type of scientific evidence |
|---|---|
| Ia | Scientific evidence obtained from meta-analyses of randomized clinical trials. |
| Ib | Scientific evidence obtained from at least one randomized clinical trial |
| IIa | Scientific evidence obtained from at least one well-designed, non-randomized controlled prospective study |
| IIb | Scientific evidence obtained from at least one well-designed, quasi-experimental study |
| III | Scientific evidence obtained from well-designed observational studies, such as comparative studies, correlation study or case-control studies. |
| IV | Scientific evidence obtained from documents or opinions of experts committees and/or clinical experiences of renowned opinion leaders. |

**Table 2. Grades of recommendation**

| Grade | Recommendation |
|---|---|
| **A**<br>(Levels of SE Ia, Ib) | It requires at least one randomized clinical trial as part of the scientific evidence with overall good quality and consistency in terms of the specific recommendation |
| **B**<br>(Levels of SE IIa, IIb, III) | It requires methodologically correct clinical trials that are not randomized clinical trials on the topic of recommendation. It includes studies that do not meet A or C criteria. |
| **C**<br>(Level of SE IV) | It requires documents or opinions of experts committees and/or clinical experiences of renowned opinion leaders. It indicates the absence of high quality, directly applicable clinical studies |

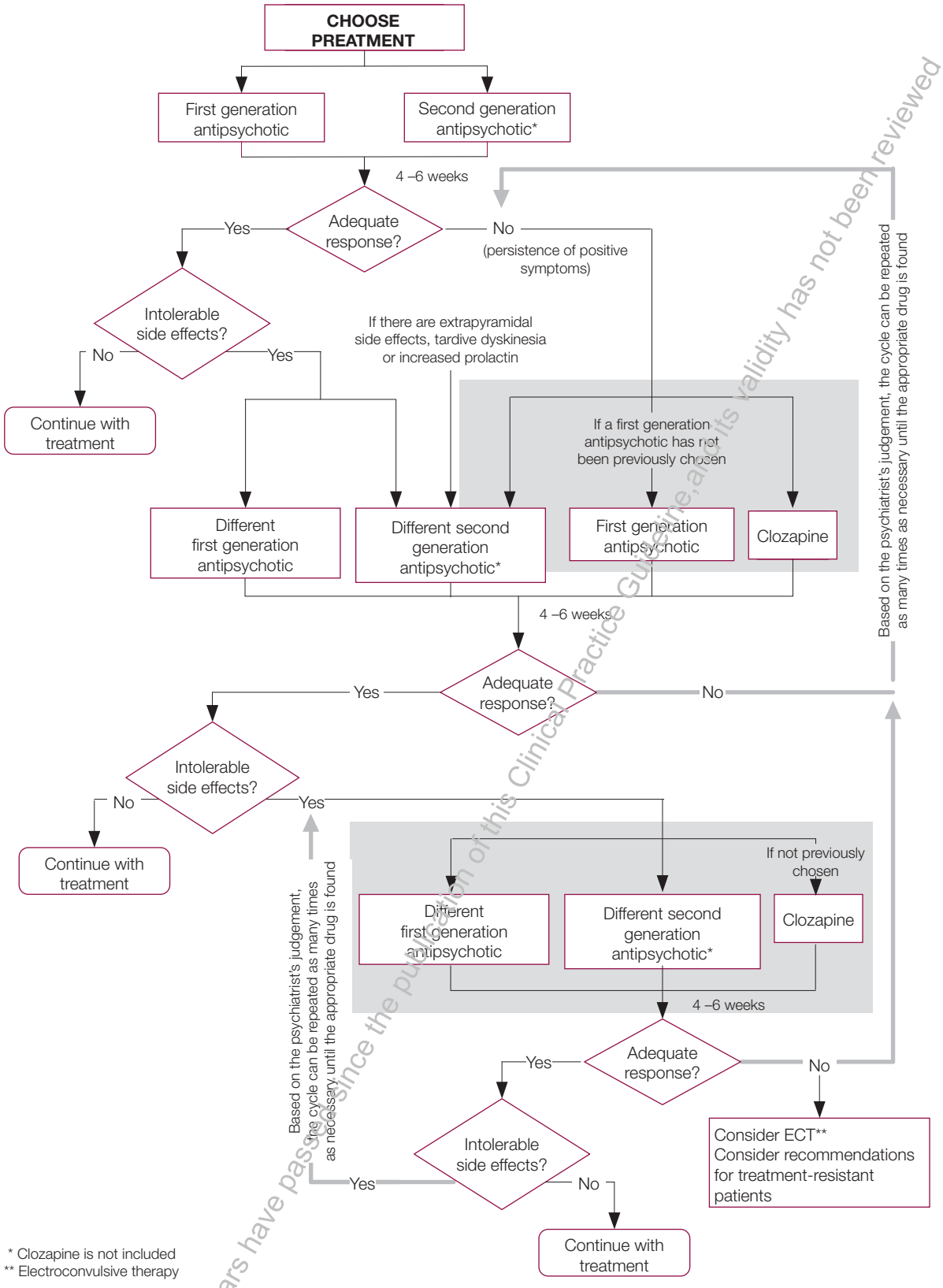
SE: Scientific evidence

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# Annex 2. Figures and tables

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**Figure 1. Algorithm of pharmacological intervention**




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**Table 3- Depot antipsychotics***

| Drug | I.M. Minimum effective dose | Duration (days) | Standard dose |
|---|---|---|---|
| Zuclopenthixol acetate | 50 mg | 3 days | 1-3 ml (1 ml = 50 mg) |
| Fluphenazine decanoate | 12.5 mg | 10 days | 0.5-2 ml (1 ml = 25 mg) |
| Haloperidol decanoate | 50-60 mg | 15 days | 1-6 ml (1 ml = 50 mg) |
| Zuclopenthixol decanoate | 100 mg | 15 days | 1-2 ml (1 ml = 200 mg) |
| Pipotiazine palmitate | 50 mg | 15 days | 2-6 ml (1 ml = 25 mg) |
| Sustained-release risperidone | 25-50 mg | 14 days | 50 mg |

*Adapted from Chinchilla[78] and TPG[73].

**Table 4. Recommended adult dosage of first generation (conventional) antipsychotics**

| Antipsychotic (Agent) | Starting dose | Gradual dose increase | Standard dosage interval | Maximum dosage |
|---|---|---|---|---|
| **Chlorpromazine, hydrochloride** | 25 mg 3 times daily (or 75 mg at night)<br><br>In 25-50 mg deep intramuscular injection every 6-8 hours (for palliating acute symptoms; however, refer to Precautions and Side effects) | Adjust to a maintenance dose of 75-300 mg/day according to the response obtained (however, psychosis requires up to 1 g/day) | 75-300 mg/day normal maintenance dose, according to the response obtained | 1 g/day |
| **Clotiapine** | Initially, 120-160 mg/day in divided doses | | | Maximum dose 360 mg/day |
| **Haloperidol** | Start with 1.5-3 mg 2-3 times a day<br>[0.5-2 mg/8-12 h] or<br>3-5 mg 2-3 times daily if the patient has a severe or | Adjust the maintenance dose to the minimum effective dose (as low as 5-10 mg/day) according to the response | | In intramuscular or intravenous injection: daily total maximum of 18 mg |

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| | resistant disorder.<br><br>Refractory schizophrenia may require up to 30 mg/day<br><br>In intramuscular or intravenous injections: start with 2-10 mg. Patients with severe disorders sometimes require a starting dose of up to 18 mg | obtained.<br><br>In intramuscular or intravenous injection: continue every 4-8 hours according to the response obtained | | |
| **Levomepromazine** | Start with 25-50 mg/day, in divided doses.<br><br>In bedridden patients: start with 100-200 mg/day, generally taken in three doses | Increase according to need.<br><br>In bedridden patients: increase, if necessary, up to 1 g/day | | |
| **Perphenazine** | Start with 4 mg daily | Adjust according to response obtained | | Maximum 24 mg/day |
| **Periciazine** | Start with 75 mg/day, taken in several doses | Increase weekly in 25 mg increments, according to the response obtained | | Maximum daily dose: 300 mg/day |
| **Pimozide** | Start with 2 mg/day | Increase at intervals no shorter than a week in 2-4 mg increments, according to the response obtained | Standard dosage interval: 2-20 mg/day | |
| **Sulpiride** | 200-400 mg twice daily<br><br>In intramuscular injection: 600-800 mg/day (during 15-20 days). | | | Maximum 800 mg/day, if there are mostly negative symptoms and 2.4 g/day, if there are mostly positive symptoms |

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| | | | | |
|---|---|---|---|---|
| **Thioproperazine** | Generally speaking, 30-40 mg/day, in 3-4 doses | | | |
| **Trifluoperazine** | Start with 5 mg twice daily or 10 mg/day in modified release form | Increase by 5 mg at one week, and subsequently at three day intervals, according to the response obtained | | |
| **Zuclopenthixol Acetate** | In deep intramuscular injection into the gluteus maximus muscle or into the external side of the thigh: 50-150 mg | Repeat if necessary after 2-3 days (another dose may be necessary 1-2 days after the first injection) | If maintenance treatment is required, switch to an oral antipsychotic 2-3 days after the last injection or to a longer acting antipsychotic in injection form (depot), which is administered at the same times as the last injection of zuclopenthixol acetate | Maximum accumulated dose of 400 mg per cycle and maximum number of injections is 4. Maximum duration of treatment is 2 weeks |
| **Zuclopenthixol, dihydrochloride** | Start with 20-30 mg/day, in divided doses | Increase up to a maximum of 150 mg/day if necessary | Standard maintenance dose of 20-50 mg/day | Increase up to a maximum of 150 mg/day if necessary |

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## Table 5. Comparative table of standard adult dosage intervals of first generation (conventional) antipsychotics

| Antipsychotic (Agent) | TPG[73] | APA[4] | Canadian[2] | WFSBP[76] | | PORT[40] | RTM-III[77] | Minchilla et al.[78] |
|---|---|---|---|---|---|---|---|---|
| | | | | 1st episode | multiple episodes | | | |
| **Chlorpromazine, hydrochloride** | Standard maintenance doses of 75-300 mg/day according to the response obtained | 300-1000 mg/day | | 300-500 mg/day | 300-1000 mg/day | 300-600 mg/day | 25-2000 mg/day | 300-1500 mg |
| **Clotiapine** | Initially, 120-160 mg/day in several doses. Maximum dose of 360 mg/day | — | | | | | 40-160 mg/day | 100-200 mg |
| **Haloperidol** | Adjust the maintenance dose to the minimum effective dose (as low as 5-10 mg/day) according to the response obtained | 5-20 mg/day | | 1-4 mg/day | 3-15 mg/day | 6-12 mg/day | 1-50 mg/day | 5-30 mg |
| **Levomepromazine** | Start with 25-50 mg/day, in several doses<br><br>Increase if needed. | — | | | | | 25-1500 mg/day | 100-300 mg |
| **Perphenazine** | Start with 4 mg 3 times daily. Adjust according to the response obtained, up to a maximum of 24 mg/day. | 16-64 mg/day | | 6-36 mg/day | 12-42 mg/day | 30-60 mg/day | 4-64 mg/day | 30-150 mg |
| **Periciazine** | Start with 75 mg/day, taken in divided doses. Increase weekly by 25 mg increments, according to the response obtained. Maximum normal daily dose: 300 mg/day | — | | | | | — | — |
| **Pimozide** | Normal dosage interval: 2-20 mg/day | — | | 1-4 mg/day | 2-12 mg/day | | 2-20 mg/day | 4-12 mg |
| **Sulpiride** | 200-400 mg 2 times a day<br><br>In intramuscular injection: 600-800 mg/day (during 15-20 days).<br><br>Maximum 800 mg/day, if there are mostly negative symptoms and 2.4 g/day if there are mostly positive symptoms | — | | | | | 400-2000 mg/day | 400-600 mg |
| **Thioproperazine** | Generally speaking, 30-40 mg/day, in 3-4 doses | | | | | | 30-120 mg/day | — |
| **Trifluoperazine** | Start with 5 mg twice daily or 10 mg/day in modified release form. Increase by 5 mg at one week, and subsequently at three day intervals, according to the response obtained | 15-50 mg/day | | | | 15-30 mg/day | 2-40 mg/day | 15-25 mg |
| **Zuclopenthixol, acetate** | If maintenance treatment is required, switch to an oral antipsychotic 2-3 days after the last injection or to a longer acting antipsychotic in injection form (depot), which is administered at the same times as the last injection of zuclopenthixol acetate | — | | | | | | |
| **Zuclopenthixol, dihydrochloride** | Standard maintenance dose of 20-50 mg/day | — | | 2-10 mg/day | 25-50 mg/day | | | |

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## Table 6. Recommended adult dosage of second generation (atypical) antipsychotics*

| Antipsychotic (Agent) | Starting dose | Gradual dose increase | Standard dosage interval | Maximum dosage |
|---|---|---|---|---|
| **Amisulpride** | | | 400-800 mg/day, in two doses | 1.2 g/day |
| **Aripiprazole** | | | 10-15 mg/day | 30 mg/day |
| **Clozapine** | First day: 12.5 mg, 1 or 2 times daily<br>Second day: 25-50 mg | 25-50 mg/day phases during 14-21 up to 300 mg/day taken in divided doses | 200-450 mg/day | 900 mg/day |
| **Olanzapine** | Oral administration: 10 mg/day<br>Intramuscular injection: 5-10 mg followed by 5-10 mg after two hours if necessary | Oral administration: adjusted to the normal interval | Oral administration:5-20 mg/day<br>Intramuscular injection: 10 mg | Oral administration: > 20 mg/day shall only be administered after an examination (maximum 20 mg/day) |
| **Paliperidone** | Start with 3 mg/day, once daily. | Increase according to clinical response or tolerability | 3-12 mg/day | 12 mg/day |
| **Quetiapine** | First day: 25 mg 2 times/day | Second day: 50 mg 2 times/day<br>Third day: 100 mg 2 times/day<br>Fourth day: 150 mg 2 times/day | 300-450 mg/day taken in 2 doses | 750 mg/day |
| **Risperidone** | First day: 2 mg taken 1-2 times/day<br>Second day: 4 mg taken 1-2 times/day | | 4-6 mg/day | > 10 mg/day are justified only if benefits exceed risks (maximum 16 mg/day) |
| **Sertindole** | 4 mg/day | 4 mg, in 4-5 day intervals | 12-20 mg, in one single daily dose | 24 mg/day |
| **Ziprasidone** | Intramuscular injection: 19-20 mg followed by 10 mg/2 hours | | Oral administration: 40 mg 2 times /day | Oral administration: 80 mg 2 times/day<br>Intramuscular injection: 40 mg/day (maximum of 3 consecutive days) |

*Adapted from the TPG[73]

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## Table 7. Comparative table of standard adult dosage of second generation (atypical) antipsychotics

| Antipsychotic (Agent) | GPT[73] | APA[4] | Canadian[2] | WFSBP[76] | | PORT[40] | RTM-III[77] | Chinchilla et al. [78] |
|---|---|---|---|---|---|---|---|---|
| | | | | 1st episode | multiple episodes | | | |
| **Amisulpride** | 400-800 mg/day, taken in two doses | — | | 100-300 mg/day | 400-800 mg/day | | | 200-800 mg/day |
| **Aripiprazole** | 10-15 mg/day | 10-30 mg/day | | 15-(30) mg/day | 15-30 mg/day | 10-30 mg/day | | 10-30 mg/day |
| **Clozapine** | 200-450 mg/day | 150-600 mg/day | 300-600 mg/day | 100-250 mg/day | 200-450 mg/day | 150-600 mg/day | 100-900 mg/day | 200-600 mg/day |
| **Olanzapine** | Oral administration: 5-20 mg/day<br><br>Intramuscular injection: 10 mg | 10-30 mg/day | 10-20 mg/day | 5-15 mg/day | 5-20 mg/day | 10-20 mg/day | 5-30 mg/day | 10-30 mg/day |
| **Quetiapine** | 300-450 mg/day taken in 2 doses | 300-800 mg/day | 600 mg/day | 300-600 mg/day | 400-750 mg/day | 300-750 mg/day | | 600-1500 mg/day |
| **Risperidone** | 4-6 mg/day | 2-8 mg/day | Oral administration: 2-6 mg/day<br><br>IM*: 25-37.5 every 2 weeks | 1-4 mg/day | 3-6-(10) mg/day | 2-8 mg/day | 1-18 mg/day | 6-12 mg/day |
| **Sertindole** | 12-20 mg, in one single daily dose | — | | | | | | 8-24 mg/day |
| **Ziprasidone** | Oral route: 40 mg 2 twice /daily | 120-200 mg/day | | 40-80 mg/day | 80-160 mg/day | 120-160 mg/day | | 120-240 mg/day |

- IM= Intramuscular

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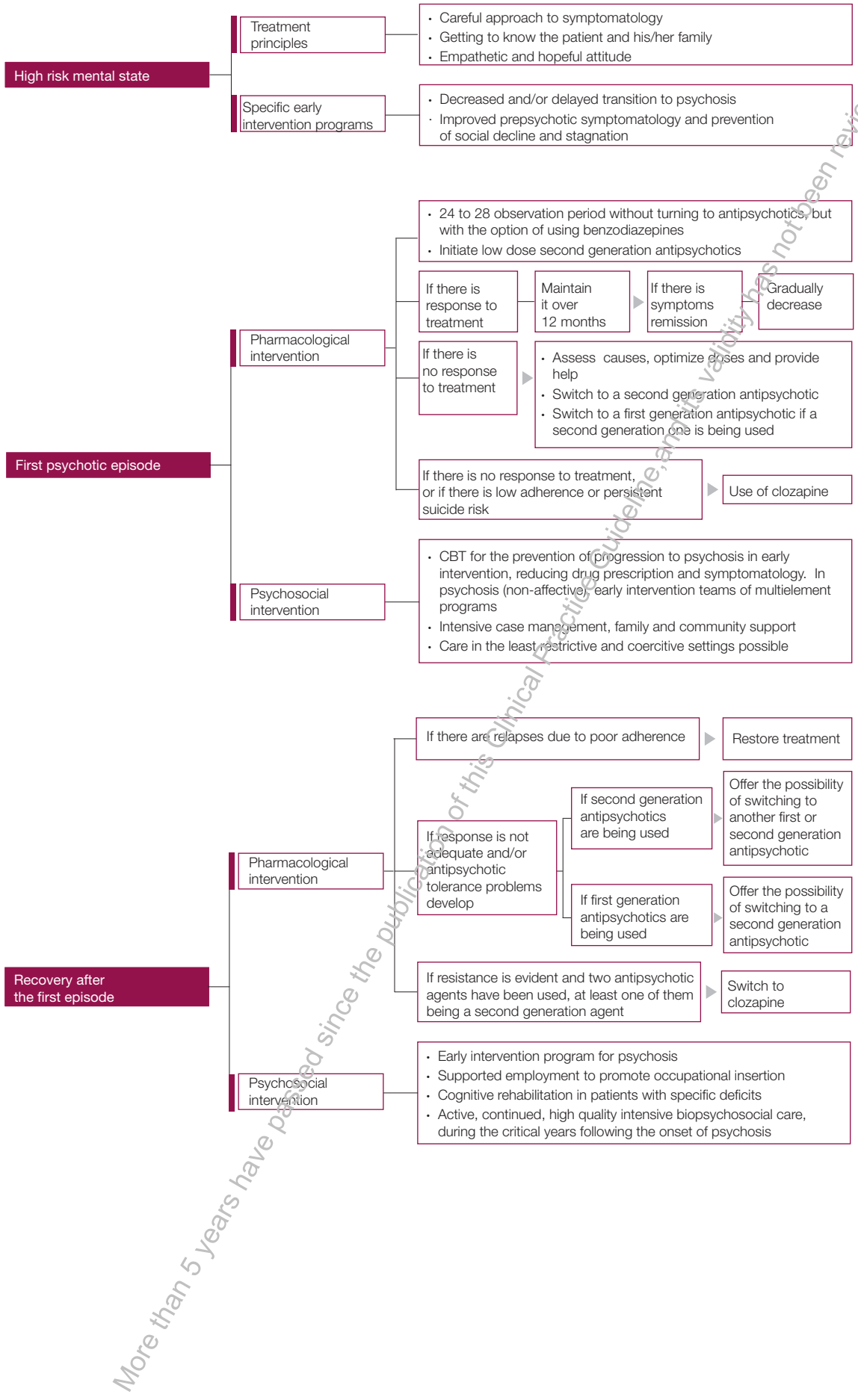
**Table 8. Management of the patient receiving clozapine treatment***

| White blood cell count | Neutrophil granulocytes | Measures that should be adopted |
|---|---|---|
| < 3,500/mm$^3$ | | Follow-up of white blood cell count and formula |
| < 3,500/mm$^3$ | < 2,000 – 1,500/mm$^3$ | Follow-up of granulocytes and white blood cells 2 times/week |
| < 3,000/mm$^3$ | < 1,500/mm$^3$ | Immediately withdraw treatment<br>Monitor the patient with daily blood counts |
| < 2,000/mm$^3$ | < 1,000/mm$^3$ | Hospitalization |

* White blood cell count results should be sent to the Division of Pharmacoepidemiology and Pharmacosurveillance of the Spanish Drug Agency.

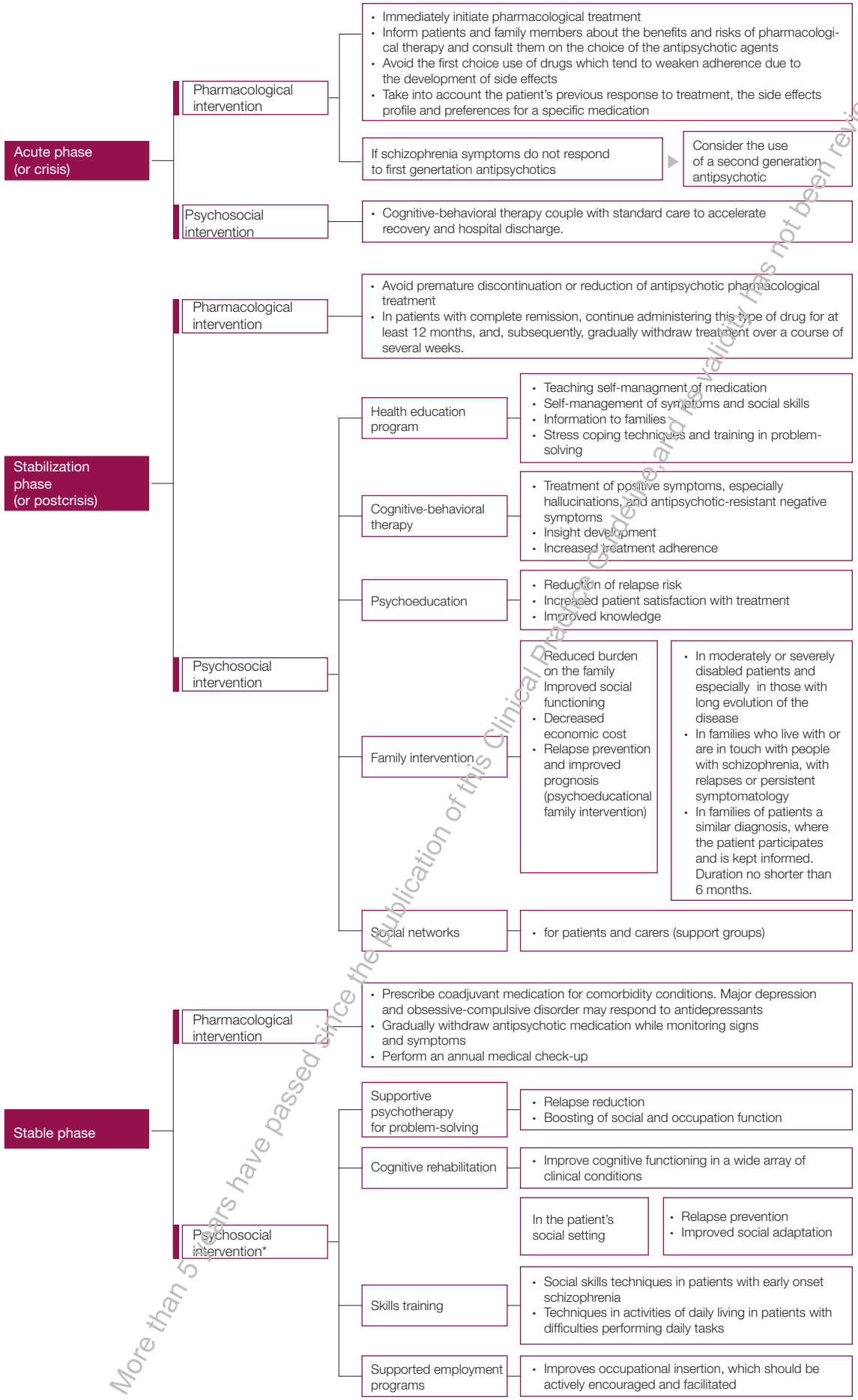
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**Figure 2. Interventions according to the phases of incipient psychosis**




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**Figure 3. Interventions according to the phases of schizophrenia**




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* Psychosocial interventions that are effective in the stabilization phase are also effective in the stable phase

# Annex 3. Information for patients

# Schizophrenia Guide

## Living with Schizophrenia

**A guide aimed at people affected by schizophrenia**

This CPG has been funded by the agreement between the Carlos III Institute of Health, an autonomous organism of the Ministry of Health and Consumer Affairs (MSC), and the Catalan Agency for Health Technology Assessment and Research, within the framework of collaboration forecasted in the Quality Plan for the National Health System.

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### AUTHORS

Working Group of the Clinical Practice Guideline for Schizophrenia and Incipient Psychotic Disorder.

This guideline is aimed at people affected by schizophrenia and is part of the document: Working Group of the Clinical Practice Guideline for Schizophrenia and Incipient Psychotic Disorder. Mental Health Forum, coordination.

Clinical Practice Guideline for Schizophrenia and Incipient Psychotic Disorder. Madrid: Quality Plan for the National Health System of the Ministry of Health and Consumer Affairs. Agency for Health Technology Assessment and Research, 2009. This document is available in the GuiaSalud guidelines catalogue of the National Health System of GuíaSalud (www.guiasalud.es) and at the CAHTA's website (www.aartrm.net).

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Mental Health Forum

Agency for Health Technology Assessment and Research

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This document is available in the GuiaSalud guidelines catalogue of the National Health System (www.guiasalud.es) and at the CAHTA website (www.aatrm.net).

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# PRESENTATION

This guide is aimed at people with schizophrenia and their families, friends or people they may have different types of relationships with.

It is based on the recommendations of the Clinical Practice Guideline for the Management of the Patient with Schizophrenia, which has been developed by the Mental Health Forum and the Agency for Health Technology Assessment and Research.

The objective is to inform and help people who suffer from schizophrenia with the aim of understanding this disorder better and to be involved in its treatment and recovery process. The document gives a general overview of the disorder and describes its symptoms, course, available treatments and interventions, and provides recommendations based on the results of current research.

The annexes of this document include some definitions of the medical terms used in this guideline, and a list of organizations and addresses that people affected by schizophrenia can turn to in order to obtain more information.

**LIVING WITH SCHIZOPHRENIA**

**SCHIZOPHRENIA GUIDE**

# SCHIZOPHRENIA

### WHAT IS SCHIZOPHRENIA?

Schizophrenia is a mental disorder that is included within the group known as psychotic disorders. People who have schizophrenia present severely distorted thoughts, perception and emotions, have lost touch with reality and experience hallucinations, a phenomenon in which people hear and/or feel things that others do not.

People with schizophrenia also present other symptoms, such as delusions, which consist of strange ideas that are not based on reality or social consensus. Additionally, their emotions are affected by the loss of habits and interests, social withdrawal, depression and/or irritability.

No symptom, by itself, is characteristic of this disorder, nor do all affected people present each and every symptom described.

People with schizophrenia usually present severely distorted thoughts and emotions.

### WHO SUFFERS FROM SCHIZOPHRENIA?

Any person can suffer from schizophrenia, which develops in men and women in a similar manner.

The onset of the disorder often occurs during adolescence –or even in childhood- or at the beginning of adulthood. It seems onset is earlier in men.

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## WHAT CAUSES SCHIZOPHRENIA?

The cause of schizophrenia remains unknown, but research indicates that it is a combination of genetic and environmental factors which create a state of vulnerability in the person and a predisposition to develop the disorder if certain circumstances are present.

A combination of factors produce predisposition to this disorder

## CAN IT BE CURED?

Schizophrenia can have several courses, including total remission. The disorder can also present long-term remissions and exacerbations. However, there is a lot of information available on treatment options for people with schizophrenia, treatments which are aimed at improving their quality of life.

Remission and stabilization of the disorder enables patients to carry out life with autonomy and independence, taking on family and employment responsibilities.

A person who is vulnerable to the disease should be alert to factors which may trigger a crisis, with the aim of trying to prevent it or minimize its effects. It is important that at the onset of a crisis help resources can be mobilised: family, professionals, etc.

Schizophrenia can be treated, achieving improved quality of life.

## INITIAL SYMPTOMS

Before a crisis, affected people usually experience strange changes in behaviour, perception and mood. The presence of these symptoms can cause some confusion, especially in the family.

Symptoms may vary greatly from one person to another, but they can be identified as changes in what had been normal behaviour up until that moment. Some of these symptoms are:

- Changes in normal activity (work, school,…), in daily routine (disturbances in eating habits, personal hygiene,…), in the sleep/wake cycle.
- Social withdrawal, suspicious or mistrustful attitude.
- Unusual beliefs and/or obsessions.
- Changes in perception (hallucinations).

These changes that take place before a crisis are known as prodromes and alert to the fact that something is wrong, and can help to prevent or address crises. It should be noted that the presence of prodromes does not necessarily mean that they will lead to full-fledged schizophrenia or that there will be a relapse.

If the patient feels different or notices significant changes in normal behaviour, he/she should consult the doctor, so a correct diagnosis can be made.

It is important that at the onset of a crisis help resources can be mobilised (family, friends, professionals, etc.)

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## THE WORLD OF SCHIZOPHRENIA

People who have a schizophrenic disorder present different types of symptoms. However, no symptom is specific to schizophrenia.

The characteristic symptoms of schizophrenia are classified into three categories: positive, negative and disorganization.

> Positive symptoms add something to the life of these patients, such as hallucinations and delusions (they add perception disturbances).
>
> Negative symptoms are produced by the lack of something, such as habits and interests, apathy, isolation, attention difficulties.
>
> Disorganization symptoms affect thought processes, which may be altered (disorganized behaviour and/or speech, poor attention).

All these symptoms may entail several degrees of disability, given that they sometimes affect the patient's ability to carry out an autonomous life (capacity to work, relationships or emotional links).

## COURSE OF THE DISORDER

The onset of schizophrenia can be gradual or sudden. On the other hand, its course is variable. It is usually interspersed by crisis periods (acute phase) and stable moments of total or partial remission of symptoms (stable phase). Between these two phases there may be periods of reduced intensity of symptoms, which may last about six months after a crisis (stabilization phase).

The course of the disorder is variable.

## DIAGNOSIS

In order to diagnose schizophrenia, a mental health specialist (psychiatrist or psychologist) will conduct a clinical study of the symptoms that the patient has presented for some time, once the patient has been referred by the general practitioner. Laboratory and/or complementary tests will also be performed to rule out other diseases or use of toxic substances.

It is important that the patient explains all the changes he/she has been experiencing, with the aim of facilitating the specialist's task of making a correct diagnosis.

## CAN SCHIZOPHRENIA BE PREVENTED?

The initial signs of changes in normal behaviour can alert to the fact that something is wrong. At this time the help of healthcare professionals should be sought. It is important that an early diagnosis of the disorder be performed during this time.

The elements of primary prevention at the onset of a crisis are to boost personal resources, increase tolerance to stress, decrease psychosocial stress factors, improve interpersonal skills and to have a good therapeutic alliance which enables the implementation of proper treatment.

Prevention is increased if the patient follows a healthy and stable lifestyle, and his/her personal and self-care skills are boosted. This type of prevention factors should be promoted, while

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avoiding others which could indicate higher risk of destabilization (stressful situations, lack of adherence to medication, drug use, etc.).

Treatment is essential to prevent crises.

# TREATMENT

The treatment of schizophrenia is comprehensive, meaning it combines different types of treatment: medical and psychosocial therapies.

It is important that the patient gets help as soon as possible and for the healthcare team to develop a treatment plan, with active involvement of the patient, his/her family and people he/she may be involved in one way or another. The treatment plan should take into account the type of treatment and the setting where it will be carried out, as well as the preferences of the patient and his/her family.

More detailed information on medication and psychosocial interventions currently used in schizophrenia can be found in the *Clinical Practice Guideline for the Management of the Patient with Schizophrenia and Incipient Psychotic Disorder*.

The therapeutic approach to schizophrenia is comprehensive, combining different types of treatment.

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## MEDICAL TREATMENT

Medication is a very important part of the treatment of people who have a schizophrenic disorder. Certain drugs have been shown to attenuate symptoms in crisis periods (acute episodes), to prevent relapses and to improve symptoms between crises.

Antipsychotics are the main drug used, given that they reduce symptoms and prevent relapses. Other medications are also used to stabilize mood and to tackle side effects (coadjuvant medications).

There are two large groups of antipsychotics:

a. First generation or conventional antipsychotics (haloperidol, chlorpromazine, clotiapine, sulpiride, etc.).

b. More modern second generation or atypical antipsychotics (clozapine, olanzapine, risperidone, sertindole or quetiapine, ziprasidone, amisulpride and aripiprazole).

All of these drugs are effective in adequate doses at reducing most schizophrenia symptoms.

### How does medication work?

Individual characteristics, type of symptoms, side effects of medication, and preferences determine the type of medication and dose that is adequate for each person. For treatment to work effectively, it is important to take the medication exactly as was indicated by the doctor, without discontinuing it or change dosage.

It is essential to maintain good communication with the doctor with the aim of providing accurate information of the symptoms experienced, or any difficulties which may arise. At the same time, it is necessary for the doctor to inform on the types of treatments that can be performed and their side effects, hence including the patient in the search for the best treatment in his/her particular case.

Not everyone responds to medication in the same way. Antipsychotics are administered with the dose that has been proven most effective for each person. If there is poor response, another optimum dose should be established, or other types of antipsychotics and treatments which help to reduce symptoms should be sought.

Research has proven that in treatment-resistant patients the use of an atypical antipsychotic, clozapine, has been effective.

For people who have difficulties remembering to take daily medication, depot drugs may be useful. These drugs are injectable antipsychotics that maintain their effect over longer periods of time (two or three weeks), depending on the type of medication.

**What side effects may develop?**

Antipsychotic medication can produce other effects in the body which are secondary to the benefit they yield and which can be treated.

It is important that patients inform their doctor on any changes in their symptoms and any side effects that their medication may be causing. The doctor will modify and/or adjust the dose of medication according to the patient's needs.

The most frequent side effects are those affecting the nervous and muscular systems (extrapyramidal), including: disturbances in muscle tone control (dystonia), inability to stay quiet or seated (akathisia), tremors (Parkinson's), rigidity and muscle weakness, etc. Another muscular side effect is uncontrollable movements of the mouth and face (tardive dyskinesia).

Other side effects are: sedation; weight gain; antiadrenergic effects such as dry mouth, blurred vision, constipation, tachycardia or urine retention; anticholinergic effects such as memory and cognitive impairment, confusion, delirium, somnolence and hallucinations; galactorrhea (spontaneous flow of milk from the nipples), sexual dysfunctions, menstrual disorder (oligomenorrhea), etc.

Research has shown that all second generation or atypical antipsychotics cause fewer extrapyramidal side effects that first generation or conventional drugs.

If any change is experienced due to medication, the doctor should be informed so he/she can either switch medication or adjust the dose according to the patient's needs.

**Is other medication necessary?**

The doctor in charge may consider it necessary to prescribe other drugs that, coupled with antipsychotics, help to reduce schizophrenia symptoms. For example, mood stabilizers (such as lithium), antianxiety drugs (such as benzodiazepines), antidepressants or drugs that reduce the side effects of antipsychotics (such as Antiparkinson drugs, anticholinergic drugs, etc.).

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**How long should medication be taken for?**

In order for an antipsychotic to have an effect on the crisis, two weeks to two months are usually required. Afterwards, once the crisis has been overcome, dose is gradually decreased until reaching an adequate dose.

Due to the risk of fast relapse after a crisis, it is not recommended to prematurely discontinue or reduce medication. Patient and doctor will agree upon the duration of medication use which, in first crises, is usually one to two years. In the case of relapse, two to five years of medication are required. Patients who have multiple episodes need continued medication. However, treatment and dose should be adapted to each person.

## PSYCHOSOCIAL TREATMENT

Psychosocial therapy is another key element, together with medication, in the treatment of schizophrenia. The aim of this type of therapy is to reduce the vulnerability of the person with schizophrenia when faced with stressful situations by boosting his/her adaptation and social functioning, and to achieve the best quality of life possible.

There are different types of therapies and the choice of one or another will depend on the patient (based on his/her characteristics, needs and preferences) and on available resources at that time.

In these therapies it is common and essential to establish a trust-based relationship with the professional and the team responsible for treatment.

In the initial moments of a crisis, psychosocial interventions, aside from informing on the disorder, treatment and prognosis, also help to identify and reduce any factors that may be stressful to the patient. In the phase of stabilization of the disorder, it is recommended to apply psychological interventions that help to:

a) Elaborate on the impact of the crisis.

b) Address the effects on identity, self-esteem, relationships and life projects.

c) Receive support in solving problems of daily life, by means of an alliance with the therapists which fosters hope, empathy, optimism and stability in the care process.

For treatment to work effectively, it is important to establish a trust-based relationship with the team in charge of treatment.

Interventions are also aimed at families or people who have significant relationships with schizophrenia patients to help them understand the disorder and the effect it may have on behaviour. Subsequently, in the stable or maintenance phase, the objective is to improve the quality of life of the patient and his/her family, promoting disorder management strategies to prevent relapses, receiving the support necessary to cope with daily life problems and promoting the development or rehabilitation of skills to carry out training or employment activities, relationships or self-care as autonomously as possible.

### Support to schizophrenia patients

Families and other people who are close to patients with schizophrenia embody one of the greatest support sources to tackle the disorder. It is important to include these people in treatment, given that they can be of great help in identifying early signs of relapse, in the access to and follow-up of treatment and in providing support when the patient resumes daily life

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activities. The patient's opinion on how the family should be involved should be taken into account.

Family intervention, as a treatment, can be very useful for family members or people who live with schizophrenia patients, providing information and advice on schizophrenia and its symptoms, helping to reduce family stress and improving communication. These contributions undoubtedly yield benefits in the recovery of people with schizophrenia.

The inclusion of families in treatment can be very useful to the person who has schizophrenia and his/her recovery.

## HARD TIMES IN THE LIFE OF PEOPLE WITH THIS DISORDER

At different times in life, it may become difficult to cope with the effects of the disorder and other life problems: relationship conflicts or isolation, difficulties in studies or work, etc., which may lead to depression, anxiety, substance abuse, suicidal ideas…

It is important to seek the help of specialized professionals to find strategies which help to address and resolve these difficulties, and to avoid the complications derived from prolonging situations of suffering.

## WHERE IS TREATMENT CARRIED OUT?

People with schizophrenia should be treated in the least restrictive setting possible. There are different treatment settings available:

a. Outpatient treatment (mental health centre and rehabilitation service).
b. Modalities of care and intensive follow-up in the community.
c. Partial hospitalization (day hospital).
d. Total hospitalization: acute and subacute units.

Choosing one treatment setting over another depends mainly on the severity and persistence of symptoms and on the contention and support capacity the setting provides. It is also important to take into account the patient's and family's opinion in this respect.

If possible, patients with schizophrenia should be treated in the community. Stressful situations should be reduced as much as possible. The most common treatment modality is outpatient treatment. This type of treatment is carried out by mental health centres and specific teams aimed at rehabilitation and social reinsertion (rehabilitation services, occupational insertion services and leisure-time support services). In some cases, home interventions are necessary, be it via home-based support or by providing alternative housing in apartments or residences. Hospitalization may sometimes be necessary depending on the type of treatment applied, or to ensure better protection and support to the person with the disorder.

The modalities of care and intensive follow-up in the community are aimed at people with persistent disorders who are not linked to healthcare services or who have difficulties receiving continued care. There are different types of intervention such as assertive community treatment (organized within the framework of a specific team) or case management (a case manager carries out follow-up of the patient and coordinates the services involved in his/her management). The objective of these interventions is to ensure linkage to services and

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treatment compliance to improve the functional level and quality of life of people who have schizophrenia and their families.

## COPING WITH SCHIZOPHRENIA

Amongst the recommendations that have been presented in this guideline, which may be useful to tackle schizophrenia, the following should be highlighted:

- To be informed on the disorder and its treatment.
- To detect early warning signs and seek specialist help.
- To build a trust-based relationship with the team of professionals involved in treatment, in order to obtain the necessary help.
- To participate with the doctor in deciding the best treatment in each case.
- To maintain the medical treatment prescribed and combine it with psychosocial therapies indicated by the specialist.
- To adjust different interventions (psychoeducation, cognitive-behavioural therapy or group therapy, cognitive rehabilitation, etc.), according to the evolution of the disorder and individual needs.
- To provide health education for families of patients with schizophrenia and actively include them in treatment.
- To maintain a good health state (by following a well-balanced diet and exercising, resting, avoiding the use of drugs, etc.) in a favourable and supportive environment.
- To work on the integration of the disorder as one more aspect of the person's identity: "be a student of…", "a fan of…", "son/daughter of…", "father of…", "friend of…", "skilled at…", "clumsy at…", "loved by…".

## WHAT DOES THE FUTURE HOLD?

The future is bright. The more information becomes available on the causes of the disorder, and as more effective treatments are developed, the better care will be provided to people with schizophrenia so that they can lead a more independent lifestyle and enjoy improved quality of life.

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# TERMINOLOGY

**Hallucination**: False perception of an object or stimulus which does not exist, but which the individual considers to be real. Auditive hallucinations are the most common hallucinations in schizophrenia.

**Antipsychotics:** Group of drugs used especially in the treatment of psychosis and manic states. They are also called neuroleptics.

**Cognition**: Series of intellectual processes which enable an individual to acquire information on his/her surroundings and elaborate it by means of perception, memory, imagination, comprehension, judgement or reasoning. People with schizophrenia may present impairment of this function.

**Crisis**: Sudden or gradual onset of symptoms.

**Delusion:** False beliefs which are not based on reality or social consensus and which cannot be corrected with logical reasoning. Symptom of psychosis.

**Prodrome:** Symptom or sign prior to a crisis. Precursor of the disease.

**Psychosis:** Severe mental disorder characterized by personality and thought disturbances, with loss or lack of touch with reality. It is not specific to schizophrenia.

**Symptoms**: Abnormal functional or sensitive subjective phenomenon, which indicates the existence of disease.

**Psychosocial therapies:** Treatment of mental disorders using psychological methods based on the interpersonal relationship between the patient and mental health professional. There are different types of intervention and they can be performed individually or in groups.

**Vulnerability**: Predisposition to present a disorder due to adverse circumstances for the person.

# Where can I find more information and support?

- For more information, consult the Clinical Practice Guideline, on which the recommendations presented in this document are based:

  **Catalan Agency for Health Technology Assessment and Research (CAHTA)**

  Roc Boronat, 81-95 (2nd floor)
  E-08005 BARCELONA
  Tel.: 93 551 38 88
  Fax. 93 551 75 10
  www.aatrm.net

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- GuiaSalud

  www.guiasalud.es

- Associations for families and the mentally ill

  **Spanish Federation of Associations for Families and the Mentally Ill (FEAFES)**

  FEAFES is the Spanish Federation which has been grouping federations and associations of people with mental illness and their families throughout Spain since 1983. It currently includes over 180 organizations.

  Hernández Mas, 20-24
  28053 MADRID
  Tel.: 91 507 92 48
  Fax: 91 785 70 76
  E-mail: feafes@feafes.com
  Web: www.feafes.com

  **Association of Mental Health Users (ADEMM)**
  ADEMM, Users of Mental Health of Catalonia, is a non-profit association which was created and managed by its own affected members.

  Tel.: 93 217 09 37
  mobile: 616 563 197
  www.ademm@ademm-usm.org

- Other websites of interest

  **Spanish Association of Neuropsychiatry. Mental Health Professionals**

  www.aen.es

  **Spanish Society of Psychiatry**

  www.sepsiq.org/index2.html

  **Spanish Society of Biological Psychiatry**

  www.sepsiq.org/sepb/sepb.asp

  **Spanish Foundation of Psychiatry and Mental Health**

  www.fepsm.org/indexf.htm

  **Ministry of Health and Consumer Affairs**

  www.msc.es

  **World Health Organization (WHO)**

  www.who.int/es

  **World Psychiatric Association**

  http://www.wpanet.org/

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**National Guideline Clearinghouse**

International database of Clinical Practice Guidelines (CPGs), with over one thousand evidence-based CPGs. It provides a tool to perform searches and comparisons between the different CPGs selected.
http://www.guideline.gov/

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# Annex 4. Abbreviations

| | |
|---|---|
| **AASE** | Atypical antipsychotics side effects |
| **ACT** | Assertive community treatment |
| **ADL** | Activities of daily living |
| **APA** | American Psychiatric Association |
| **CBT** | Cognitive-behavioural therapy |
| **CM** | Case management |
| **CPG** | Clinical Practice Guideline |
| **DSM-IV-TR** | Diagnostic and Statistical Manual of Mental Disorders |
| **DUP** | Duration of untreated psychosis |
| **ECT** | Electroconvulsive therapy |
| **EE** | Expressed emotion |
| **ESE** | Extrapyramidal side effects |
| **FI** | Family intervention |
| **GAF** | Global Assessment of Functioning |
| **GAS** | Global Assessment Scale |
| **HRMS** | High risk mental state |
| **ICD-10** | Classification of Mental and Behavioural Disorders |
| **IPT** | Integrated psychological therapy |
| **NICE** | National Institute for Clinical Excellence |
| **PORT** | The schizophrenia patient outcomes research team |

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| | |
|---|---|
| **RCT** | Randomized clinical trial |
| **SRSE** | Systematic review of scientific evidence |
| **SSRI** | Selective serotonin reuptake inhibitors |
| **TPG** | Therapeutic Prescription Guideline |
| **WFSBP** | World Federation of Societies of Biological Psychiatry |

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# Annex 5. Declaration of interest

## Conflicts of interest:

A conflict of interest arises in circumstances under which the professional judgement over a primary interest such as patient safety or the value of research may be influenced in excess by another secondary interest, be it in terms of a financial benefit, prestige and personal or professional promotion.[1]

The most easily identifiable conflicts of interest are usually economic However, other types of circumstances such as personal relationships, links to direct family members or involvement in academic projects that have to do with the Clinical Practice Guideline (CPG) (participation in CPG or consensus for adaptation to the Project).

The relationships between medical professionals and the health industry (pharmaceutical industry, health technology, etc.) generally include six types of financial relationships:[2]

- Support to attend meetings and congresses (registrations, grants, travel expenses, etc.).
- Fees to act as lecturer or speaker in an organised meeting for the industry.
- Funding for educational programmes or training activities.
- Support funding and support for research work.
- Employment as consultant for a pharmaceutical company.
- Share holder or holder of economic interests in a pharmaceutical company.

In its turn, the elaboration of a CPG encompasses two potential types of conflicts of interest:

- Personal interests: these imply fees or personal benefits to a given member of the team.
- Non-personal interests: these imply funding which benefits the department or unit under the executive responsibility of a member of the team, without this person personally receiving such funding. Such interest may include economic help to create a unit or department, financial support for the hiring of staff to work at such units, or funding for the research conducted by the unit.

The potential for a conflict of interest exists regardless of whether or not the professional considers such relations to exert an influence on their scientific judgement.

There follows a question form on the declaration of conflicts of interest that has been designed with the aim of compiling all the previously mentioned aspects.

## References

(1) Thompson DF. Understanding financial conflicts of interest. N Engl J Med 1993 Aug 19;329(8):573-6.

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(2) Choudhry NK, Stelfox HT, Detsky AS. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. JAMA 2002 Feb 6;287(5):612-7.

# Declaration of Conflicts of Interest Form

**First and last names**: .....

**Institution for which the professional works**: .....

**Institution that links the professional to the CPG**, e.g.: Scientific society, etc. (only to be answered if different to the previous question):

.....

**Contact telephone number**: .....

Participation in the guideline as**:**

1- Development group ☐

2- Expert collaborator ☐

3- External Reviewer ☐

Having read the policy on the Development of Evidence-Based CPGs for assistance in the decision-making process in the National health System (NHS) regarding the declaration of conflicts of interest, I hereby issue the following declaration of conflicts of interest in relation to the subject of the CPG for the last three years.

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**A- Personal interests**

☐ **NO**

☐ **YES**

If YES, please specify**:**

| | Activity | Institution | Date |
|---|---|---|---|
| Funding for meetings and congresses, attendance to courses (registrations, travel expenses, housing …) | | | |
| Lecturer fees (conferences, courses …) | | | |
| Funding for educational programmes or courses (hiring of personnel, rental of facilities …) | | | |
| Funding to participate in a research project | | | |
| Consultancy for a pharmaceutical company / other technologies | | | |
| Share holder/commercial interest in a company (patents…) | | | |
| Economic interests in a private company in the health sector (as owner, employee, share holder, private consultant…) that might become significant in relation to the authorship of the guide | | | |
| Conflicts of interest that might be significant in the development of a clinical practice guideline | | | |

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**B- Non-personnel interests**

☐ **NO**

☐ **YES**

| | Activity | Institution | Date |
|---|---|---|---|
| Funding or financial aid for the creation of a unit or department | | | |
| Significant provision of material to the unit or department | | | |
| Hiring or financial aid to hire personnel to work at the unit or department | | | |
| Financial aid for the funding of research work | | | |
| Funding for educational programmes or courses for the unit | | | |

**C- Other possible conflicts of interest possible not included in the previous section (specify)**

| |
|---|
| |

Signature:

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# Annex 6. Comparison of the methodological quality of CPGs and recommendations on schizophrenia according to the AGREE questionnaire

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The bibliographic search yielded the following 11 CPGs and recommendations for the management of schizophrenia and incipient psychotic disorder:

- GPC New Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders, 2004. [New Zealand, 2004]
- Management of persons with psychoses. Department of Defense Federal Government Agency [U.S.]. Department of Veterans Affairs - Federal Government Agency [U.S.] Veterans Health Administration - Federal Government Agency [U.S.], 2004. [Federal Government Agency, 2004]
- Practice guideline for the treatment of patients with schizophrenia. Second edition. American Psychiatric Association - Medical Specialty Society, 1997 (revised 2004). [APA, revised 2004]
- Schizophrenia. Singapore Ministry of Health - National Government Agency [Non-U.S.], 2003. [Singapore, 2003]
- Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care. National Collaborating Centre for Mental Health - National Government Agency [Non-U.S.], 2002. [NICE, 2002]
- Clinical Practical Guidelines. The Canadian Journal of Psychiatry, 2005. [CPG, 2005]
- Ministerio de Salud. Guía clínica primer episodio esquizofrenia. 1st Ed. Santiago: Minsal, 2005. [Ministerio de Salud Chile, 2005]
- The schizophrenia patient outcomes research team (PORT): Updated treatment recommendations, 2003. [PORT, updated 2003]
- The Texas Medication Algorithm Project Antipsychotic Algorithm for Schizophrenia, 2003. [TMAP, updated 2003]
- Early psychosis. A review of the treatment literature. British Columbia Ministry of Children and Family Development, 2004. [British Columbia, 2004]
- International clinical practice guidelines for early psychosis. British Journal of Psychiatry, 2005. [British Journal, 2005]

In each one of them different approaches to the type of outlook, the population it is aimed at or the review methodology employed, are differentiated. The following table classifies the identified CPGs in terms of the different approaches:

| | |
|---|---|
| **Comprehensive approach** | NICE, 2002; APA, revised 2004; Singapore, 2003; Federal Government Agency, 2004; CPG, 2005; Ministerio de Salud Chile, 2005 |
| **Specific approach** | |
| Only pharmacological treatment | TMAP, updated 2003; PORT, updated 2003 |
| Only Incipient Psychosis | British Columbia, 2004; British Journal, 2005; |
| **Target population** | |
| Patients with psychosis or schizophrenia | Federal Government Agency, 2004; |
| Adult patients (≥18 years) with schizophrenia | NICE, 2002; APA, revised 2004; Singapore, 2003; |
| **Review method** | Review of the scientific literature on CPG, consensuated review |

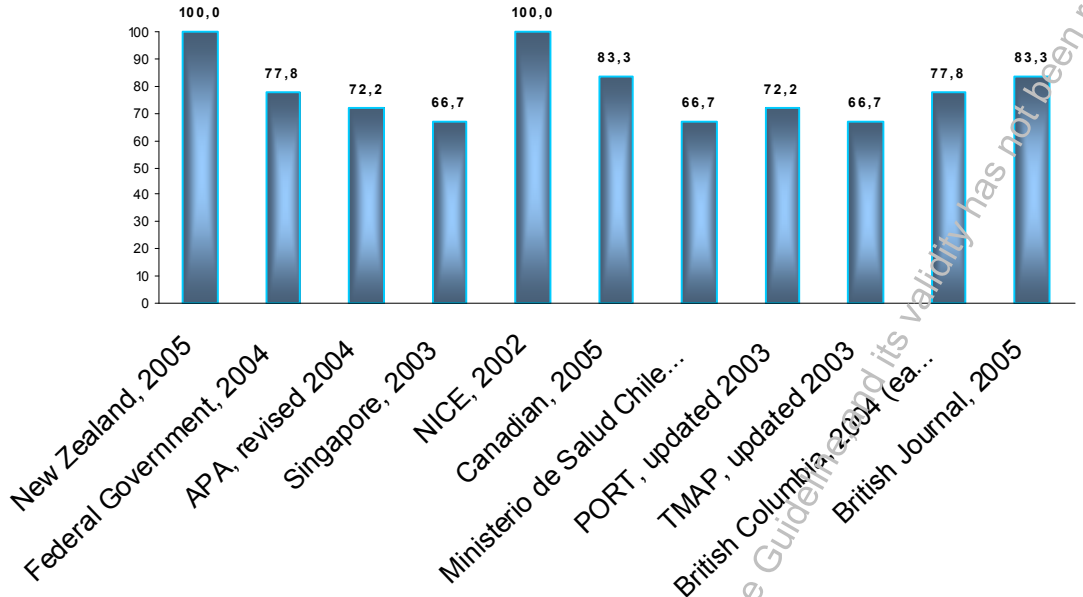
The AGREE (Appraisal of Guidelines for Research and Evaluation) questionnaire was applied to the 11 CPGs by two independent reviewers. This questionnaire includes 23 items distributed in six domains:[k] 1) scope and objectives (items 1-3), referring to the general objective of the guideline, specific clinical questions and the patient target population; 2) stakeholder involvement (items 4-7); referring to the degree to which the guideline represents the points of views of the users it is aimed at; c) rigour of development (items 8-14), referring to the process used to synthesize scientific evidence, the methods used to formulate and update recommendations; d) clarity and presentation (items 15-18), referring to the guideline's language and format; e) applicability (items 19-21), referring to possible consequences of the application of the guideline in organization, behavioural and cost-related aspects; f) editorial independence (items 22-23), on the Independence of recommendation and the acknowledgement of conflicts of interest on the part of the guide's development team.

The following graphs show the overall results obtained in every domain for each CPG (Graphs 1-6). Scores are expressed over 100 and are standardized according to the maximum and minimum score possible in each domain. In accordance with the recommendation of the AGREE research team, the scores pertaining to these six domains are necessarily independent and cannot be aggregated to obtain a total score. It is important to acknowledge that although the results of this questionnaire can be used to compare CPGs, AGREE's recommendation is that no limits that identify "good" or "bad" CPGs can be established.

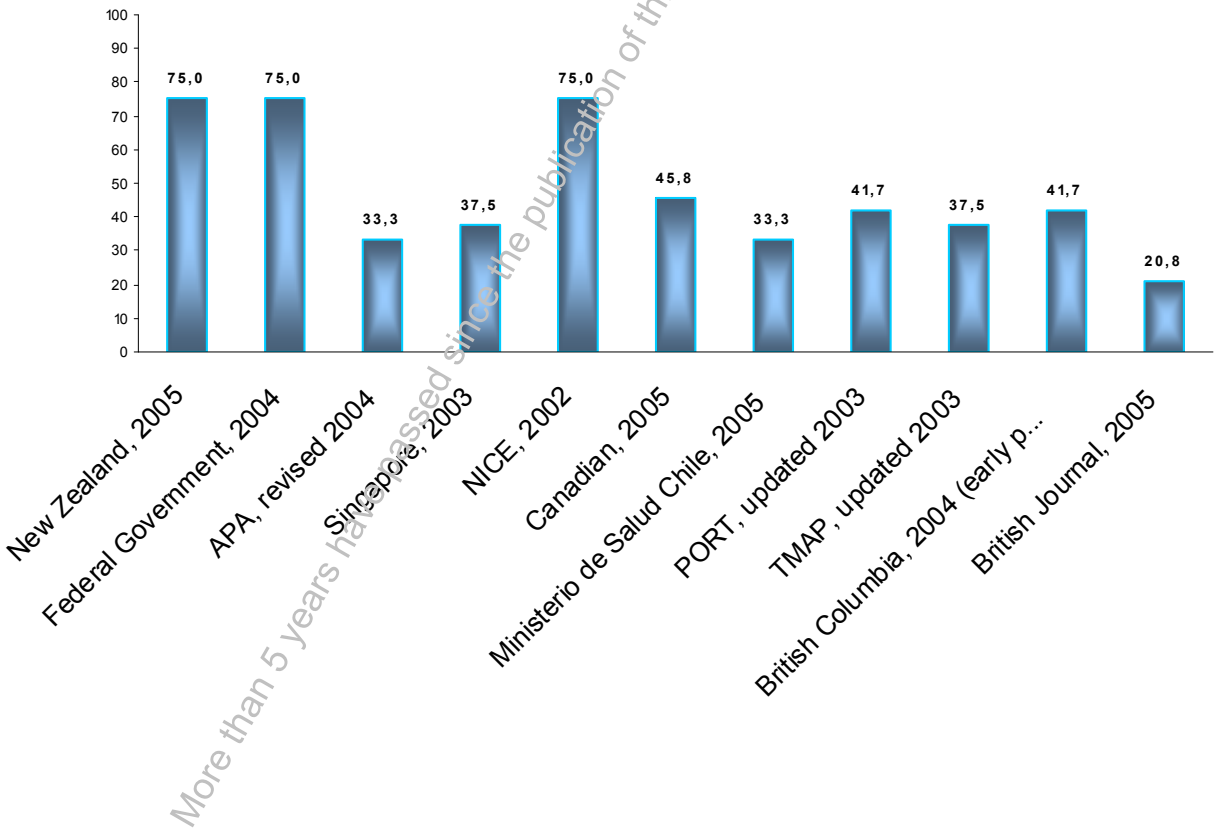
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[k] The AGREE Collaboration. AGREE Instrument Spanish version, www.agreecollaboration.org

**Domain 1: Scope and objectives (items 1-3)**

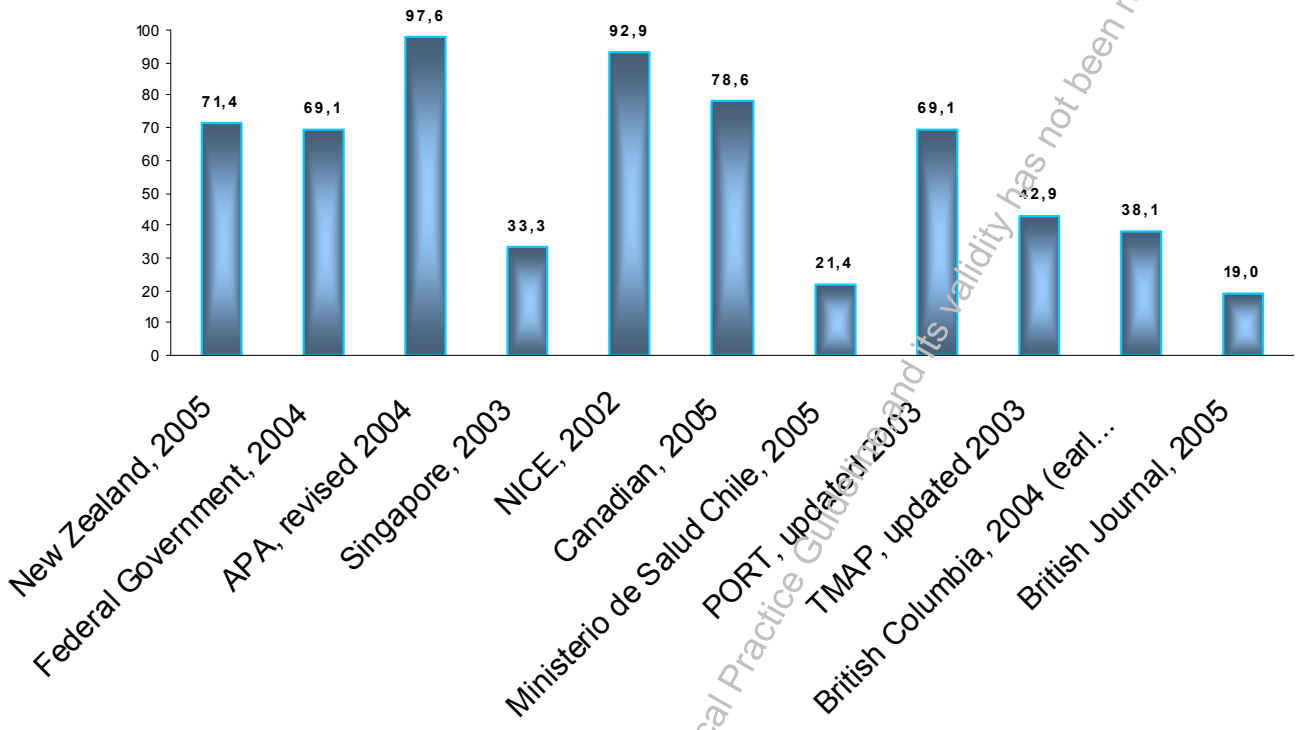



**Domain 2: Stakeholder involvement (items 4-7)**

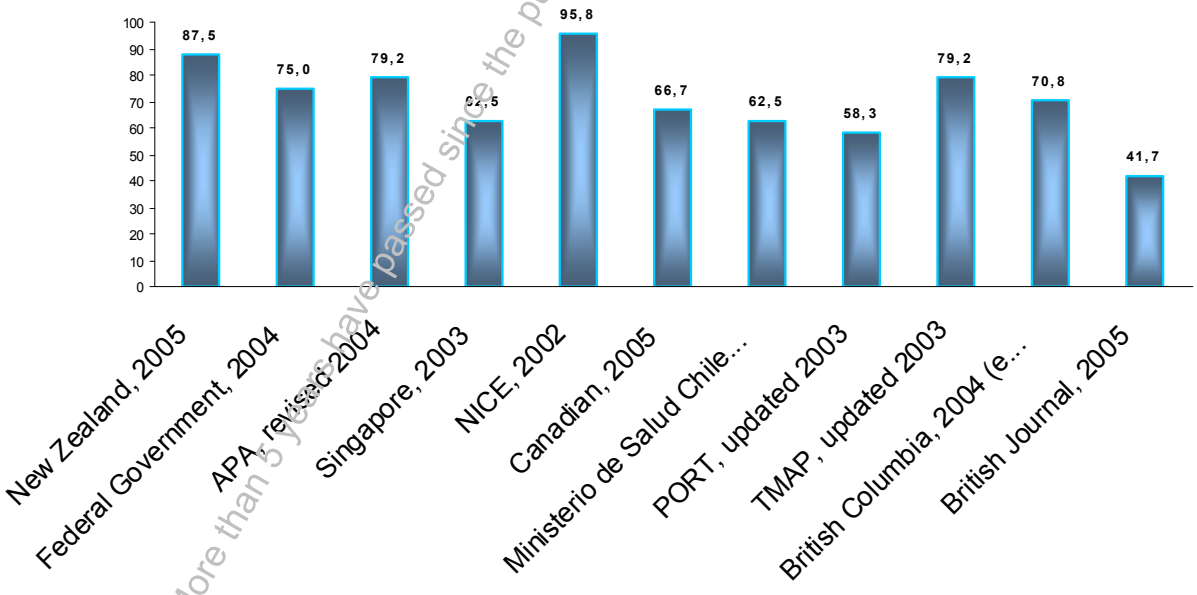



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**Domain 3: Rigour in development (items 8-14)**

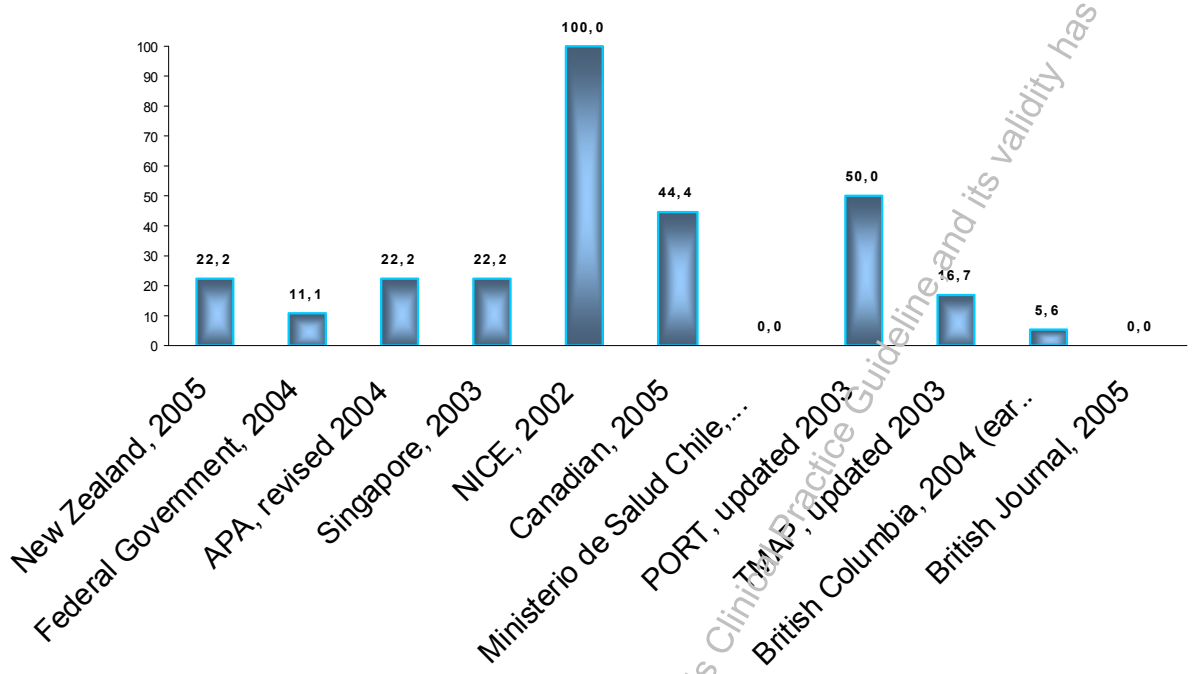



**Domain 4: Clarity and presentation (items 15-18)**



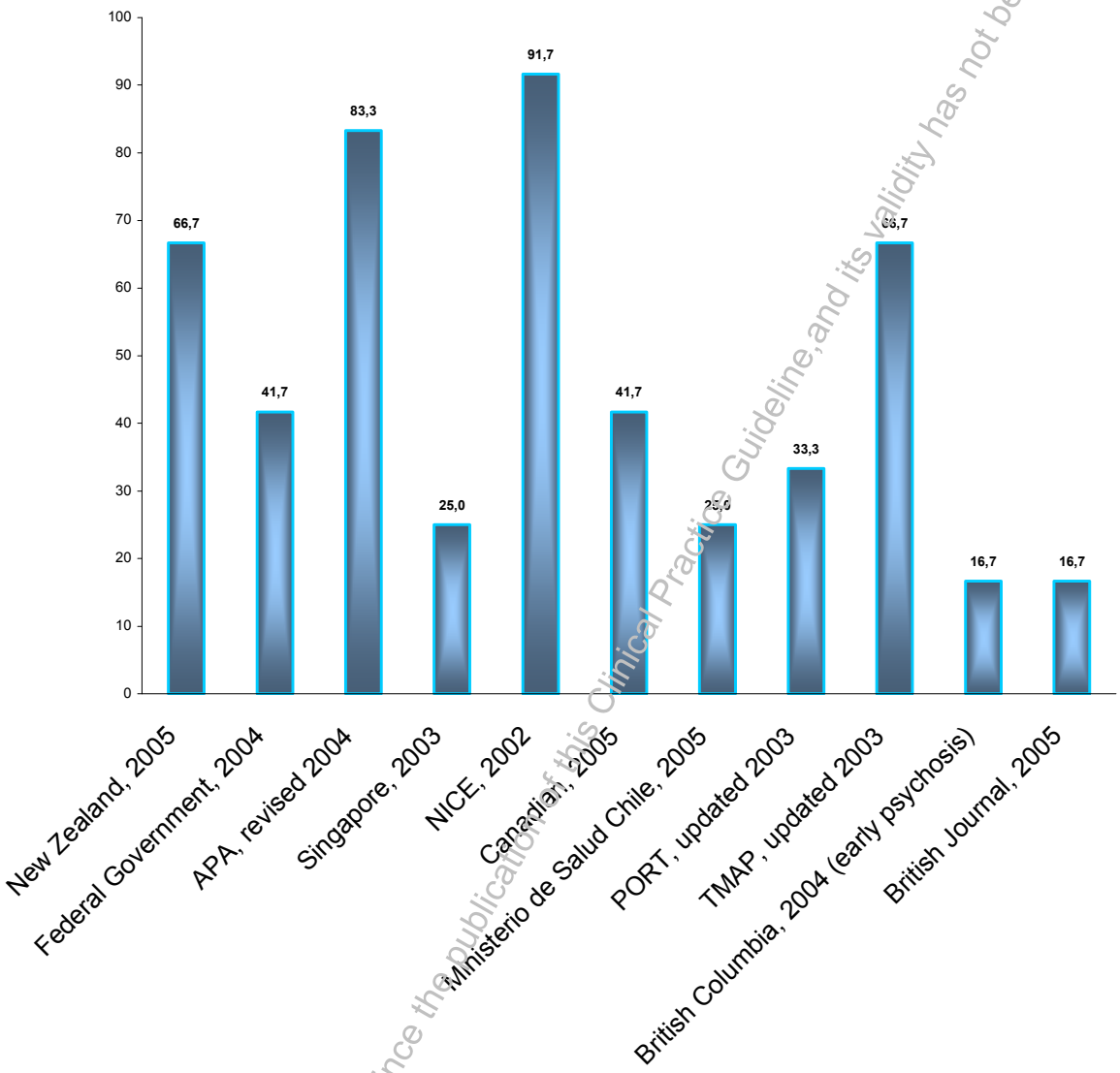

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**Domain 5: Applicability (items 19-21)**




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**Domain 6: Editorial independence (items 22-23)**




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The criteria established to select the best CPGs after the administration of the AGREE questionnaire were:

- To select the CPGs that were best appraised by both reviewers, meaning those that were appraised as "Strongly recommend" by both appraisers.
- To perform a third evaluation in case of discrepancies, meaning that one appraiser would "Strongly recommend" the CPG and the other "Would not recommend" the same CPG.
- Of the CPGs that were not selected, extract aspects of interest for the development of the update.

In accordance with these criteria and based on the overall assessment performed by two independent appraisers, the best appraised CPGs that were selected were: NICE (2002), New Zealand (2004), APA (reviewed 2004) and CPG (2005). On the other hand, other aspects of interest were extracted from non-selected CPGs which were included in the development of the update. For example, the pharmacological content and algorithms of the Texas CPG (TMAP) or the specific content on first episodes of the British Columbia CPG (2004).

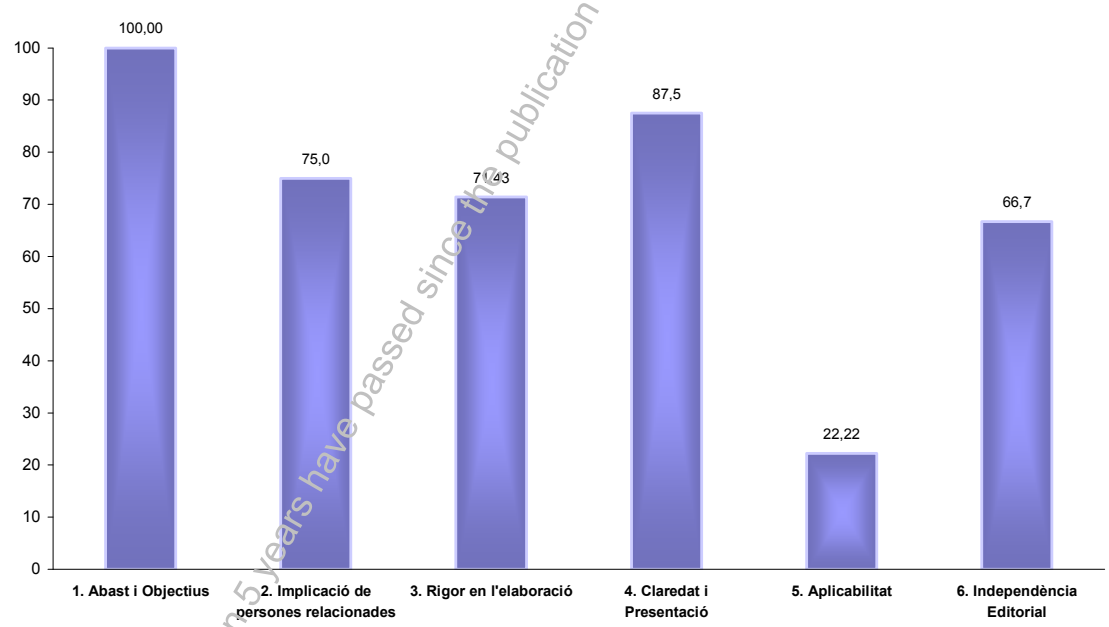
The following graphs present standardized scores (according to the maximum and minimum score possible expressed over 100) obtained from the selected CPGs for each domain and some comments of interest made by the appraisers.

**GRAPHICS: 1. Scope and objectives; 2.Stakeholder involvement; 3. Rigour of development; 4. Clarity and presentation; 5. Applicability; 6. Editorial Independence**

**CPG: New Zealand, 2005**

*Royal Australian and new Zealand college of psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. Royal Australian and New Zealand College of Psychiatrists*

The assessment of the appraised CPG shows high overall quality, with a score above 60% in most criteria. The two domains with the highest scores were 1 and 4, corresponding to scope and objectives and clarity and presentation, respectively. The domain with the lowest score was applicability. The overall assessment performed by both appraisers has been **"Strongly recommend"**.

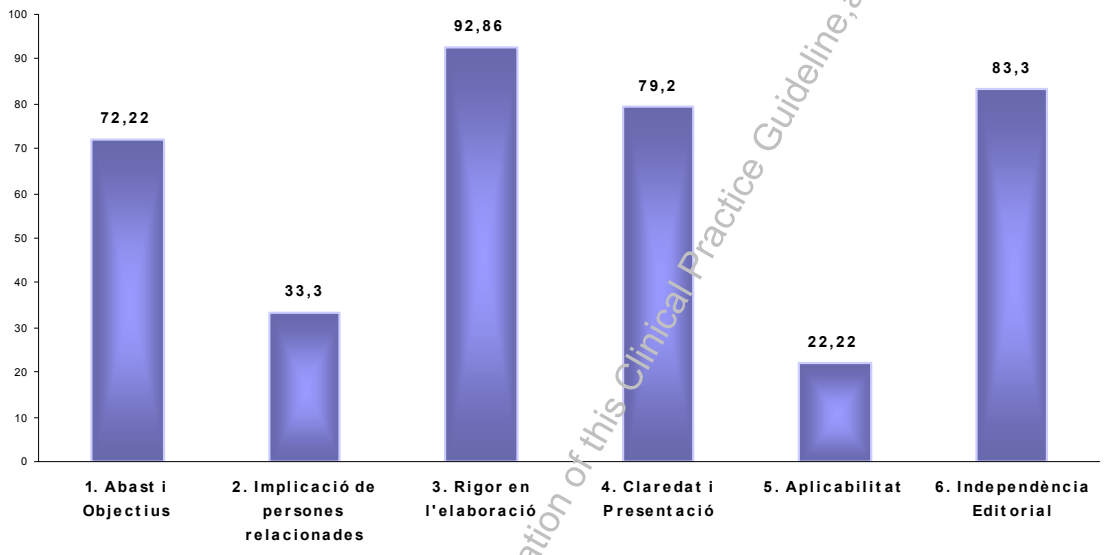



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**CPG: APA, revised 2004**

*Practice guideline for the treatment of patients with schizophrenia. Second edition. American Psychiatric Association - Medical Specialty Society, 1997 (revised 2004).*

The assessment of the appraised CPG shows high overall quality, with a score above 60% in the majority of criteria. The two domains with the highest scores were 3 and 4, corresponding to rigour in development and clarity and presentation, respectively. The domains with the lowest scores were 2 and 5, corresponding to stakeholder involvement and applicability, respectively. The overall assessment performed by both appraisers has been "**Strongly recommend**".

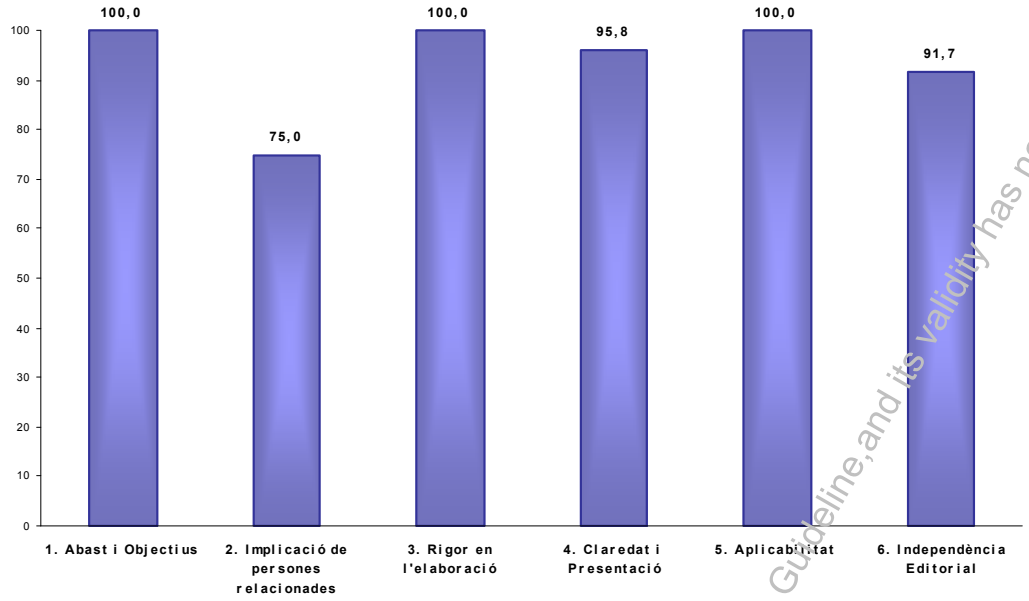



**CPG: NICE, 2002**

*Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care. National Collaborating Centre for Mental Health - National Government Agency*

The assessment of the appraised CPG shows high overall quality, with excellent scores in almost all domains. The two domains with the highest scores, each with a score of 100%, were 1 and 5, corresponding to scope and objectives and applicability, respectively. The key domains of methodological quality, rigour in development and clarity and presentation, also obtained high scores. The overall assessment performed by both appraisers was "**Strongly recommend**".

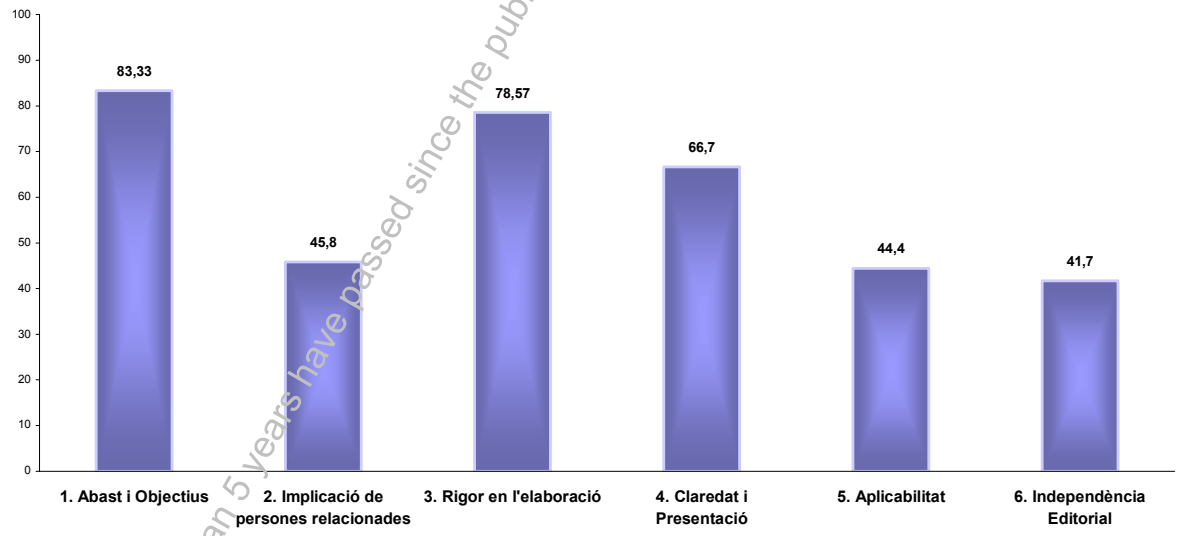
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**CPG: CPG, 2005**

*Canadian Journal of psychiatry. November, 2005.*

The assessment of the CPG appraised shows overall quality ranging from high to moderate. The domains with the highest scores were 1, 3 and 4: scope and objectives, methodological rigour and clarity and presentation. The overall assessment performed by both appraisers was "**Strongly recommend**". One of the appraisers commented that "the CPG is highly recommended and consistent in terms of methodology and content. The only aspect in need of improvement would be to facilitate its use with more visual presentation of recommendations".




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# Annex 7. Bibliographic searches and strategies used

The different searches performed were: a) general searches for CPGs and recommendations for the management of schizophrenia and incipient psychotic disorder and b) specific searches for first episodes, epidemiology and different scopes of intervention. The most comprehensive search strategies employed in PubMed are presented below. However, these were adapted to the language of other consulted databases, according to the type of search.

**a) General search for CPGs and recommendations for the management of schizophrenia and incipient psychotic disorder**

| | |
|---|---|
| **Strategy** | (Schizophrenia and Disorders with Psychotic Features"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR schizophren*) **AND (guideline[pt] OR practice guideline[pt] OR consensus development conference[pt] OR consens*[ti] OR guideline*[ti] OR recommendation*[ti])** |

**b) Specific searches:**

**First episodes**

| | |
|---|---|
| **Strategy** | #5 (#1) OR (#2) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]) OR "clinical trial"[pt] OR trial*[ti] OR efficacy[ti] OR effectiv*[ti] OR versus[ti])<br>#4 (#1 OR #2) AND (guideline[pt] OR practice guideline[pt] OR consensus development conference[pt] OR consens*[ti] OR guideline*[ti] OR recommendation*[ti] OR algorithm*[ti] OR statement*[ti])<br>#3 (#1) OR (#2) AND systematic[sb]<br>#2 (psychos*[ti] OR psychot*[ti] OR schiz*[ti]) OR ("Psychotic Disorders"[MeSH] OR "Schizophrenia"[MeSH]) OR ("Schizophrenia and Disorders with Psychotic Features"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR schizophren*) AND ("first episode*"[ti]) OR "first episode*" OR "first-episode*" )<br>#1 (earl*[ti] AND (psychos*[ti] OR psychot*[ti] OR schizophren*[ti] OR schiz*)) |

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## Epidemiology

| | |
|---|---|
| **Strategy** | #5 #1 OR #4<br>#4 #2 AND #3<br>#3 epidemiol*[ti] OR prevalence[ti] OR incidence[ti] OR mortality[ti]<br>#2 Schizophrenia[MAJR] OR schizophren*[ti] OR schiz*[ti]<br>#1 ("Schizophrenia/epidemiology"[MAJR] OR "Schizophrenia/mortality"[MAJR]) |

## Pharmacological interventions

| | |
|---|---|
| **Strategy for substances** | #6 #1 AND (#2 OR #3 OR #4 OR #5)<br>#5 Antipsychotic* OR haloperidol OR trifluoperazine OR perfenazine OR thioridazine OR zuclopenthixol OR pimozide OR clothiapine OR sulpiride OR chlorpromazine OR levomepromazine OR clozapine OR risperidone OR olanzapine OR sertindole OR quetiapine OR ziprasidone OR amisulpride OR aripiprazole OR "Risperidone consta" Field: Substance Name<br>#4 Antipsychotic* OR haloperidol OR trifluoperazine OR perfenazine OR thioridazine OR zuclopenthixol OR pimozide OR clothiapine OR sulpiride OR chlorpromazine OR levomepromazine OR clozapine OR risperidone OR olanzapine OR sertindole OR quetiapine OR ziprasidone OR amisulpride OR aripiprazole OR "Risperidone consta" Field: MeSH Terms<br>#3 Antipsychotic* OR haloperidol OR trifluoperazine OR perfenazine OR thioridazine OR zuclopenthixol OR pimozide OR clothiapine OR sulpiride OR chlorpromazine OR levomepromazine OR clozapine OR risperidone OR olanzapine OR sertindole OR quetiapine OR ziprasidone OR amisulpride OR aripiprazole OR "Risperidone consta" Field: Title<br>#2 ("Antipsychotic Agents"[Mesh] OR "Antipsychotic Agents "[Pharmacological Action])<br>#1 "Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) |
| **Strategies for metabolic syndrome and cardiovascular syndrome associated with schizophrenia** | #5 #1 AND #4<br>#4 #2 OR #3<br>#3 ("Metabolic Diseases"[Mesh])OR metabolic[ti] OR "metabolic syndrome"<br>#2 ("Cardiovascular Diseases"[Mesh]) OR "cardiovascular syndrome" |

Mirena has been withdrawn from the pharmaceutical market since the publication of this clinical practice guideline and its validity has not been reviewed

| | |
|---|---|
| | #1 ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) |
| **Strategies for electroconvulsive therapy and side effects** | #4 #1 AND #2 AND #3 AND systematic[sb]<br>#3 adverse effects[sh]<br>#2 ("Electroconvulsive Therapy"[Mesh]) OR electroshock[ti] OR electroconvulsive[ti] OR ECT[ti]<br>#1 "Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) |

## Psychosocial interventions

| | |
|---|---|
| **Strategy for psychotherapies** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) OR (earl*[ti] OR "first break"[ti] OR "recent onset"[ti] OR "recent-onset"[ti] OR "new onset"[ti] OR "first episode"[ti] OR "first episodes"[ti]) AND (psychos*[ti] OR psychot*[ti] OR schiz*[ti] OR bipolar[ti] OR "psychotic disorders"[MESH] OR schizophrenia[MESH])) **AND ((psychotherap*[ti] OR ((behavior[ti] OR cognitive[ti] OR psychoanal*[ti]) AND (treat*[ti] OR therap*[ti] OR intervention*[ti])) OR (dynamic*[ti] AND (psycho*[ti] OR intervention*[ti])) OR psychodynamic* OR "insight oriented") OR ("Psychotherapy"[Mesh:NoExp] OR "Behavior Therapy"[Mesh] OR "cognitive therapy"[mesh] OR "crisis intervention"[mesh]OR "psychoanalytic therapy"[mesh] OR "psychotherapeutic processes"[mesh] OR "transference (psychology)"[mesh] OR "psychotherapy, brief"[mesh] OR "psychotherapy, rational-emotive"[mesh] OR "psychotherapy, group"[mesh])** |
| **Strategy for relapses,** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal |

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| | |
|---|---|
| **recurrences and programmes** | Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) OR (earl*[ti] OR "first break"[ti] OR "recent onset"[ti] OR "recent-onset"[ti] OR "new onset"[ti] OR "first episode"[ti] OR "first episodes"[ti]) AND (psychos*[ti] OR psychot*[ti] OR schiz*[ti] OR bipolar[ti] OR "psychotic disorders"[MESH] OR schizophrenia[MESH])) **AND (relaps* OR recurren* OR recurrence[MESH]) AND program*)** |
| **Strategy for compliance/ adherence** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) OR (earl*[ti] OR "first break"[ti] OR "recent onset"[ti] OR "recent-onset"[ti] OR "new onset"[ti] OR "first episode"[ti] OR "first episodes"[ti]) AND (psychos*[ti] OR psychot*[ti] OR schiz*[ti] OR bipolar[ti] OR "psychotic disorders"[MESH] OR schizophrenia[MESH])) **AND "Patient Compliance"[Mesh] OR compliance OR adherence** |
| **Strategy for *counselling*** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) OR (earl*[ti] OR "first break"[ti] OR "recent onset"[ti] OR "recent-onset"[ti] OR "new onset"[ti] OR "first episode"[ti] OR "first episodes"[ti]) AND (psychos*[ti] OR psychot*[ti] OR schiz*[ti] OR bipolar[ti] OR "psychotic disorders"[MESH] OR schizophrenia[MESH])) **AND (counseling[MESH] OR counsel*)** |
| **Strategy for supportive psychotherapy, therapy with combined modalities, multimodal therapy** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) OR (earl*[ti] OR "first break"[ti] OR "recent onset"[ti] OR "recent-onset"[ti] OR "new onset"[ti] OR "first episode"[ti] OR "first episodes"[ti]) AND |

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| | |
|---|---|
| | (psychos*[ti] OR psychot*[ti] OR schiz*[ti] OR bipolar[ti] OR "psychotic disorders"[MESH] OR schizophrenia[MESH])) **AND (supportive psychotherapy" OR "combined modality therapy" OR multimodal)** |
| **Strategy for family therapy** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) OR (earl*[ti] OR "first break"[ti] OR "recent onset"[ti] OR "recent-onset"[ti] OR "new onset"[ti] OR "first episode"[ti] OR "first episodes"[ti]) AND (psychos*[ti] OR psychot*[ti] OR schiz*[ti] OR bipolar[ti] OR "psychotic disorders"[MESH] OR schizophrenia[MESH])) **AND (Caregivers[MESH] OR caregiver*[ti] OR "family burden"[ti/ab] OR famil*[ti] OR Family Therapy[MESH] OR "family therapy"[ti/ab] OR "family intervention*"[ti/ab])** |
| **Strategy for psychoeducation** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) OR (earl*[ti] OR "first break"[ti] OR "recent onset"[ti] OR "recent-onset"[ti] OR "new onset"[ti] OR "first episode"[ti] OR "first episodes"[ti]) AND (psychos*[ti] OR psychot*[ti] OR schiz*[ti] OR bipolar[ti] OR "psychotic disorders"[MESH] OR schizophrenia[MESH])) **AND (psychoeducation*[ti/ab] OR "psycho education" OR (education*[ti/ab] OR instruction*[ti] OR education[sh] OR education[mh])** |
| **Strategy for interpersonal intervention** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) OR (earl*[ti] OR "first break"[ti] OR "recent onset"[ti] OR "recent-onset"[ti] OR "new onset"[ti] OR "first episode"[ti] OR "first episodes"[ti]) AND (psychos*[ti] OR psychot*[ti] OR schiz*[ti] OR bipolar[ti] OR "psychotic disorders"[MESH] OR schizophrenia[MESH])) **AND** |

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| | **"Interpersonal Relations"[MESH] OR "interpersonal therap*" OR "interpersonal treatment*" OR "interpersonal intervention*" OR interperson*[ti]** |
| **Strategy for services in the community** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) OR (earl*[ti] OR "first break"[ti] OR "recent onset"[ti] OR "recent-onset"[ti] OR "new onset"[ti] OR "first episode"[ti] OR "first episodes"[ti]) AND (psychos*[ti] OR psychot*[ti] OR schiz*[ti] OR bipolar[ti] OR "psychotic disorders"[MESH] OR schizophrenia[MESH])) **AND ("Community Mental Health Services"[Mesh] OR "community mental health centers"[MESH] OR communit*[ti] OR "community mental health services")** |

## Psychosocial rehabilitation

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| **Strategy for schizophrenia and rehabilitation** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) **AND rehabilitation[sh]** |
| **Strategy for art therapy** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) AND **"Sensory Art Therapies"[MESH] OR "Acoustic Stimulation"[ti] OR Aromatherapy[ti] OR "Art Therapy"[ti] OR "Color Therapy"[ti] OR "Dance Therapy"[ti] OR "Music Therapy"[ti] OR "Play Therapy"[ti] OR Psychodrama[ti] OR "Role Playing"[ti]** |
| **Strategy for problem-solving, cognitive treatment** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) **AND "Cognition Disorders/rehabilitation"[MESH] OR "cognitive** |

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| | **remediation"[ti/ab] OR Neuropsychological Tests[MESH] OR Problem Solving[Mesh] OR "cognitive training"[ti/ab]** |
| **Strategy for activities of daily living** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) **AND Activities of Daily Living[MESH] OR (activi*[ti] AND daily[ti] AND (living[ti] OR life[ti]))** |
| **Strategy for vocational employment** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) AND **(employ*[ti] OR "Rehabilitation, Vocational"[mesh] OR "Employment, Supported"* OR "occupational Therapy"[MESH] OR Social Adjustment[mesh] OR "supported employment"[ti/ab] OR "vocational rehabilitation"[ti/ab] OR "occupational therapy"[ti/ab] OR "prevocational training"[ti/ab] OR "vocational training"[ti/ab] OR (vocation*[ti] AND train*[ti]) OR (prevocation*[ti] AND train*[ti]) OR "Job Club" OR (shelter*[ti] AND (workshop* OR work* OR job OR employ*)))** |
| **Strategy for peer groups/social support/recovery/hobby** | ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) **AND ("Peer Group"[MESH] OR "social support"[MESH] OR (peer[ti] AND group*[ti]) OR ("Self-Help Groups"[Mesh:NoExp]) OR "social support"[ti/ab] OR "psychosocial support system"[ti/ab] Or "psychosocial support systems"[ti/ab] OR "social network"[ti/ab] OR "social networks"[ti/ab] OR "self help groups" OR "self help group" OR "therapeutic social club" OR "therapeutic social clubs" OR Stereotyping[MESH] OR stigma*[ti] OR stereotyp*[ti] OR "Leisure Activities"[MESH] OR Holiday*[ti] OR Recreation[ti] OR Camping[ti] OR Dancing[ti] OR Gardening[ti] OR Hobbies[ti] OR hobby[ti] OR sport*[ti] OR relaxation[ti] OR recovery[ti/ab])** |
| **Strategy for rehabilitation and cognitive disorders** | ("Cognition Disorders/rehabilitation"[Majr]) AND systematic[sb] |
| **Strategy for housing"** | (("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, |

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| | Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti])) **AND (("Residential Facilities"[Mesh:NoExp]) OR "Assisted Living Facilities"[Mesh] OR "Group Homes"[MESH] OR "Halfway Houses"[MESH] OR residen*[ti] OR housing[ti] OR facili*[ti] OR (home*[ti] NOT nursing[ti]))** |
| **Strategy for acquisition of skills/social support** | (("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti])) **AND ((skill*[ti] AND train*[ti]) OR (social[ti] AND skill*[ti]) OR "training skills"[ti/ab] OR socialization[MESH] OR "social support"[Mesh] OR "social functioning"[ti/ab] OR (social[ti] AND function*[ti]))** |

## Modalities of care to the community

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| **Strategy** | (systematic[sb] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trial[pt] OR random*[ti] OR placebo*[ti] OR blind*[ti] OR OR trial*[ti] OR outcome*[ti]) **AND ((assertive*[ti] OR "case management"[ti] OR community[ti] OR "care programme approach"[ti] OR ("Community Mental Health Services"[Mesh]) OR ("Assertiveness"[Mesh]) OR ("Case Management"[Mesh]))** AND ("Schizophrenia"[MeSH] OR "Schizophrenic Language"[MeSH] OR "Schizophrenic Psychology"[MeSH] OR "Schizotypal Personality Disorder"[MeSH] OR "Schizophrenia, Disorganized"[MeSH] OR "Schizophrenia, Paranoid"[MeSH] OR "Schizophrenia, Childhood"[MeSH] OR "Schizophrenia, Catatonic"[MeSH] OR "Schizophrenia and Disorders with Psychotic Features"[MeSH] OR schizophren* OR schiz*[ti]) |

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# Annex 8. CPG review questionnaire and summary of external reviews performed

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## CPG Review Questionnaire

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| **Title of the clinical practice guideline** |
| **Reviewer** |

**External reviewer (mark the chosen answer with an X):**

1. Are the overall objectives of this guideline specifically described?

   Strongly agree ☐ Agree ☐ Disagree ☐ Strongly disagree ☐

2. Is the definition of the health problem clearly described?

   Strongly agree ☐ Agree ☐ Disagree ☐ Strongly disagree ☐

3. Are diagnostic criteria clearly described?

   Strongly agree ☐ Agree ☐ Disagree ☐ Strongly disagree ☐

4. Are recommendations specific and clear?

   Strongly agree ☐ Agree ☐ Disagree ☐ Strongly disagree ☐

5. Is there an explicit connection between the primary recommendations and the degree of scientific evidence endorsing them?

   Strongly agree ☐ Agree ☐ Disagree ☐ Strongly disagree ☐

6. Please assess (1-10) the applicability of this clinical practice guideline in the healthcare reality

## Additional comments

*Please make the specific comments, observations and suggestions that you think would improve this clinical practice guideline. If you do not agree with a certain recommendation, please provide the studies which could modify it with their corresponding bibliographic references.*

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