



FULFILLING THE GLASS: Association between an Integrated Psychosocial Intervention and Pharmacological Treatment in Patients with Schizophrenia

A two – year prospective study



Final Degree Project

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“El día en que se hable de la esquizofrenia del mismo modo que se comenta que el abuelo sufre diabetes, se habrá dado un gran paso”

Luis Rojas Marcos

To each member of the Psychiatric Rehabilitation Unit, especially to Dr. Isabel Mitjà.

Thank you for making me feel like at home.

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Abstract

Title: FULFILLING THE GLASS: Association between an integrated psychosocial intervention and pharmacological treatment in patients with schizophrenia. A two – year prospective study.

Background: Schizophrenia is one of the most prevalent and disabling psychiatric diseases. Several intervention programs have been implemented in order to assess schizophrenia from a community and integrated view. Despite the well-known effectiveness of psychosocial interventions, little is known about the effect they have in the pharmacological treatment with antipsychotics indicated in this group of patients. Despite their effectiveness, antipsychotics are known to have important secondary effects, highlighting cardiovascular side effects for being highly prevalent, and for being the most important cause of natural death among those patients. Moreover, antipsychotics account for a non - despicable proportion of the global cost of the disease, contributing to make schizophrenia the most expensive psychiatric disorder.

Aim: To analyze the effect an integrated psychosocial intervention has on the dose of antipsychotic used in the maintenance phase treatment (defined as a Global Assessment of Functioning scale (GAF) ≥ 70) in patients with a diagnosis of severe schizophrenia. Secondary, it would be interesting to determine its effect on the cardiovascular disease risk and metabolic syndrome, as well as on the global cost of the disease.

Methods: A prospective cohort study will be performed following 148 patients diagnosed with severe schizophrenia consulting to any service of *the Xarxa de Salut Mental de la província de Girona* due to an exacerbation of the disease. Patients will be collected in a non – probabilistic consecutive method and will be classified in two groups, both following interventions used in the routine clinical practice: an integrated psychosocial intervention program plus pharmacological treatment or only pharmacological treatment plus standardized visits. Patients will be categorized using a propensity score matching method regarding sex, age, family support and initial GAF score, in order to diminish selection bias. Patients will be followed during a 2 – year period, and the dose of antipsychotic needed in the maintenance phase at the end of the study will be compared in both groups, using bioequivalence transformations into olanzapine and categorizing patients according to the dose required. Maintenance will be defined using the GAF scale. The cardiovascular disease risk will be compared at the beginning and the end of the study in both groups, using the REGICOR scale, as well as the Metabolic Syndrome prevalence. Finally, an estimation of the global cost of the disease will be analyzed in both groups. Several co – variates will be taken into account in the statistical analysis in order to determine possible confounding factors, using a Multiple Logistic Lineal Regression Model for qualitative variables, and a Multiple General Lineal Model for quantitative variables.

Key words: schizophrenia, severe mental disorder, psychosocial intervention, antipsychotic, antipsychotic dose, cardiovascular disease, metabolic syndrome, GAF scale, REGICOR, schizophrenia cost.

Abbreviations

FGA: First generation antipsychotic

SGA: Second generation antipsychotic

CBT: Cognitive behavioral therapy

EE: Expressed emotion

BFT: Behavioral family therapy

RG: Relatives group

ACT: Assertive community treatment

XSM: Xarxa de Salut Mental de la Província de Girona

NIMH: National Institute of Mental Health

GAF scale: Global assessment of functioning scale

CVD: cardiovascular disease

REGICOR: Registre Gironí del Cor

HDL: high density lipoprotein

BP: Blood Pressure

MS: Metabolic syndrome

BMI: Body mass index

CEIC: Comité ético de investigación clínica

PANSS: Positive and Negative Syndrome Scale

IAS: Institut d'Assistència Sanitària

ENCEPP: European Network of Centers for Pharmacoepidemiology and Pharmacovigilance

Introduction

Schizophrenia

Schizophrenia is the commonest and most important psychotic disease in the actual society (1). Its prevalence is known to be around 1 for each 100 habitants (0,3-0,7% (2)) with an incidence from 7 to 14 cases for each 100.000 habitants, according to the World Health Organization. In Spain there are around 400.000 people diagnosed of schizophrenia (3).

The age of onset is between the late teens and the mid – 30s, being slightly more prevalent among males, with a 1.42:1.00 ratio (4), with the peak of onset being earlier than in females (2). Schizophrenia is more prevalent in urban areas, having higher rates of the disease than the rural population (5,6).

To diagnose schizophrenia, two main criteria can be used: DSM – V criteria ([See appendix 1](#)) and ICD – 10 criteria ([See appendix 2](#)).

To better understand schizophrenia, its symptomatology can be divided in two main groups, as proposed by N. Andreasen: Positive symptoms, which are not part of the normal experience, and occur due to the disease (Hallucinations and Delusions), and Negative symptoms, normal psychological functions deteriorated and diminished because of the disease (7,8). Both types of symptoms are discussed below.

Course and Staging

The onset of schizophrenia may be abrupt or insidious, being the last one the most prevalent. A prodromal phase has been identified, in which the patient has the so called negative symptoms, which include a loss of interest in work, social activities, personal appearance or hygiene, together with anxiety, preoccupation, irritability and mild degrees of depression. Patients can also experience atypical interests (1,4). The extension of this phase can range from days to weeks, or, in some cases, even months (4).

During the acute phase, the onset of positive symptoms, including hallucinations, mainly auditory, and delusions can be identified. The last ones are mostly delusions of control, influence or passivity, referred as “made” feelings, impulses or acts (1,2,9).

There is a disorganized thought and speech, being the person affected unable to take care of him/herself. An abnormal motor behavior can occur, conducting in some cases to a catatonic status (2).

In this phase negative symptoms including a diminished emotional expression, avolition, alogia, anhedonia and a lack of interest in social interactions can exacerbate (2,4).

After the acute episode, the affected suffers a decrease in the intensity of the symptomatology, mostly positive, getting to the stabilization phase, where they can remain for a period of 6 to 12 months (4).

During the life-course, the patient can remain into a maintenance or stable phase, in which there is an extinction of the symptomatology, or if present, remains stable and significantly milder, being the person able to control it. During this stage it is common the persistence of some degree of the negative symptomatology, determining the prognosis of the disease, mostly in the form of an alteration of the affectivity and social retraction. Cognitive impairment also tends to persist during this phase, contributing to the disability associated with schizophrenia. People affected by schizophrenia may remain at this stage, or, most commonly, will have some relapses and fluctuations, going through the rest of the phases again (2,4,10).

The staging concept is important not only for the temporal distribution of symptomatology, but also to understand the neuroimaging changes observed in patients with schizophrenia over time. Furthermore, the treatment of schizophrenia will be adjusted according to the actual stage (4,11).

Some studies have revealed that one of the main impairments seen in patients suffering from schizophrenia is an increase in the number of dopamine receptors, leading to an increased activity of the neurotransmitter. That could be the cause of the positive symptomatology seen in the disease, being the negative related with structural changes in the brain, and possibly with molecular impairments in serotonin, noradrenalin, glutamate or GABA pathways (11,12). That would explain the course of the disease, as well as the antipsychotics' efficacy in positive symptoms, with little effect in the negatives (see "Pharmacological treatment of schizophrenia").

Mortality

Mortality among the population suffering from schizophrenia is overall two to three times greater than in the general population. Moreover, it is 2.6 times higher than it would be expected because of the disease itself. That means that there are some other factors contributing to its mortality (13).

The most important single cause of death among this population is suicide, being from 8.5 to 14.5 times more frequent than in the general population (13–15). The highest risk is seen in young men during the first year of the disease, and is higher in patients with dual pathology with substance abuse (13,15).

Around two thirds of the excess of mortality in patients with schizophrenia correspond to natural causes of death (15). The commonest cause is cardiovascular disease (13).

According to the World Heart Federation, several variables have been identified as major cardiovascular risk factors: High blood pressure, High blood cholesterol, smoking, obesity, diabetes, physical inactivity, unhealthy diet, high blood triglycerides and low HDL, age, gender and a family history of cardiovascular disease (16).

Cardiovascular disease is related with schizophrenia in several ways: the disease itself is associated with an elevated rate of obesity, as well as an increase in tobacco smoking, insulin-resistance and metabolic syndrome (11,17). Moreover, patients with schizophrenia tend to have unhealthier life styles, following an inadequate diet with little physical activity (2,13,18).

Added to those effects, pharmacological treatment with antipsychotics has an important impact in the majority of metabolic and cardiovascular risk factors, as will be discussed below.

Pharmacological Treatment for Schizophrenia

An integrated treatment including pharmacological and psychosocial measures is essential in order to treat schizophrenia on its whole sphere, as both sides have its importance and are crucial to achieve recovery (17,19).

Regarding pharmacological treatment with antipsychotics, it is widely used to treat acute episodes of the disease, to prevent relapses and to improve residual symptomatology remaining in the stable phase (4).

First Generation Antipsychotics

First Generation Antipsychotics (FGA) are known to improve the positive symptomatology seen in schizophrenia, despite having little effect on the negative symptoms. This can be explained by their high affinity for dopamine D2 receptors, for which are competitive antagonists. The ones with higher affinity for this receptors, known as the high potency FGA, will need less dose and time in order to achieve their objective, whereas the ones having less affinity, the low potency FGA, will need higher doses and more time to achieve their results (4,20).

Of the numerous FGA available, the most used are Haloperidol, despite having several side effects (4), and Perphenazine for having a moderate side – effects profile (20).

Despite their efficacy on improving positive symptomatology, FGA are known for having a wide range of secondary effects, being the main cause of treatment discontinuation. The most prevalent are:

- *Sedation*: Mostly during the initial phases. This is the main secondary effect in the low potency antipsychotics.
- *Extrapyramidal effects*: Can be acute, such as Parkinsonism, dystonia or akathisia, or chronic, including dyskinesia, late dystonia or Malign Neuroleptic Syndrome. Extrapyramidal effects are most common among the high potency FGA.
- *Prolactin elevation*: One of the most common side effects among the High potency FGA.
- *Anticholinergic and antiadrenergic effects*: Including mouth dryness, blurred view, constipation, tachycardia, urinary retention and thermoregulation abnormalities. These are the most common side effects among the first generation antipsychotics.
- *Cardiovascular and metabolic effects*: One of the main causes of death among those patients. Weight gain, mostly central obesity, can be seen in 40% of patients treated with FGA (4,20,21), especially in low potency FGA (chlorpromazine, thioridazine) (18).

Regarding metabolic syndrome, although is more frequently seen with second generation antipsychotics, it has been documented in patients using chlorpromazine (18).

Finally, an increased risk of sudden cardiac death has been documented, with a prolonged QT interval, in pimozide, thioridazine and mesoridazine (4,22).

Second Generation Antipsychotics

Second generation antipsychotics (SGA) differ from the first generation in their lower affinity for dopamine D2 receptors, decreasing extrapyramidal side effects, whereas their affinity for serotonin and norepinephrine receptors is higher, being a possible cause of its higher effect in negative symptoms (20).

SGA use has increased notably over time, due to its higher efficacy on negative and affective symptoms compared to the FGA, as well as their lower range of secondary effects related to dopamine receptors (4).

Olanzapine has been seen to be the SGA with less discontinuation of treatment due to lack of efficacy and with longer duration of its effects, having less exacerbations, even though being the one with a highest incidence of weight gain and metabolic complications (20).

Other SGA frequently used are aripiprazole, clozapine, quetiapine and risperidone.

Although in some cases have been described, extrapyramidal effects are less frequent than in FGA (4,20). The most common side effect in SGA is metabolic syndrome: clozapine and olanzapine are the ones known to cause higher rates of weight gain, development of diabetes and glucose deregulation and dyslipidemia, especially affecting triglycerides, thus adding to the higher risk people with schizophrenia already have (13,23–25). Moreover, increases in blood pressure among patients using olanzapine and quetiapine have been documented (23). There is evidence supporting that the explanation to the development of those side effects may be their higher affinity for histaminic and serotonergic receptors, contributing to the dopaminergic effects (18,26).

Other secondary effects seen are QT prolongation with risperidone and quetiapine, increasing the risk of sudden cardiac death (22), anticholinergic side effects with quetiapine or even agranulocytosis with clozapine (4).

The current recommendations for the use of antipsychotics propose the preferable use of a second generation antipsychotic as a first option. Clozapine will be only used after the failure of two different antipsychotics (4,27). When a complete remission of the symptomatology is achieved, treatment should be continued for a minimum of 12 months, proceeding then to the progressive reduction during several weeks, carefully controlling the appearance of any sign of relapse (4,11). In most patients, however, a maintenance dose will be needed for life.

Psychosocial Intervention in Schizophrenia

Psychosocial interventions are one of the main aspects to achieve the **recovery** of patients with schizophrenia. Recovery is not only focused on symptomatology stability, but in an achievement of autonomic functioning and community integration, in the acquirement of social and personal competencies considered relevant to the patient's life. It is also about the capacitation of the patient towards the management of the disease, his/her empowerment (4,10,28).

There are several services and techniques included in the psychosocial intervention program, which will be used according to the patient needs and capacities, making a personalized intervention to each patient. The most used interventions are described below.

Cognitive Behavioral Therapy

Cognitive Behavioral Therapy (CBT) is based on the development of relationships between the patient's thoughts, feelings and actions and his/her actual or past symptoms. It works with the monitoring of those relationships, the promotion of more rational or adaptive pathways to solve conflicts and with stress reduction strategies (4,28,29). CBT tries to explain the patient's behavior by understanding the cognition and to modify it by finding reasonable and accepted logical explanations to those thoughts (10).

There is several evidence supporting that CBT induces an improvement in symptomatology, mostly positive (10,29–33), as well as depression (4,32,34), social functioning (4,30,32,33), relapses and time of hospitalizations (4,10,34), quality of life, treatment abandonment and insight of the disease (4,29) compared with standard treatment (pharmacological treatment, routine care and case management when needed). No statistically significant differences are found when comparing costs (32).

One of the main causes of involuntary hospitalization has been seen to be a lack of insight of the disease. Involuntary hospitalizations leads, at the same time, to less motivation and treatment engagement (35). CBT reduces the number of involuntary hospitalizations among patients, improving treatment outcomes.

Psychoeducation

Psychoeducation is an intervention aiming to provide specific information and knowledge about the disease and about different techniques to confront the problems than can arise from it (4). Psychoeducation goes to both the patient and his/her family or caregivers. Some studies have shown that combined psychoeducation in both families and the patient is traduced in a reduction of the symptomatology, relapses, number of days hospitalized and an improvement in the GAF scale, treatment adherence, quality of life, knowledge about the disease and satisfaction (31,34,36).

Family Intervention

This intervention is based on the building of a strong alliance with the family and caregivers of the person affected with schizophrenia. Its aim is to provide information about the disease, to help families manage the stress caused by the situation and to cope with the adversities that can appear during the course of the disease. The main difference with psychoeducation is its focus on the reduction of the so called Expressed Emotion (EE) (4,37).

EE refers to the attitudes the family has towards the patient, going from hostility and criticism to overprotection. The effect EE has in both the family and the patient has been analyzed, concluding that families expressing a high level of EE tend to see the problems occurring worse and more difficult to solve than the group expressing a low EE. Moreover, they tend to use the evasion strategy to cope with the situation more than families with lower EE. Families with a high EE feel frustration sooner, and tend to look down on the patients' perspective. This leads to an increase in the number of relapses and a deterioration of the patient cognitive functioning (10,37). On the opposite side, families with a low EE tend to have more coping strategies, and to feel sympathy toward the patients' behavior and personality (37).

There is evidence showing that family interventions reduce the number of readmissions and relapses (28,29,31,38), as well as symptomatology (29). They also increase treatment adherence (28,29,31,38), and the wellbeing and care of both the family and the person affected, improving family relationships (28,29,31). Yet at 1985, Falloon demonstrated this evidence, showing as well that the pharmacological dose used was lower in the group following a family intervention (39).

Family interventions can be conducted individually in the form of a behavioral family therapy (BFT), as proposed by Falloon in 1985 (10,39), or in a relatives group (RG). A study conducted by I. Montero in our midst revealed that both family therapies are effective in reducing the number

of relapses, readmissions and symptomatology, despite being the BFT more effective in those families with high levels of EE (40).

Cognitive Rehabilitation

Since the beginning of the disease, some degree of cognitive impairment can be observed in people affected with schizophrenia. That includes functions such as attention, memory, and executive functioning (2,4).

Cognitive rehabilitation aims to improve their functioning using different strategies:

- Restoration of the previous cognitive functioning, aiming to reduce the cognitive impairment.
- Compensation: accepting the lack and trying to compensate it with different approaches, using strategies at the patient's social environment such as reminders or notes aiming to diminish the impact the cognitive impairment can have in the person's life.

Cognitive rehabilitation has shown to improve self – stem and mood of patients with schizophrenia, as well as their cognitive functioning and day – to – day living (4,34).

Executive functions, sustained attention and memory have been related to the positive and negative symptomatology of schizophrenia. An improvement in clinical tests evaluating those functions translates a decrease in the symptomatology after cognitive rehabilitation programs (4,28). Cognitive improvement has also been linked with better outcomes in other interventions performed (10).

Social Skills Training

Social skills are defined as a group of behaviors needed to achieve an adequate social interaction, independent living and other outcomes needed to community functioning. They include verbal and non – verbal communication, self – consciousness of internal feelings and emotions, social perception, adapted response capacity and social reinforcement (4,29).

The social skills training intervention aims to reduce the stress caused by social interactions and to achieve the necessary skills to interact and adapt to different social situations. It is highly linked with psychoeducation, as the last one is needed in order to achieve a correct social skills acquisition (10). Three models haven been used to achieve this purpose:

- Motor Skills Model: Complex social situations are divided in various simple steps, which will be learnt using role playing.

- Social Problem Solving Model: Focused on the areas that have to change due to the disease (medication use, free time, control of the symptomatology, personal care). Each area will be approached separately, focusing on those aspects in which there is a lack.
- Cognitive Solving Model: Mainly focused on the cognitive impairment, whose correction leads to a social learning process. The positive reinforcement method is used in here.

Social skills training has demonstrated an improvement in social interactions in patients with schizophrenia, as well as in their symptomatology, social functioning and quality of life (4,31). Several reviews evaluating the efficacy of different psychosocial interventions showed that social skills training diminishes relapses, increasing adherence to treatment and knowledge of the disease, as well as quality of life. Others showed a discrete improvement in negative symptomatology. However, some patients found difficulties in applying the skills learnt into their environment (29,31).

Assertive Community Treatment

Assertive community treatment (ACT) is based on a personalized intervention with a high contact frequency with provision of comprehensive medical and social advice at home or in a supervised care environment. ACT is specially thought for patients at high risk of relapse or with a bad adherence to treatment and elevated possibilities of disengagement (29,31).

ACT has shown to reduce hospitalization rates and symptomatology, improving quality of life among the American population. However, those findings have been inconsistent in European countries (29,31). Nevertheless, it has been demonstrated an improvement in community service use and adherence to treatment (29,31,41).

Some studies also found that patients following an ACT were more likely to have an employment and to be working more effectively (29).

Other resources available in an integrated intervention

Supported Employment

Mostly for people with enough psychopathological stability and ready to live in the community.

Two types of supported employment strategies are mainly used:

- Pre – working training: rehabilitation of capacities and competences needed to adapt to the labor market, prior to the reinsertion. It also provides orientation to the work search. It

includes pre – working service, orientation service to the ordinary business and training service.

- Working support: incorporation in the labor market in special work centers and support in the maintenance of the work place.

Supported employment strategies lead to an increase in the number of patients with schizophrenia working, as well as a reduction in hospitalizations and an improvement of their insight (4). Regarding their work place, they achieve more competences, work more hours and earn more wages than without the intervention. However, supported employment techniques should be offered together with other psychosocial interventions such as CBT or social skills training, in order to improve patients' capacities and cognitive performance (29).

Living Resources

An adequate living place is the basis to the complete adaptation and reinsertion of patients affected by schizophrenia. Several types of living supports are available in our midst (4,42):

- Autonomic living: In which the patient lives independently, only with individualized following from external resources when arranged.
- Domiciliary help: Intervention in the patient's home, living alone or with relatives, providing help in day to day activities and self – care.
- Protected living: Consisting in a flat with 4 – 6 places with professional support and assessment in the daily living activities and integration.
- Residence: With 24 hours a day assistance. For people with an impossibility of living autonomy.

Independent living resources in any of the services offered has been associated with an improvement in quality of life, life conditions and social relationships (4).

An Integrated Psychosocial Intervention

A brief summary of the existing evidence regarding each psychosocial intervention has been exposed, but it is important to outline the benefits of an integration of all the interventions mentioned, as, even if effective, a single treatment modality would be insufficient (30).

Several studies have evaluated the efficacy of an integrated psychosocial intervention. A prospective study conducted in Croatia analyzed the effect an integrated psychosocial

intervention during a period of 4 months had in patients with a diagnosis of schizophrenia, compared to those only receiving pharmacological treatment. The results show an improvement in the symptomatology and psychopathology, with lower PANSS scores, as well as an improvement in quality of life, satisfaction and social contacts with their close friends and relatives (43). Another study comparing an integrated psychosocial intervention with case management showed higher rates of improvement in clinical outcomes, disability and caregiver stress, achieving recovery in a shorter period of time in the group following the psychosocial intervention program (19). A clinical trial conducted in our midst evaluating the efficacy of a one – year integrated psychosocial intervention applied to both the patient and the family, observed an improvement in symptomatology, interpersonal functioning, social behavior and family confrontation of the situation, being those improvements maintained 4 years after the intervention (44).

When analyzing the cost – effectiveness of an integrated psychosocial intervention, Zhang et al. demonstrated an incremental ratio of the cost – effectiveness of the psychosocial intervention compared to treatment as usual, with an improvement in quality of life and a non - statistically significant increase in the global costs of the intervention, as well as a reduction of the number of relapses during the follow – up period, reducing re – hospitalization costs (45).

Global costs of schizophrenia

Schizophrenia is a chronic disease, associated with a long – lasting significant health, social and financial burden, for patients, families, caregivers and the society. The impact of schizophrenia on health care budgets is substantial, representing in some countries between 1.5 and 3 percent of the global National health care expenditures (46). Some of the factors related to the high cost of schizophrenia are its high prevalence, early onset, chronic course, long periods of hospitalization, indefinite treatment, support and supervision needs, bad therapeutic adherence and suicide. All those findings make schizophrenia the most expensive psychiatric disease (47), accounting for a 10% of the global economic charge of Mental Disorders in Europe (48).

Apart from the [intangible costs](#) the disease has (depression, pain or quality of life), costs of schizophrenia can be divided in two main spheres:

Direct costs

Including hospital admissions, psychosocial services, work and living support services and pharmacological treatment.

Inpatient admissions have always been the largest contributor to the direct costs of schizophrenia, accounting for more than 90 percent of all direct costs in some countries. Since the development of a more comprehensive community care and psychosocial interventions, inpatient admissions have reduced its importance in the global costs of the disease, going from an 80 percent to a 37 percent in Germany (49), or from a 41 percent to a 17 percent in Italy (50). However, between one and two-thirds of the total health care cost of schizophrenia, can be attributed to hospitalization, even in countries where community care has been implemented (46,47). In Spain, 20.6% of the direct costs correspond to hospitalization, and 10.4% to emergency consultancy (51).

When available, community services and psychosocial interventions represent a significant proportion of overall costs (52). However, an study conducted in Mannheim showed that the average cost per patient - year of community services was about 43 percent of the average cost per patient - year of long term care in a hospital (49). Another study comparing the global costs of an integrated psychosocial intervention with standard treatment (including antipsychotics and a brief case management intervention) did not find statistically significant differences regarding the monthly cost of the intervention, whereas observing an improvement in the quality of life (45).

Pharmacological costs account for approximately 1 – 6 % of the global costs of schizophrenia (47), arriving to 7.8% in some developed countries such as Spain (51).

Indirect costs

Productivity loss and time cost due to mortality, unemployment and disability are accounted. Caregivers' costs are also relevant.

Indirect costs represent from 48 to 86.5 percent of the global cost of schizophrenia (47,50,51). According to Lee et Al. productivity loss accounts for the highest proportion of indirect costs (53). Furthermore, about a third of all sickness absence from work has been attributed to common mental disorders, affecting to the productivity at the workplace (46).

Productivity loss and time cost also affect caregivers. It has been shown that caregivers spend on average 6 to 9 hours per day providing support. 44.8% of family caregivers feel their daily routine altered because of the disease (51). Thus, added to additional costs through household expenditure and travel costs, leads to a 17 percent of the total indirect costs of schizophrenia (46).

Justification of the study

As it has been exposed, schizophrenia is one of the most prevalent psychotic diseases. According to the World Health Organization, it is one of the most frequent causes of global disability (54), thus being an important reason to invest in its different aspects.

It is widely known that pharmacological treatment is an important and necessary part of the treatment of schizophrenia, causing an improvement in its symptomatology, mostly in the positive symptoms, as well as in its global functioning (4,20,21). However, several aspects related to antipsychotics lead to controversy regarding their use:

- Despite being effective, the negative symptomatology observed in schizophrenia still remains after pharmacological treatment. This symptomatology is known to be responsible of the prognosis of the disease (4,20).
- Antipsychotics have a wide range of secondary effects. First generation antipsychotics are well known to cause mostly extrapyramidal and anticholinergic effects, as well as sedation and cardiovascular and metabolic effects, as mentioned. That was one of the main reasons for the onset of second generation antipsychotics. However, the prevalence of cardiovascular and metabolic side effects with its use is even higher, leading to an important range of comorbidities (4,20,21).

Regarding cardiovascular and metabolic side effects, it has been well documented the higher prevalence of metabolic syndrome, high blood pressure, dyslipidemia and diabetes among patients using antipsychotics, thus increasing their cardiovascular disease risk (23–25). Even though lifestyle has an important role in the development of cardiovascular risk factors and cardiovascular disease, antipsychotics have been shown to be one of the main causes of the development of those abnormalities in the short term and with its chronic use (4,18,23). Moreover, cardiovascular disease is one of the main causes of mortality in patients suffering from schizophrenia (2,13,15).

Mortality is known to be two to three times higher than in the general population, and 2.6 times higher than it would be expected because of the disease itself, being around two thirds of this excess due to cardiovascular disease (13).

Because of all the reasons mentioned above, it is a matter of fact that despite the effectiveness of antipsychotic treatment, it also has its weaknesses, and those are relevant enough to try to find a way to, at least, reduce the dosage enough to reduce at the same time the secondary effects antipsychotics produce, without, undoubtedly, affecting the patient improvement.

Since several years ago, different techniques englobed in the so called psychosocial intervention have been used in order to improve the recovery of patients with schizophrenia, aiming to cover the aspects pharmacotherapy was not able to. As it has been commented before, all these psychosocial interventions have an effect improving positive and negative symptomatology, quality of life, number of relapses and re - hospitalizations, patients' satisfaction, social interaction and family involvement, therapeutic adherence, attitude and understanding of the disease, among others. Despite each individual intervention has demonstrated its effectiveness in several aspects, an integrated intervention has proved to have better outcomes and to be more long lasting when personalized to each patient according to their necessities (30,43–45,55).

However, despite several studies evaluating the efficacy psychosocial interventions have on the commented aspects of schizophrenia and its consequences, little research has been done regarding their effect on the antipsychotic dose used in the maintenance phase treatment of the disease. Only two studies have been found regarding those aspects, and they have some limitations that must be considered:

- In 1977, Paul and Lenz conducted a study evaluating the effect the token economy intervention had in patients with schizophrenia. They observed that, with the application of this intervention, the dose needed to maintain patients' symptomatology controlled was lower than without the intervention (39,56). However, they could not demonstrate an improvement in all clinical areas of the disease, and it opens an important ethical debate regarding the type of intervention they were using.
- Falloon performed at 1985 a two year study analyzing the effects a family therapy had in several outcomes of schizophrenia compared to only receiving individual case management. The results showed an improvement in the symptomatology, as well as in the readmission rate, and the maintenance doses of antipsychotics were lower (a mean of 27.5% less of dosage) (57). However, Falloon only included families with a high Expressed Emotion,

limiting the efficacy of this intervention only to those group of patients. Moreover, he only evaluated an individual technique, not taking into account an integrated intervention.

The results obtained at those studies, despite having its limitations, open an interesting area of study regarding this aspect. Moreover, none evaluated the effects the dosage reduction had in one of the most important causes of death in patients with schizophrenia, which is strongly related to pharmacological treatment, cardiovascular disease.

Finally, it is important to outline that despite all the existing evidence supporting the use of an integrated psychosocial intervention, a non-despicable number of the population affected by schizophrenia do not receive this type of intervention, a part of it, or do not receive the correct one according to their necessities (4,51,55). One of the causes that could explain this situation could be the extra costs this type of treatment may have. However, taking into account its efficacy reducing readmissions and relapses, that would diminish the costs of the hospitalization and emergency services, which account for the highest proportion of the global cost of the disease (46,47). Moreover, it would be interesting to evaluate, once known the effect a psychosocial intervention has on both the pharmacological treatment and the cardiovascular and metabolic risk factors, how those changes affect the global cost of the disease. For that reason, it has been considered an important point to address in the present study.

Hypothesis

Patients with a diagnosis of severe schizophrenia following an integrated psychosocial intervention plus pharmacological treatment will require lower doses of antipsychotics in the maintenance phase compared to patients only receiving pharmacological treatment plus standardized visits.

This dose reduction is associated with a decrease in the cardiovascular disease risk and the metabolic syndrome prevalence, as well as a reduction in the global cost of the disease.

Objectives

Primary Objective

To compare the antipsychotic dose needed in the maintenance phase in patients with a diagnosis of severe schizophrenia following an integrated psychosocial intervention plus pharmacological treatment to those only receiving pharmacological treatment and a minimum of programmed visits.

Secondary objectives

To analyze the cardiovascular disease risk and the prevalence of metabolic syndrome in patients following an integrated psychosocial intervention and pharmacological treatment versus patients only following pharmacological treatment plus standardized visits.

To estimate the global costs of schizophrenia in patients following an integrated psychosocial intervention plus pharmacological treatment versus patients only receiving pharmacological treatment and standardized visits.

Methodology

Study design

A prospective, longitudinal, observational cohort study will be performed.

Study subjects

Patients with a diagnosis of schizophrenia according to ICD-10 or DSM-V criteria with an onset of an acute episode or exacerbation, defined as a worsening of their basal situation, which can include any of the following: changes in sleep patterns, behavior changes (isolation), irritability and increased internal tension, excessive worrying about banal things, auto - referential comments, changes in usual activities and patterns, hallucinations, premonitory thoughts manifested and doubts about the reality.

Those changes have led to the attendance to any of the services included in the *Xarxa de Salut Mental de la Província de Girona (XSM)* (See appendix 3). Patients' diagnosis have been classified as a severe mental disease, according to the National Institute of Mental Health (NIMH) criteria (See Appendix 4). Patients have not been receiving any psychosocial or resource intervention from the XSM during the year prior to the onset of the acute episode.

Inclusion criteria

- Patients from 20 to 60 years old. Patients with less than 20 years or more than 60 will be excluded as they are atypical ages for the onset of schizophrenia, and could influence in the results obtained.
- Patients with a diagnosis of schizophrenia according to ICD-10 or DSM-V criteria.
- Patients whose schizophrenia is catalogued as a severe mental disease according to the criteria followed in the National Institute of Mental Health (NIMH).
- Patients admitted in any service of the XSM due to an exacerbation of the disease.
- Patients who have not received any psychosocial or resource intervention from the XSM during the previous year.
- Patients who have signed the previous informed consent to participate in the study provided by any of the services of the XSM.

Exclusion criteria

- Patients with a diagnosis of another psychotic disorder causing the acute episode: schizoaffective disorder, delusional disorder, brief psychotic disorder, schizophreniform disorder
- Patients with a first episode of psychosis.
- Patients with a psychosis caused by substance/ medication abuse/use.
- Patients with another medical condition causing the psychotic episode.
- Patients with another mental disease causing the psychotic episode: mood disorders, anxiety disorders, personality disorder.
- Patients with a substance abuse disorder.
- Patients who are not Caucasian.

Sample selection

The sample will be selected with a non – probabilistic consecutive method, recruited from patients attending to the services of the XSM for the onset of an exacerbation of schizophrenia, if fulfilling the criteria mentioned, as they come, for a period of one year, or until the sample needed is obtained. The follow-up will start at their arrival and will continue during a period of two years. The sample will be integrated by patients living in one of the following areas: Gironès – Pla de l'Estany, Baix empordà, Alt Empordà, La Selva Interior, La Selva Marítima, La Garrotxa and Ripollès.

In order to ensure participants' enrollment, the importance of the study findings in order to diminish pharmacological dosage and thus decrease the cardiovascular disease risk will be exposed, as well as the growth of a personalized psychosocial intervention use. Information confidentiality will be ensured and an informed consent will be provided. To the participants in the control group, the possibility of the use of the psychosocial intervention program will be offered at any time, being then retired from the study.

The sample will be divided in two groups both receiving routine clinical practice interventions: one group will follow an integrated psychosocial and resource intervention, including the required therapies from the following: cognitive behavioral therapy, psychoeducation, family intervention, cognitive rehabilitation, social skills training, assertive community treatment, supported employment and living resources plus pharmacological treatment and standardized

visits, and the second group will only receive pharmacological treatment with a minimum of a trimestral visit with the psychiatrist, social worker and nurse when attending to the Mental Health Center, or a daily visit if admitted in the sub – acute unit.

It has not been possible to perform a randomized clinical trial due to ethical issues, as there are several studies proving the efficacy of an integrated psychosocial intervention in various aspects of schizophrenia, such as symptomatology, quality of life or relapse rates, and as the main ideology of the XSM is to treat with a personalized psychosocial intervention to all the patients aiming to receive it. For that reason, the comparison group will consist of patients who do not accept following an integrated psychosocial intervention program. Due to that selection criteria, there may be pre – existing differences between these groups that could affect results and might potentially confound the results of this analysis. To adjust for this differences, a Propensity Score (PS) Matching technique will be employed. PS matching is a multivariate matching technique designed to account for potential confounds, which will be examined for differences between groups. Patients will be matched according to the following variables, in a 1:1 relationship:

- **Gender:** patients will be divided in two categories, male – female.
- **Age:** patients from 20 to 60 years old will be categorized in three groups: from 20 to 35 years, from 36 to 50 years and from 51 to 60 years.
- **Family support:** considered as a minimum of one person of 18 years or older referred by the patient as a support in everyday activities or in crisis situations and who have contact with the patient at least once every two weeks on average, or a minimum of 11 hours per month. This information will be collected from the clinical history of the patient and the initial interview and recorded as Yes or No. An interview with the family support will be performed in order to confirm the information.
- **Global Assessment of Functioning scale (GAF) at the beginning of the study (t=0):** registered at the arrival to the XSM, previous to the start of any treatment. The results will be categorized in four groups: 69 - 51, 50 – 31, 30 – 11, 10 – 1. The collecting methods and GAF functioning are explained below (See “Dependent variable” and “Data collection”).

Sample size

The sample size and power calculator GRANMO was used to achieve the sample size needed. Using the ARCSINUS approximation and accepting a risk α of 0.05 and a β risk of 0.20 in a two – sided test, 74 patients following an integrated psychosocial intervention plus pharmacological treatment and 74 patients only following pharmacological treatment plus standardized visits are necessary to recognize as statistically significant the difference between two proportions which are expected to be of at least 0.3 in the first group and 0.1 in the second group. It has been anticipated a dropout rate of 20%.

According to the data available in the *Mental Health and Addiction Management Area* located in Parc Hospitalari Martí i Julià, the annual prevalence of people attended from schizophrenia in all the Mental Health Centers from the XSM is 16.09%, corresponding to 2219 people of the 13783 visited. According to clinical experience, approximately 25% of the 2219 patients attended will be consulting for a worsening of their basal situation (555 patients). It is expected that a minimum of a 50% of the available sample will fulfill the inclusion criteria with no exclusion criteria (278 patients). Finally, assuming a minimum acceptance inclusion in the study of a 60%, a sample of 167 patients will be available in one year. Thus, it can be concluded that the needed sample will be available in a period of one year recruitment.

Study variables

Independent variable¹

Integrated psychosocial intervention program

Detailed information about each intervention has been explained above (See “Introduction: Psychosocial intervention in Schizophrenia”). A brief summary of the specific methods that will be used in the present study is given here.

Each intervention will be performed according to the patients’ needs. Times of duration have been selected according to the actual evidence and recommendations, but each participant may need more or less sessions of each intervention, and some patients may not need all the interventions available. The team working in each intervention will decide which ones are needed to each patient according to their current situation and progress.

¹ It is important to clarify that, as mentioned, this is an observational study, and the use of a psychosocial intervention program and pharmacological treatment as explained in the present protocol is provided by the XSM in the routine clinical practice to any patient attending.

Patients will be receiving a psychosocial intervention program in different centers depending on their state:

- Patients will be hospitalized at a sub – acute unit when the intensity of the symptomatology is considered severe enough, with auto or hetero aggressive conducts, or when the familiar environment is not adequate to treat ambulatory.
- Patients will be transferred to the day hospital when their disease is severe enough to not to be treated at an ambulatory level but there are no aggressive attitudes, and the environment to live is favorable enough to try to avoid hospitalization.
- Patients will be treated at the Mental Health Center when the symptomatology could be intervened without hospitalization, as there is no aggressive attitudes or violence, and having the patient an adequate environment, with both the family and him/herself preferring it.
- Patients will start receiving a psychosocial intervention program at the Rehabilitation Center when they have been stable for over a year at the Mental Health Center, receiving then trimestral psychiatric and nurse visits at the Mental Health Center, and the psychosocial intervention at the rehabilitation center. Patients admitted in the sub – acute unit can start receiving some of their psychosocial interventions at the rehabilitation center when considered by the team.

It has to be noticed that during the 2 - year follow - up period, patients will probably be treated in more than one institution, because as they improve their needs will change, and the objective of the intervention is to introduce them to normal life as soon as possible.

Psychologists, psychiatrists, nurses, social workers and occupational therapists providing all psychosocial interventions have been previously formed on the field, attending to different courses provided by the XSM, and to any of the professionals who have not received the necessary formation, it will be provided in order to reduce variability and avoid any information bias.

A table with the most relevant aspects of each intervention is given here. A detailed explanation of each intervention is provided in [Appendix 5](#).

| | Content | Beginning | Duration | Frequency | Responsible |
|-------------------------------------|--|----------------------------|--------------|--|------------------------|
| Cognitive Behavioral Therapy | Monitoring and acceptance of the patients' thoughts, feelings and actions. Promotion of logical pathways to solve conflicts and stress reduction strategies. Development of a new comprehension of the patients' experiences. | At the acute phase | 4 – 9 months | Twice a week at Hospitalization Once a week at Day Hospital Monthly at Mental Health Center Group therapy will be performed every two weeks | Psychologist |
| Cognitive Rehabilitation | Restauration of the previous cognitive functioning. Compensation in the patients' environment. | At the stabilization phase | 4 - 9 months | Twice a week at Hospitalization Once a week at Day Hospital Monthly at Mental Health Center | Psychologist |
| Social Skills Training | Role playing, Feed-back and positive reinforcement techniques involving free – time, basic communication and work abilities, friendship and couple relationships, medication use, symptomatology and substance abuse management and community reincorporation. | At the stabilization phase | 4 - 9 months | Twice a week at Hospitalization Once a week at Day Hospital Monthly at Mental Health Center | Psychologist and nurse |

Table 1: Interventions included into the Psychosocial Intervention Program. *Source: Author*

| | | | | | |
|---|---|--|---|---|--|
| <p>Psychoeducation</p> | <p>Information and knowledge about the disease. Specific doubts and how to solve daily problems arising. Individual or in groups</p> | <p>At the stabilization phase</p> | <p>9 months</p> | <p>Three times a week at Hospitalization Once a week at Day Hospital Monthly at Mental Health Center</p> | <p>Expert – user and psychologist</p> |
| <p>Family Intervention</p> | <p>Information about the disease, stress management, management of the adversities and conduct problems that can appear. Behavioral Family Therapy (BFT) (individual) and Relatives Group (RG).</p> | <p>At the acute phase</p> | <p>9 months – 2 years The relatives group will be a 10 session module</p> | <p>Once a week at Hospitalization and Day Hospital Monthly at Mental Health Center Twice a week the relatives group</p> | <p>Psychologist and psychiatrist</p> |
| <p>Assertive Community Treatment</p> | <p>Visits at home or at the supervised living place with revision and education in difficulties experienced in medication use or daily living.</p> | <p>When the patient starts living independently and is at high risk of disengagement</p> | <p>Until needed</p> | <p>Once a week, with progressive diminution</p> | <p>Nurse and occupational therapist</p> |
| <p>Supported Employment</p> | <p>Pre – working service, orientation service to the ordinary business, training service, special work places and job maintenance services.</p> | <p>At the stabilization phase</p> | <p>Until needed</p> | <p>—</p> | <p>Social worker Drissa foundation</p> |

Table 1: Continuation. Interventions included into the Psychosocial Intervention Program. Source: Author

| | | | | | |
|---|--|-----------------------------------|--|---|---|
| <p>Living Resources and Pis Escola</p> | <p><u>Autonomic living</u>: No help is needed at the living place. Arranged visits at the Mental Health Center.</p> <p><u>Domiciliary help</u>: In daily activities and self – care, at the patients’ home.</p> <p><u>Protected living</u>: shared flat for 4-6 people with support in daily activities and integration.</p> <p><u>Residence “La Maçana”</u>: providing continuous assistance for people with impossibility to live independently</p> <p><u>Pis escola</u>: preparation to start living independently, regarding self – care, productivity, free time, fomentation of a healthy and active lifestyle and identification and solving of dangerous situations at home.</p> | <p>At the stabilization phase</p> | <p>Pis escola: 3 weeks</p> <p>Living resources: Until needed</p> | <p>Domiciliary help: once a week</p> <p>Protected living: Daily</p> <p>Residence: 24h a day</p> <p>Pis escola: twice a week in a 5 hour session</p> | <p>Nurse and occupational therapist</p> |
|---|--|-----------------------------------|--|---|---|

Table 1: Continuation. Interventions included into the Psychosocial Intervention Program. Source: Author

Pharmacological treatment plus standardized visits

Pharmacological treatment will be provided to both groups of participants since the arrival to any service of the XSM. Pharmacological treatment will be chosen by the psychiatrist according to the previous treatment received and its efficacy. It is recommended the continuity of a pharmacological treatment in patients with schizophrenia if it is known to be effective (4). If not possible, an antipsychotic will be chosen according to its effectiveness and side effects.

A standardized visit program will be arranged to all participants in order to control their progress, understood as an initial visit at weeks 4 and 6, followed by a trimestral visit with a psychiatrist, a social worker and a nurse at the Mental Health Center of reference. When admitted in the sub – acute unit, daily visits are conducted during the hospitalization period.

Dependent Variables

Antipsychotic dose required in the maintenance phase

Maintenance will be defined as a GAF \geq 70. GAF is a frequently applied tool for assessing the psychosocial level of functioning, evaluating both symptom severity and functioning, ranging from 1 to 100, with higher scores indicating better functioning (See Appendix 6). Despite having been eliminated from DSM – V due to its subjectivity, some recent studies have demonstrated its efficacy and correlation with other available scales (58,59), and is still used for the diagnosis of Severe Mental Illness in the National Institute of Mental Health (NIMH) criteria and in the spanish *Guía de práctica clínica de intervenciones psicosociales en el Trastorno Mental Grave* (28). For that reason, and because of its brevity and its high inter – rater reliability with little rater training (58), GAF will be used in the present study.

Knowing the subjectivity of the scale, and to reduce as much as possible variability and the information bias it can produce, a formation course will be provided to all the professionals applying the questionnaire in order to ensure homogeneity among different practitioners. A psychiatrist will apply the scale considering the clinical interview, daily functioning and, if available, the family and caregivers testimony. In order to increase validity, a psychologist will be also applying the GAF scale at the arrival day. When discrepancies among both evaluations, the service manager will apply the test.

The dose of antipsychotic required for a maintenance of a GAF \geq 70 at the end of the study will be obtained. Equivalence tables will be used to compare doses depending on the drug selected

and its posology (See Appendix 7). The minimum effective dose method has been used to obtain equivalences. It consists on the division of the minimum dose which is more efficacious than placebo of two antipsychotics to obtain the equivalence between them. Despite different existing methods to obtain equivalences, this has been seen to be the most used (60).

Equivalences will be obtained comparing each antipsychotic with 1mg olanzapine.

Patients will be divided according to the standardized doses of olanzapine, in the following categories, at the beginning and at the end of the study:

| Very Low (5mg) | Low (7.5mg) | Moderate (10mg) | Moderate – high (15mg) | High (20mg) | Very high (>20mg) |
|----------------|-------------|-----------------|------------------------|-------------|-------------------|
| | | | | | |

Table 2: Classification of the dose of antipsychotic used. *Source: Author*

When transforming the different antipsychotic doses frequently used into 1 mg Olanzapine, they tend to result in similar doses to the ones given in the classification. However, if a different result is obtained, it will be classified into the closest category.

Despite existing a posological dose of 2.5 mg, it is not used for the treatment of schizophrenia, so it will not be included in the present study.

A reduction in categories from the beginning of the study to the end is expected in both groups, as the pharmacological dose after a worsening differs from the dose used for the maintenance phase. Thus, a reduction of around a 25% in the dose needed is expected in both groups, which is the reduction required to decrease one category in the classification mentioned. However, based on the little existing evidence (57), a higher reduction is expected in the group following a psychosocial intervention, of around a 25% more than the group not following the intervention, reducing then two categories. To compare the pharmacological dose needed in the maintenance phase treatment, the proportion of patients who have decreased in at least two categories since the beginning of the study will be analyzed. A special situation has to be mentioned for patients who have received a dose of 10 mg or less at the beginning of the study. In those cases, it is difficult to expect a reduction only with pharmacological treatment. Thus, the proportion of patients who have reduced at least one category will be taken into account.

Cardiovascular Disease Risk and Metabolic Syndrome

The risk of developing cardiovascular disease (CVD) will be used as a marker of a long term secondary effect influenced by antipsychotics. All cardiovascular side effects have been documented to occur both in the short and the long term, appearing in some studies at relatively short periods of time (23,25,61), being observable at the time period of the present study.

Different scores are available for the risk estimation of cardiovascular disease. Studies evaluating the cardiovascular disease risk in patients using antipsychotics have already been conducted, using the Framingham Heart Study Formula (23). An adaptation of the Framingham study formula is available for the Spanish population, the REGICOR. Some studies have demonstrated that REGICOR is the most accurate scale to evaluate cardiovascular risk among the Spanish population (62,63). For that reason, a cardiovascular disease risk over a 10 – year period will be calculated using the Spanish adaptation to the Framingham Heart study formula, the REGICOR.

To measure the CVD risk, data regarding age, sex, smoking habits (yes – no), blood pressure, diabetes (yes - no), HDL and total cholesterol will be obtained.

| | |
|---------------------|---|
| Diabetes | Fasting glucose \geq 126 mg/dL |
| | Random glucose \geq 200 mg/dL |
| | Diabetes actual diagnosis |
| | Diabetes treatment |
| Hypertension | Systolic pressure \geq 140 mmHg and/or Diastolic pressure \geq 90 mmHg |
| | Antihypertensive medication |
| | Hypertension actual diagnosis |
| Smoker | \geq 1 cigarette per day during the last year |

Table 3: Diagnostic criteria of Diabetes, Hypertension and Smoking. *Source: Author*

All data will be collected by a trained nurse as exposed below (See “Data collection”), providing a formation course to all nurses in charge in order to reduce variability. With all the data collected, the REGICOR CVD risk will be calculated. (See Appendix 8).

The 10 – year cardiovascular disease risk will be classified in low (< 5%), moderate (5 – 9%), high (10 – 14%) or very high (\geq 15%). To compare the CVD risk in both groups, the proportion of

patients who have reduced at least one category in the REGICOR classification from the beginning of the study to the end will be considered. For patients who were at the low or moderate category, the proportion of patients who have maintained will be considered. Among them, the proportion of patients taking antihypertensive or dyslipidemia treatment will be evaluated and compared, as it could be a possibly confounding factor (See “Co – variates”).

Other factors will be analyzed, as they may have an influence in the evolution of the cardiovascular disease risk, and it has been considered that they need to be taken into account. These include a family history of diabetes, hypertension, dyslipidemia or coronary heart disease, exercise and dietary habits (See “Co-variates”).

Metabolic syndrome (MS) has been shown to be a risk factor for developing cardiovascular disease, and several studies demonstrate its association with the use of antipsychotics (18,23). Metabolic syndrome also tends to appear at relatively early stages of the disease (23,25,61), so its onset could be recorded at the present study. For the diagnosis of metabolic syndrome, three of the following must be present:

| | |
|--|---|
| | Central obesity, defined as a waist circumference > 88 cm for women or > 102 cm for men, or a BMI > 30 kg/m ² . This criteria must be present for the diagnosis of metabolic syndrome. |
| | Triglyceride levels ≥ 150 mg/dL or treatment for dyslipidemia |
| | HDL cholesterol < 40 mg/dL in males or < 50 mg/dL in females |
| | Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥85 mmHg or treatment for a diagnosed hypertension. |
| | Fasting plasma glucose ≥ 110 mg/dL or a diagnosis of type 2 diabetes. |

Table 4: Diagnostic criteria of Metabolic Syndrome. *Source: Author.* Information obtained from *The IDF Consensus worldwide definition of the Metabolic Syndrome* (64)

A diagnosis of metabolic syndrome will be done when necessary. The prevalence of metabolic syndrome among both groups will be compared.

As it has been exposed previously, not all antipsychotics have the same effect in cardiovascular disease and metabolic risk factors. Thus, in order to clarify results, patients will be classified according to the antipsychotic used in both groups, and all the comparisons mentioned will be done according to the pharmacological treatment used.

Global cost of the disease

An estimation of the global cost of schizophrenia during the study period will be calculated regarding the following aspects:

1. **Antipsychotic costs:** The antipsychotic cost per patient will be calculated obtaining data from the Vademecum guide of the individual cost of the antipsychotic used in each case, depending on the dose and its posology. The annual cost of the antipsychotic used for maintenance treatment will be calculated for each patient and compared in both groups, according to the type of antipsychotic.
2. **Concomitant medication costs:** an important number of patients with schizophrenia take concomitant antidepressants or anxiolytics to help improving the residual symptomatology (4). The number of patients taking those concomitant medications at the end of the study will be obtained from the clinical history of each patient. The individual cost of the antidepressant/anxiolytic used in each case will be obtained from the Vademecum guide. The time each patient has taken those medications during the study period will be obtained, and the global cost of the concomitant medication will be calculated. The mean cost of each group will be obtained.
3. **Cardiovascular risk factors treatment costs:** the cost of the pharmacological treatment of diabetes, dyslipidemia and hypertension will be obtained from the Vademecum guide. The number of patients receiving treatment for the conditions mentioned at the end of the study will be collected from the clinical history registered for each participant. The costs for the treatment of cardiovascular risk factors during the study period will be calculated. The mean costs of both groups of patients will be calculated and compared.
4. **Hospitalization for the actual episode costs:** only for those patients who have needed a hospitalization at the acute or sub – acute unit due to the exacerbation episode. The daily cost of a hospitalization at the acute and sub – acute unit is estimated to be 284.31€ per patient at the acute unit, and 161.12€ per patient at the sub – acute unit². The number of days hospitalized for the present episode will be obtained from the clinical course of the patient. The global cost of the hospitalization will be obtained for each patient. The mean cost for each group will be obtained and compared.

5. **Re-hospitalizations costs:** the daily cost of a hospitalization both at the acute and the sub – acute unit is estimated to be 284.31€ per patient at the acute unit, and 161.12€ per patient at the sub – acute. The number of re – hospitalizations and the duration of each per patient will be obtained from Hospitalization courses from the clinical history of each participant. Only re – hospitalizations for mental health issues due to schizophrenia will be considered. A hospitalization the first 14 days after discharge is considered part of the actual episode, and will not be taken into account in this category.
- The cost of the total of days hospitalized for each patient will be calculated, and the mean global costs of re – hospitalizations in both groups will be obtained and compared.
6. **Emergency consultation costs:** the cost of an emergency consultation is estimated to be 136.12€ per emergency consultation². The number of emergency visits due to their medical condition during the study period will be obtained from clinical courses onto their clinical history. The mean of costs produced by emergency consultations will be calculated in both groups and compared.
7. **Psychosocial intervention costs:** the cost per patient of the following services: Rehabilitation Center, Day Hospital, Mental Health Center, supported employment and living resources, including all personnel salaries, infrastructure costs and material costs, is estimated to be 96.54€ per visit at the Mental Health Center and the Rehabilitation Center, 67.24€ per day at the day hospital and 71.97€ per day at the Residence “La Maçana”². The global costs of psychosocial intervention during the study period will be calculated and compared.
8. **Productivity loss:** the number of unemployed participants from both groups at the end of the study will be compared, obtaining data from personal information recorded in the clinical history of each participant. Productivity loss will be calculated using the average daily wage in Spain³ and the number of days unemployed during the study period.
- In both groups, the cost will be obtained accounting for the proportion of patients who could have been actively working according to the unemployment tax in Spain⁴.

² Data corresponding to 2015 obtained from The Mental Health and Addiction Management Area, located in Parc Hospitalari Martí i Julià. Data regarding the costs of Pis Escola, Protected living and Drissa Foundation has been requested and will be obtained during the course of the present study.

³ The minimum inter-professional salary in 2017 is estimated to be 23.59 € per day. Page 36 | 98

⁴ The unemployment tax in Spain was 18.9% in 2016.

9. **Time cost:** among the participants working in both groups, the number of absences at work due to mental health problems during the study period will be obtained from clinical history and interview. The monetary value of healthy time will be calculated with the Human Capital Method (46), multiplying the average daily wage in Spain, and the number of days of work lost due to the disease.
10. **Caregiver costs:** Time cost and productivity loss of the caregiver will be also calculated. Other caregivers' costs will be calculated using a section of the European Version of the Involvement Evaluation Questionnaire (See Appendix 9). This questionnaire evaluates the consequences a severe mental disorder has in the caregiver of the person affected. It is important to outline that the complete questionnaire will not be used, and the section regarding costs will be used as a guide for caregivers to give a more detailed information about the effects the disease has in their economy. Despite not using the whole scale nor the punctuation system, its mention has been considered necessary.

With all the data, an estimation of the global cost during the study period in both groups will be obtained and compared.

Co- variates

It is considered appropriate the collection of some variables which could be of possible confusion or interaction. Taking into account the variables already used at the matching propensity score, the following will also be collected:

1. **Education level:** education level will be divided in the following categories: none, primary school, secondary school or higher education, according to the personal history recorded.
2. **Marital status:** single, separated or married/with a couple. Information will be obtained from the clinical history.
3. **Time since the diagnosis of schizophrenia:** patients will be divided in two groups: from 2 to 5 years, or more than 5 years. Data will be obtained from the clinical history of the patient.

4. **Number of hospitalizations at the beginning of the study (t=0):** data will be obtained from the clinical history of the participants, and will be categorized in none, between 1 and 2 or more than 2.
5. **Working status at the beginning of the study (t=0):** divided in employed or unemployed, obtaining information from the clinical history and the interview with the participant.
6. **Insight:** insight is a multidimensional concept, meaning not only the recognition of the illness and its consequences, but the ability to attribute those consequences to the illness itself. Insight has been proposed to be a sum of neuropsychological, cognitive and psychological defense models. It has been related with treatment compliance, dangerousness, suicide and prognosis (65,66). The Spanish adapted version of the Insight Scale – Birchwood will be used in the present study ([See Appendix 10](#)). It is a self – reported scale that evaluates the three main categories representing the definition of insight: need for treatment, awareness of illness and appropriate relabeling of symptoms. Each question can be labeled in yes – no – not sure, and each category will have a punctuation from 0 to 4. A punctuation of 9 or higher is considered a good insight (66,67). Insight will be evaluated at the beginning of the study (t=0). In those patients who had not accepted any psychosocial intervention and decide to accept it during the course of the study, or in those who had accepted and decide to quit, despite being excluded, the Insight Scale Birchwood will be applied again in order to evaluate possible causes of the acceptance or refusal of the intervention. Patients will be classified in Good insight (≥ 9) or Bad insight (< 9).
7. **Pharmacological treatment chosen at the beginning of the study (t=0):** Pharmacological treatment will be chosen at the arrival of the patient by the psychiatrist, as explained above. This co – variate is of relevant importance mostly for the Cardiovascular Disease Risk and Metabolic Syndrome prevalence.
8. **Antipsychotic treatment prior to the consultation:** considered as a regular antipsychotic treatment following the instructions arranged with the psychiatrist during the previous 3 months. Patients will be classified in yes - no.
9. **Concomitant treatment at the beginning (t=0) and the end of the study (t=2):** as mentioned, a several number of patients with schizophrenia take concomitant

antidepressants or anxiolytics. Patients will be classified in none, antidepressants, anxiolytics, both or other, obtaining information from clinical history and interview.

10. **Antihypertensive and dyslipidemia treatment at the beginning (t=0) and the end (t=2) of the study:** Patients will be classified in none, antihypertensive, dyslipidemia or both. Information will be obtained from clinical interview and medical history.
11. **Dietary habits at the beginning (t=0) and the end of the study (t=2):** A food diary will be recorded from the two previous days of each meeting. Patients will be classified according to the proportion of calories obtained from refined sugar in < 10%, 10-50% and > 50%, and according to the proportion of calories obtained from saturated fats in <10%, between 10-50% and >50%.
12. **Exercise routine at the beginning (t=0) and the end (t=2) of the study:** Patients will be classified as active if they participate in sportive or fast – walking activities during 30 minutes a day a minimum of three days a week, and as non – active if not fulfilling the previous criteria. This information will be obtained from clinical interview.
13. **A family history of diabetes, hypertension, dyslipidemia or coronary heart disease:** This information will be obtained from clinical history and interview, and patients will be classified in yes – no.

The last four co-variables mentioned are of relevant importance especially to assess the Cardiovascular Disease Risk and Metabolic Syndrome prevalence. Data obtained at t=0 will be analyzed with the results of the main variables at t=0, and the information obtained at t=2 with the results at t=2.

Data collection

Patients' recruitment will be performed during a period of one year or until the needed sample is fulfilled. Since the recruitment of a participant, data will be collected for a period of 2 years. At the admission information about the study and the informed consent will be provided.

Pharmacological treatment will start at the arrival and the type and dose of antipsychotic will be collected. The same information will be collected at the end of the study period. Modifications

in the dose and type of antipsychotic will be evaluated at week 6, month 6, month 12 and month 18, coinciding to the GAF score evaluation. The regular use of an antipsychotic during the previous three months will be collected.

The use of concomitant medication will be collected with the same frequency as the antipsychotic treatment.

Sociodemographic data, including gender, age, marital status, working status, familiar support and education level will be collected at the admission and the following day.

The number of re – hospitalizations will be collected at the baseline and at the end of the study, in order to evaluate the global costs.

At the appointment 1, the day after consultancy, a psychosocial intervention program will be offered to the patient by the psychiatrist, and depending on his/her acceptance, will be classified in one group or another. The acceptance of the psychosocial intervention will be considered during the first month since the arrival. If a patient who had refused an integrated psychosocial intervention starts any after this period, or a patient who had started any stops attending, he/she will be excluded from the study.

The Insight Scale Birchwood Spanish Adaptation will be applied during this first appointment, by a psychiatrist. If a patient who had refused the psychosocial intervention program accepts it after a month, or a patient who had accepted refuses, despite being excluded from the study, the Insight Scale will be applied again.

The GAF score will be obtained at baseline in order to classify the participants, and at the end of the study in order to ensure stability. The GAF score will be also evaluated at week 6, month 6, month 12 and month 18 to readjust the pharmacological treatment when needed. A psychiatrist will apply the scale considering the clinical interview, daily functioning and, if available, the family and caregivers' testimony. In order to increase validity, a psychologist will also be applying the GAF scale at the arrival day. When discrepancies between evaluations occur, the service manager will apply the test.

Cardiovascular disease risk factors and metabolic syndrome will be collected at the beginning of the study and at week 6, month 3, month 6, month 12, month 18 and at the end of the study regarding age, sex, smoking habits, blood pressure, diabetes, HDL and total cholesterol. This data will be collected by a trained nurse in the assigned center.

Blood pressure will be obtained after a 5 minute rest with a calibrated automatic sphygmomanometer, registering the best of two measurements, separated by a 10 minute period. A blood sample to obtain glucose, HDL and total cholesterol levels will be extracted after a 10 to 14 h fasting period.

A family history of diabetes, hypertension, dyslipidemia or coronary heart disease will be recorded at the first appointment with the nurse. Exercise, dietary habits, antihypertensive or dyslipidemia treatment, circumference waist and BMI will be collected at baseline, week 6, month 3, month 6, month 12, month 18, and at the end of the study.

The diagnosis of metabolic syndrome will be recorded, when necessary, at the beginning and at the end of the study.

Finally, the data to evaluate the global costs will be collected at the end of the study period, calculating each aspect as has been mentioned. The Involvement Evaluation Questionnaire will be applied to the caregivers in that phase too.

All the data collected will be recorded in a case report form, illustrated in [Appendix 11](#).

| | Baseline | Day1 | Week4 | Week6 | Month3 | Month6 | Month12 | Month18 | Month24 |
|--|----------|------|-------|-------|--------|--------|---------|---------|-----------------------|
| Informed consent | X | | | | | | | | |
| Sociodemographic data | X | X | | | | | | | X (working status) |
| Time since the diagnosis of schizophrenia | X | | | | | | | | |
| Number of re – hospitalizations | X | | | | | | | | X |
| GAF score | X | | | X | | X | X | X | X |
| Insight | | X | | | | | | | |
| Pharmacological treatment | X | | | X | | X | X | X | X |
| Psychosocial intervention participation | | X | X | | | | | | |
| CVD risk factors and metabolic syndrome | | X | | X | X | X | X | X | X |
| Global costs | | | | | | | | | X |

Statistical Analysis

Univariate analysis

Qualitative variables, such as a psychosocial intervention program implementation, categorized as yes or no, antipsychotic dose (very low, low, moderate, moderate – high, high and very high), the metabolic syndrome prevalence (yes or no) and the cardiovascular disease risk (low, moderate, high or very high) will be described using frequency tables where describing absolute and relative frequencies, and represented by bar charts.

Quantitative variables such as the global costs of the disease will be described using means and standard deviations, and represented by histograms.

Co - variates will be described using frequency tables and represented by bar charts.

Bivariate analysis

To compare qualitative variables such as the dose of antipsychotic needed in the maintenance phase, the cardiovascular disease risk and the metabolic syndrome prevalence in both groups, following a psychosocial intervention plus pharmacological treatment or only a pharmacological treatment with standardized visits, the X² method will be used. As explained, some of those variables are going to be dichotomized (the proportion of patients reducing X categories in the classification will be analyzed) in order to determine association.

To compare the continuous variable global cost of the disease in both groups, a T student method will be performed.

Multivariate analysis

Multivariate analysis will be performed using the Multiple Logistic Linear Regression Model to assess the relationship between a psychosocial intervention and qualitative variables, such as the antipsychotic dose in maintenance treatment, the cardiovascular disease risk and metabolic syndrome prevalence, adjusting for co – variates. A p value < 0.05 will be considered statistically significant.

Multivariate analysis will be performed using a Multiple General Lineal Model to assess the relationship between a psychosocial intervention and the differences in the global cost of the disease adjusting for co – variates. A p value < 0.05 will be considered statistically significant.

Ethical and Legal Considerations

The present study will be conducted according to the requirements expressed in the *Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects* signed by the World Health Association in 1964 and last revised in October 2013.

In addition, the processing of personal data required in this study, its communication, cession and confidentiality is in compliance with the Spanish *Ley Orgánica 15/1999, del 13 de Diciembre, de Protección de Datos de Carácter Personal*. This study guarantees the confidentiality and anonymity of all the data obtained to carry out the present investigation.

The principles expressed in the *Ley Orgánica 41/2002, del 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica* will be followed as well, and before any participant being included in the present study, all the appropriate clinical, ethical and legal information will be exposed. An informed consent will be provided, and it must be signed by the participant or the legal tutor when incapacitated (See [Appendix 12](#)).

As the present investigation works with a pharmacological treatment, before carrying out the study, this protocol will be presented to the *Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)*, as well as to the *Comité Ético de Investigación Clínica (CEIC)* from the Institut d'Assistència Sanitària, in order to be evaluated and approved by it, following the principles expressed in the *Real Decreto 1090/2015, de 4 de Diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con Medicamentos y el Registro Español de Estudios Clínicos*. After its acceptance by the CEIC and AEMPS, the study will be presented to the *Direcció General de Farmàcia de la Generalitat de Catalunya*.

The present study will also be conducted following the principles expressed in the *Orden SAS/3470/2009, de 16 de Diciembre, por la que se publican las directrices sobre estudios posautorización de tipo observacional para medicamentos de uso humano*.

Finally, the study will be registered at the *European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCEPP)*.

The investigators of the present study declare no conflict of interest.

Study Limitations

The first limitation to consider in the present study is the type of study selected, a cohort study, as the best study to answer the hypothesis proposed would have been a clinical trial. A cohort study is a long period study, which increases the risk of participants' loss, as well as the global cost of the study. The reason of this type of study selection goes related to the main limitation of the study: the sample selection. Selecting the comparison group from patients who have not accepted a psychosocial intervention can lead to an important selection bias, existing possible individual factors which can lead to confounding results. Those choices can be explained by the ethical considerations confronted in the present study:

- According to the *Ley Orgánica 14/1986, de 25 de abril, General de Sanidad, Capítulo I, Artículo 10*, and the *Ley Orgánica 41/2002, del 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica, Capítulo IV, Artículo 12*, all patients have the right to have access to the services available to improve their health, as well as to all the necessary information to access to those services.
- According to the *Ley Orgánica 14/1986, de 25 de abril, General de Sanidad, capítulo III artículo 20*, regarding mental health, all the rehabilitation and social integration services needed will be developed and offered to all patients with mental health problems in order to achieve an integrated treatment and ultimately, recovery.

Taking in consideration the human rights mentioned above, and with the knowledge of existing evidence regarding the efficacy in several aspects of an integrated psychosocial intervention, such as symptomatology, quality of life or relapse rates, as explained, and as the main ideology of the XSM is to treat with a personalized psychosocial intervention to all the patients with schizophrenia aiming to receive it, it would have not been ethical to deprive a group of patients from the psychosocial services available, whenever aiming to use them. For all that reasons, it has been considered the best option, being aware of the important limitations it carries.

In order to reduce the selection bias created by those limitations, a propensity score matching method has been used, eliminating differences among groups regarding the possibly most confounding variables, and a multivariate analysis will be performed regarding other relevant co – variates.

Another limitation in the present study is the use of the GAF scale. This scale has been chosen as it was the one used at the DSM - IV manual, and has demonstrated a good correlation with the PANSS score. Moreover, it is easy to apply, and is the score used in the XSM in Girona. However, its subjectivity is well known, and can lead to an information bias. To reduce so, a formation course is implemented to all professionals using the scale, in order to unify criteria. The GAF scale will be also calculated by two professionals, a psychiatrist and a psychologist, and when discrepancies occur the service manager will evaluate the case.

The psychosocial intervention program analyzed in the present study will not be exactly equal to all participants enrolling. All will have the same options available, but a personalized intervention will be chosen according to their needs considered by the professional team. That could lead to confusion in the results obtained, so in order to diminish bias, a formation course will be conducted to all professionals providing any type of psychosocial intervention, in order to unify both the criteria to select one or another program for a patient, and the strategies implemented in each intervention. Despite the limitation, it is the best method to approximate the results to the real daily clinical practice, and one of the main objectives of the XSM: a personalized psychosocial intervention.

The fact that participants can enroll a psychosocial intervention at any time during the study can increase the risk of a selection bias due to participants' loss. However, that would imply better outcomes in the prognosis of the patient, so it must be allowed. Moreover, the Insight Scale applied at the beginning of the study will be applied again in that situation, in order to find possible causes of the integrated intervention refusal or acceptance, and it could help find some relevant information to improve those patients' interventions, and create new hypothesis to the development of future studies. Moreover, a dropout rate has already been considered when calculating the sample size.

Finally, nor Framingham nor REGICOR, the scale used to evaluate the cardiovascular disease risk, have been validated for population with schizophrenia, despite the Framingham scale having been used for other studies with patients suffering from the disease. This scale, moreover, considers patients from 35 years or older, and in the present study patients since 20 years old are selected. Despite thus being an important limitation, patients younger than 35 years will be classified in the first category regarding age, and this will not affect the results observable the way they have been formulated.

Work plan and Chronogram

Stage 1: Protocol design and acceptance

Period: 6 months, from November 2016 to April 2017.

Personnel: Principal investigator, CEIC, AEMPS.

Description: For the protocol design, a wide literature review will be done, and the present protocol will be designed and presented to University of Girona. A study proposal will also be presented to the CEIC of the *Institut d'Assistència Sanitària* and to the AEMPS, waiting for its acceptance.

Stage 2: Coordination and organization

Period: 3 months, from May 2017 to July 2017.

Personnel: Principal investigator, collaborate investigators (the service manager psychiatrist of each mental health center (7 in total), the service manager psychiatrist of the sub – acute unit, and the service manager psychiatrist of the day hospital).

Description: During this stage, a detailed explanation of the study will be provided to all the service managers from the centers participating. It will be specially underlined the importance of unified criteria when applying the GAF scale, as well as when providing any of the psychosocial interventions, and the idea of implementing a brief course regarding those aspects to all personnel from the XSM participating in any of the interventions who have not received it yet will be exposed. These courses will be provided at each individual center during this period, in order to facilitate professionals' attendance, by the service manager of the sub – acute unit.

Nurses from mental health centers and sub – acute unit will attend to a brief formation course in order to achieve homogeneity regarding cardiovascular and metabolic data collection. The course will be conducted by a trained nurse from the sub – acute unit.

The main investigators attending to the coordination meeting will be responsible of transmitting all the information provided to the professionals of their working area, ensuring everything has been understood and that data collection and intervention implementation will be done satisfactory.

Stage 3: Participants' recruitment

Period: One year: August 2017 – August 2018 or until the needed sample is fulfilled.

Personnel: All psychiatrists from Mental Health Centers and the Sub – acute unit.

Description: Doctors receiving any patient consulting for an exacerbation of schizophrenia will propose the study participation, when fulfilling inclusion criteria with no exclusion criteria.

In order to ensure participants' enrollment, the importance of the study findings will be exposed. Information confidentiality will be assured and an informed consent will be provided.

Patients will be offered an integrated psychosocial and resources intervention, and will be classified in two groups depending on the treatment:

- **A:** An integrated psychosocial intervention will be performed plus pharmacological treatment and standardized visits.
- **B:** Only pharmacological treatment plus standardized visits will be done.

Patients will have a maximum of one month to accept the entrance to a psychosocial intervention program. After that period they will be classified in group B. If any patient from the group B decides to start any psychosocial intervention after that period of time, he/she will be excluded from the study. Similarly, if any patient receiving a psychosocial intervention refuses the treatment during the first month, he/she will be changed to the group B, whereas after a month, will be excluded from the study.

Stage 4: Data collection

Period: Since the recruitment of the first participant, until the last participant has been followed for a period of two years. The maximum length will be from August 2017 to August 2020.

Personnel: Psychiatrists, nurses and psychologists from any service of the XSM treating the participants.

Description: Data collection will be done in different appointments:

- *Baseline:* At the arrival of the patient, sociodemographic data will be collected regarding sex, age, marital status, working status, education level, family support, time since the diagnosis of schizophrenia, number of hospitalizations due to the disease previous to the arrival, and pharmacological treatment with antipsychotics during the previous three months. The psychiatrist assigned will collect all this information.

The GAF score will be obtained by a psychiatrist, as well as by a psychologist, in the first visit. Pharmacological treatment selected, regarding the type of antipsychotic, its dose and posology will be also recorded. Concomitant treatment will be collected.

In both the Sub – acute unit and the Mental Health Center, when a patient with family support have attended alone, an interview will be arranged for the following day, in order to collect any information that could be missing to complete the data mentioned.

- *Appointment 1:* Another appointment may be needed in order to collect all the previous information. For that reason, the following day after admission an interview with the psychiatrist will be arranged in order to collect the missing information. During this appointment cardiovascular and metabolic risk factors will be collected by a trained nurse, at first time in the morning after a 10 to 14h fasting period: blood pressure, waist circumference, BMI and a blood sample to obtain cholesterol, HDL and glucose levels.

Information regarding smoking habits, a previous diagnosis of hypertension, diabetes or dyslipidemia and its treatment, a family history of diabetes, hypertension or coronary heart disease, dietary habits and exercise routine will be obtained in this appointment by a nurse. When all the information obtained, cardiovascular disease risk using the REGICOR scale will be calculated, as well as the metabolic syndrome diagnosis.

The Insight Score Birchwood scale will be applied during this first appointment.

The inclusion in a psychosocial intervention program as a treatment will be offered by the psychiatrist.

- *Appointment 2:* the second appointment will be at the fourth week since the beginning of the study. It will be a follow – up appointment conducted by a psychiatrist. At the end of this appointment the final group to which the patient belongs will be obtained, deciding the type of intervention received. At the sub – acute unit, daily visits will be provided by a psychiatrists during this first month, and the acceptance of the intervention can be done at any time.

- *Appointment 3:* will be at week 6. Cardiovascular disease and metabolic risk factors will be obtained again by a trained nurse, as well as dietary and exercise habits, and antihypertensive and dyslipidemia treatment.

The GAF score will be calculated by a psychiatrist and by a psychologist in a personal interview, and pharmacological treatment used will be recorded by a psychiatrist, regarding the type of antipsychotic and its dose and posology, as well as any concomitant treatment.

- *Appointment 4:* will be at week 12. Cardiovascular disease and metabolic risk factors will be collected by a trained nurse, as well as dietary and exercise habits, and antihypertensive and dyslipidemia treatment.

- *Appointment 5:* at week 24, cardiovascular disease and metabolic risk factors will be collected by a trained nurse, as well as dietary and exercise habits, and antihypertensive and dyslipidemia treatment.

The GAF score will be calculated by a psychiatrist and a psychologist in a personal interview, and pharmacological treatment used will be recorded by a psychiatrist, regarding the type of antipsychotic and its dose and posology, as well as any concomitant treatment.

- *Appointment 6:* at week 48, cardiovascular disease and metabolic risk factors will be collected by a trained nurse, as well as dietary and exercise habits, and antihypertensive and dyslipidemia treatment.

The GAF score will be calculated by a psychiatrist and a psychologist in a personal interview, and pharmacological treatment used will be recorded by a psychiatrist, regarding the type of antipsychotic and its dose and posology, as well as any concomitant treatment.

- *Appointment 7:* at week 72, cardiovascular disease and metabolic risk factors will be collected by a trained nurse, as well as dietary and exercise habits, and antihypertensive and dyslipidemia treatment.

The GAF score will be calculated by a psychiatrist and a psychologist in a personal interview, and pharmacological treatment used will be recorded by a psychiatrist, regarding the type of antipsychotic and its dose and posology, as well as any concomitant treatment.

Appointments 3, 4, 5, 6 and 7 are follow – ups appointments in order to readjust medication when necessary and to control the evolution of the patient, and data mentioned will be collected even if not needed to the specific outcomes of the present study, as they may give valuable information.

- *Appointment 8:* at week 96, the end of the study period, cardiovascular disease and metabolic risk factors will be obtained after a 10 to 14h fasting period, as well as dietary and exercise habits, and antihypertensive and dyslipidemia treatment. When all the information obtained, cardiovascular disease risk using the REGICOR scale will be calculated by a trained nurse, as well as the metabolic syndrome diagnosis.

The GAF score will be calculated by a psychiatrist and a psychologist in a personal interview at this point.

The pharmacological treatment used will be recorded by a psychiatrist, regarding the type of antipsychotic and its dose and posology, as well as any concomitant treatment.

All the data necessary to estimate the global cost of the disease in both groups will be obtained during this phase.

Stage 5: Data Analysis

Duration: One month: September 2020.

Personnel: Principal investigator, statistician.

Description: All the data obtained will be analyzed by a statistician. A univariate, bivariate and multivariate analysis will be performed in order to examine the contribution of confounding variables.

Stage 6: Results' interpretation and writing

Duration: Three months, from October 2020 to December 2020.

Personnel: Principal investigator, collaborate investigators.

Description: Data obtained from the analysis will be received and investigators will interpret the results and extract the conclusions derived. The writing of the final article will be accomplished.

Stage 7: Publication and dissemination

Duration: From January 2021.

Personnel: Principal investigator, collaborate investigator.

Description: The study results will be presented by the main investigator and one collaborate investigator in the *Congreso nacional de psiquiatría* and in the *International Congress on Schizophrenia research*.

The final article will be sent, with the intention of being published, to the *Revista Española de Psiquiatría y Salud Mental*.

The study will be registered at the *European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCEPP)*.

| | | 2016 | | 2017 | | | 2018 | | 2019 | 2020 | | | 2021 | |
|--|--|------|-----|------|-------------|------------|-----------|-----------|-----------|------|-----------|------|-----------|----------|
| | | Nov | Dec | Jan | Feb - April | May - July | Aug - Dec | Jan - Aug | Sep - Dec | | Jan - Aug | Sept | Oct - Dec | From Jan |
| Stage 1 | | | | | | | | | | | | | | |
| Protocol design | Main investigator | | | | | | | | | | | | | |
| Protocol acceptance | CEIC and AEMPS | | | | | | | | | | | | | |
| Stage 2 | | | | | | | | | | | | | | |
| Coordination and organization | Main and collaborate investigators | | | | | | | | | | | | | |
| GAF formation course | Psychiatrists, psychologists | | | | | | | | | | | | | |
| Psychosocial intervention formation course | Psychiatrists, psychologists, social workers, nurses | | | | | | | | | | | | | |
| CVD and metabolic data collection course | Nurses | | | | | | | | | | | | | |
| Stage 3 | | | | | | | | | | | | | | |
| Participants' recruitment | Psychiatrists | | | | | | | | | | | | | |
| Stage 4 | | | | | | | | | | | | | | |
| Data collection | Psychiatrists, psychologists, nurses | | | | | | | | | | | | | |
| Stage 5 | | | | | | | | | | | | | | |
| Data analysis | Main investigator, statistician | | | | | | | | | | | | | |
| Stage 6 | | | | | | | | | | | | | | |
| Results' interpretation and writing | Main and collaborate investigators | | | | | | | | | | | | | |
| Stage 7 | | | | | | | | | | | | | | |
| Publication and dissemination | Main and collaborate investigators | | | | | | | | | | | | | |

Experience of the research team

Professionals working in the *Xarxa de Salut Mental de la província de Girona* have been working in the field of an integrated psychosocial intervention and a community treatment for several years. Yet in the 1980 the development of the Mental Health Centers, Day Hospital and Rehabilitation Centers allowed the system to treat patients with a more integrated and community based approach. It was in 2004, when the hospitalization of psychiatric patients was moved to the *Parc Hospitalari Martí i Julià*, ending with the psychiatric hospital previously existing. Thus determines an important event in the XSM history, being the only region in Catalonia that has closed the old psychiatric and long stay hospital.

Other aspects making the team innovative are the coordination and collaboration model used, being all the services connected and unified. It has been the first region integrating the mental health and addictions services in an unique network, as well as including family and user groups, the tutelary foundation and working resources to the decision making group.

Furthermore, the team has participated in evaluation projects such as the Refinement European study: *Research on financing systems effect on the quality of mental health care*. It analyzed the effect of the financing system in the quality of the mental health attention, comparing the XSM system with other innovative models used in Italy, Austria, England, France, Finland, Sweden, Estonia and Rumania. The results showed that despite being the system with less hospitalization beds, with a ratio of 6 per 100000 habitants, the XSM was the one using less sanitary resources (1.17 x 1000 habitants versus 3 x 1000 habitants in Europe), with a higher treatment continuity (90% versus 57% in Europe), a lower re – hospitalization rate (18% versus 40% in Europe), a higher community / hospital resources ratio (70/30) and one of the most accessible health services (68).

With all those results, the Community model applied in the XSM in Girona is considered a reference model, having recently received the *Medalla Josep Trueta* award, and is being studied by the WHO to convert it an International Reference Model (69).

Thus, it can be concluded that the *Xarxa de Salut Mental de la província de Girona* has enough ability and experience in the community and psychosocial intervention and will be capable of carrying the present study satisfactory.

Impact on the National Health System

It is estimated that around 450 million people worldwide will suffer a mental disease during the life – course. In Spain, it accounts for around 15% of the population. In Catalonia, the prevalence – life of mental disorders is estimated to be 23.68 (51). Regarding schizophrenia, around 300.000 people are diagnosed in Spain (3).

It is important that, despite the community treatment efficacy being well known and recommended, approximately a half of people in need of treatment do not receive it, and of those receiving it, an important proportion do not get the appropriate one (4,51,55). The evidence obtained performing the present study could help to increase the use of an integrated and personalized psychosocial intervention.

Mortality rate in people suffering from schizophrenia is two to three times higher than in general population. Of this, two thirds account for natural causes, the most common of which is cardiovascular disease, being the main cause pharmacological treatment with antipsychotics (13). For that reason, an integrated intervention could reduce mortality firstly by treating the patient as a whole, and secondly, if the hypothesis of the present study is confirmed, by reducing the pharmacological dose used, thus reducing the CVD risk and metabolic syndrome. That would improve not only mortality rates but also morbidity and quality of life, which can be deteriorated due to the side effects pharmacological treatment has. The impact mental disorders have in the quality of life is considered higher than the one that can have other chronic diseases (51).

Economically, despite little studies available in Spain, it has been estimated that the annual cost of mental diseases is around 3000 million euros (51). Of those, schizophrenia is considered the most expensive psychiatric disease (47). Among the direct costs of the disease, the most important contributor is hospital admissions, accounting for around 30% of the direct costs (51). As it has been exposed, there is several evidence showing that patients following an integrated psychosocial intervention have less re – admission episodes, thus reducing the hospitalization costs.

Pharmacological treatment with antipsychotics also accounts for an important part of the costs of the disease, arriving to 7.8% of the direct costs in Spain (51). Reducing pharmacological treatment with an integrated psychosocial intervention would reduce the global costs of the disease. The reduction of the cardiovascular and metabolic risk secondary to the antipsychotic use reduction, would decrease the pharmacological treatment needed to those risk factors, reducing its costs and its impact in the national economy.

Budget

| Personnel and personnel costs | | |
|---|--|-----------------|
| Statistician | 23.85 € / h (50) | 1192.5 € |
| GAF course training travelling | 10 € per travel (6) | 60 € |
| Psychosocial intervention program training travelling | 10 € per travel (6) | 60 € |
| CVD and metabolic data collection training travelling | 10 € per travel (6) | 60 € |
| Collaborate investigators meetings | 10 € per travel (4) per investigator (6) | 240 € |
| Total | | 1552.5 € |

| Material costs | | |
|---|-----------------------------------|---------------|
| Informed consent printing | 0.05 € x print (4) x person (148) | 29.6 € |
| Insight scale printing | 0.05 x print (1) x person (148) | 7.4 € |
| Involvement evaluation questionnaire printing | 0.05 x print (1) x person (148) | 7.4 € |
| Total | | 44.4 € |

| Publication and dissemination | | |
|---|-----------|--------|
| <i>Revista Española de Psiquiatría y Salud Mental</i> publication | | 1000 € |
| Congreso nacional de psiquiatría | | |
| Inscription fee | 400 € (2) | 800 € |
| Traveling | 200 € (2) | 400 € |
| Accommodation | 400 € (2) | 800 € |
| International congress on schizophrenia research | | |
| Inscription fee | 500 € (2) | 1000 € |

| | | |
|---------------|-----------|--------|
| Traveling | 500 € (2) | 1000 € |
| Accommodation | 400 € (2) | 800 € |
| Total | | 5800 € |

| Global cost of the study | |
|-------------------------------|----------|
| Personnel and personnel costs | 1552.5 € |
| Material costs | 44.4 € |
| Publication and dissemination | 5800 € |
| Total | 7396.9 € |

Before conducting the study, its financing must be ensured.

It is remarkable that only the service manager of each Mental Health Center will attend to the programmed meetings and will be responsible of transmit all the information among their center, thus reducing traveling costs. Meetings will be conducted in Parc Hospitalari Martí i Julià, in Girona, where the sub – acute unit and the Day Hospital are located.

Formation courses will be performed in each participant center to facilitate attendance, thus reducing traveling costs. It has to be mentioned that they will be conducted by the service manager of the Sub – acute unit, who will not receive any financial compensation. CVD data collection formation course will be performed by a trained nurse from the sub – acute unit, with the same conditions mentioned.

Only one collaborate investigator (service managers from each mental health centers, sub – acute unit and day hospital) will attend, together with the main investigator, to the national and international congress.

Investigators and health professionals participating in this study will not receive any financial compensation for their participation.

Informatics material and measurement instruments are not included in the budget, as they are available in each participant center. The case report form will be completed and recorded online and introduced in a data base, so printing costs will not be produced.

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Appendix 1

DSM – V Criteria for the diagnosis of schizophrenia (2)

| | |
|----------|--|
| A | Two (or more) of the following, each present for a significant portion of time during a 1 month period (or less if successfully treated). At least one of these must be (1), (2), or (3): 1. Delusions. 2. Hallucinations. 3. Disorganized speech (e.g., frequent derailment or incoherence). 4. Grossly disorganized or catatonic behavior. 5. Negative symptoms (i.e., diminished emotional expression or avolition). |
| B | For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning). |
| C | 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 (i.e., active-phase symptoms) 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 by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences). |
| D | Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness. |
| E | The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition. |
| F | If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia are also present for at least 1 month (or less if successfully treated). |

Specify if:

The following course specifiers are only to be used after a 1-year duration of the disorder and if they are not in contradiction to the diagnostic course criteria.

First episode, currently in acute episode: First manifestation of the disorder meeting the defining diagnostic symptom and time criteria. An acute episode is a time period in which the symptom criteria are fulfilled.

First episode, currently in partial remission: Partial remission is a period of time during which an improvement after a previous episode is maintained and in which the defining criteria of the disorder are only partially fulfilled.

First episode, currently in full remission: Full remission is a period of time after a previous episode during which no disorder-specific symptoms are present.

Multiple episodes, currently in acute episode: Multiple episodes may be determined after a minimum of two episodes (i.e., after a first episode, a remission and a minimum of one relapse).

Multiple episodes, currently in partial remission

Multiple episodes, currently in full remission

Continuous: Symptoms fulfilling the diagnostic symptom criteria of the disorder are remaining for the majority of the illness course, with subthreshold symptom periods being very brief relative to the overall course.

Unspecified

Specify if:

With catatonia (refer to the criteria for catatonia associated with another mental disorder, pp. 119-120, for definition).

Coding note: Use additional code 293.89 (F06.1) catatonia associated with schizophrenia to indicate the presence of the comorbid catatonia.

Specify current severity:

Severity is rated by a quantitative assessment of the primary symptoms of psychosis, including delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, and negative symptoms. Each of these symptoms may be rated for its current severity (most severe in the last 7 days) on a 5-point scale ranging from 0 (not present) to 4 (present and severe). (See Clinician-Rated Dimensions of Psychosis Symptom Severity in the chapter “Assessment Measures.”)

Note: Diagnosis of schizophrenia can be made without using this severity specifier

Appendix 2

ICD – 10 Criteria for de diagnosis of schizophrenia (1)

| | |
|----------|--|
| A | Thought echo, thought insertion or withdrawal, and thought broadcasting. |
| B | Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception. |
| C | Hallucinatory voices giving a running commentary on the patient's behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body. |
| D | 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). |
| E | 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. |
| F | Breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms. |
| G | Catatonic behavior, such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor. |
| H | "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. |
| I | A significant and consistent change in the overall quality of some aspects of personal behavior, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal. |

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 A to D above, or symptoms from at least two of the groups referred to as E to H, 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 (F23.2) and reclassified as schizophrenia if the symptoms persist for longer periods. Symptom I in the above list applies only to the diagnosis of Simple Schizophrenia (F20.6), and a duration of at least one year is required.

Viewed retrospectively, it may be clear that a prodromal phase in which symptoms and behavior, such as loss of interest in work, social activities, and personal appearance and hygiene, together with generalized anxiety and mild degrees of depression and preoccupation, preceded the onset of psychotic symptoms by weeks or even months.

Because of the difficulty in timing onset, the 1-month duration criterion applies only to the specific symptoms listed above and not to any prodromal nonpsychotic phase.

The diagnosis of schizophrenia should not be made in the presence of extensive depressive or manic symptoms unless it is clear that schizophrenic symptoms antedated the affective disturbance. If both schizophrenic and affective symptoms develop together and are evenly balanced, the diagnosis of schizoaffective disorder (F25.-) should be made, even if the schizophrenic symptoms by themselves would have justified the diagnosis of schizophrenia.

Schizophrenia should not be diagnosed in the presence of overt brain disease or during states of drug intoxication or withdrawal. Similar disorders developing in the presence of epilepsy or other brain disease should be coded under F06.2 and those induced by drugs under F1x.5.

Pattern of course

The course of schizophrenic disorders can be classified by using the following five-character codes:

| | |
|-----------------------------|--|
| <p>20.0 Paranoid</p> | <p>A. Delusions of persecution, reference, exalted birth, special mission, bodily change, or jealousy;</p> <p>B. Hallucinatory voices that threaten the patient or give commands, or auditory hallucinations without verbal form, such as whistling, humming, or laughing;</p> <p>C. Hallucinations of smell or taste, or of sexual or other bodily sensations; visual hallucinations may occur but are rarely predominant.</p> <p>The general criteria for a diagnosis of schizophrenia (see introduction to F20 above) must be satisfied. In addition, hallucinations and/or delusions must be prominent, and disturbances of affect, volition and speech, and catatonic symptoms must be relatively inconspicuous. The hallucinations will usually be of the kind described in B and C above. Delusions</p> |
|-----------------------------|--|

| | |
|------------------------------|---|
| | <p>can be of almost any kind but delusions of control, influence, or passivity, and persecutory beliefs of various kinds are the most characteristic.</p> |
| 20.1 Hebephrenic | <p>Affective changes are prominent, delusions and hallucinations fleeting and fragmentary, behavior irresponsible and unpredictable, and mannerisms common. The mood is shallow and inappropriate and often accompanied by giggling or self-satisfied, self-absorbed smiling, or by a lofty manner, grimaces, mannerisms, pranks, hypochondriacal complaints, and reiterated phrases. Thought is disorganized and speech rambling and incoherent. There is a tendency to remain solitary, and behavior seems empty of purpose and feeling.</p> <p>The general criteria for a diagnosis of schizophrenia (see introduction to F20 above) must be satisfied. Hebephrenia should normally be diagnosed for the first time only in adolescents or young adults. The premorbid personality is characteristically, but not necessarily, rather shy and solitary. For a confident diagnosis of hebephrenia, a period of 2 or 3 months of continuous observation is usually necessary, in order to ensure that the characteristic behaviors described above are sustained.</p> |
| 20.2 Catatonic | <p>The general criteria for a diagnosis of schizophrenia (see introduction to F20 above) must be satisfied. Transitory and isolated catatonic symptoms may occur in the context of any other subtype of schizophrenia, but for a diagnosis of catatonic schizophrenia one or more of the following behaviors should dominate the clinical picture:</p> <ul style="list-style-type: none"> A. Stupor (marked decrease in reactivity to the environment and in spontaneous movements and activity) or mutism; B. Excitement (apparently purposeless motor activity, not influenced by external stimuli); C. Posturing (voluntary assumption and maintenance of inappropriate or bizarre postures); D. Negativism (an apparently motiveless resistance to all instructions or attempts to be moved, or movement in the opposite direction); E. Rigidity (maintenance of a rigid posture against efforts to be moved); F. Waxy flexibility (maintenance of limbs and body in externally imposed positions); and G. Other symptoms such as command automatism (automatic compliance with instructions), and perseveration of words and phrases. |
| 20.3 Undifferentiated | <p>This category should be reserved for disorders that:</p> <ul style="list-style-type: none"> A. Meet the general criteria for schizophrenia; B. Either without sufficient symptoms to meet the criteria for only one of the subtypes F20.0, F20.1, F20.2, F20.4, or F20.5, or with so many symptoms that the criteria for |

| | |
|---|--|
| | more than one of the paranoid (F20.0), hebephrenic (F20.1), or catatonic (F20.2) subtypes are met. |
| 20.4 Post schizophrenic depression | <p>The diagnosis should be made only if:</p> <ul style="list-style-type: none"> A. The patient has had a schizophrenic illness meeting the general criteria for schizophrenia (see introduction to F20 above) within the past 12 months; B. Some schizophrenic symptoms are still present; and C. The depressive symptoms are prominent and distressing, fulfilling at least the criteria for a depressive episode (F32.), and have been present for at least 2 weeks. |
| 20.5 Residual | <p>For a confident diagnosis, the following requirements should be met:</p> <ul style="list-style-type: none"> A. Prominent "negative" schizophrenic symptoms, i.e. psychomotor slowing, underactivity, blunting of affect, passivity and lack of initiative, poverty of quantity or content of speech, poor nonverbal communication by facial expression, eye contact, voice modulation, and posture, poor self-care and social performance; B. Evidence in the past of at least one clear-cut psychotic episode meeting the diagnostic criteria for schizophrenia; C. A period of at least 1 year during which the intensity and frequency of florid symptoms such as delusions and hallucinations have been minimal or substantially reduced and the "negative" schizophrenic syndrome has been present; D. Absence of dementia or other organic brain disease or disorder, and of chronic depression or institutionalism sufficient to explain the negative impairments. |
| 20.6 Simple | Slowly progressive development of the characteristic "negative" symptoms of residual schizophrenia (see F20.5 above) without any history of hallucinations, delusions, or other manifestations of an earlier psychotic episode, and with significant changes in personal behavior, manifest as a marked loss of interest, idleness, and social withdrawal over a period of at least one year. |
| 20.7 Others | <p>Cenesthopathic schizophrenia</p> <p>Schizophreniform disorder NOS</p> |
| 20.8 Unspecified | |

Appendix 3

Xarxa de Salut Mental de la província de Girona (42)

The *Xarxa de Salut Mental de la província de Girona* (XSM) is an integrated system conducted by l'*Institut d'Assistència Sanitària de Catalunya* (IAS), and englobes all the services available regarding mental health. The XSM is organized in two main spheres, briefly summarized as follows:

Hospital attention

Provided in the *Parc Hospitalari Martí I Julià*, in Girona.

1. Santa Caterina Hospital

- *Emergency room*: Patients can go voluntary, derived by any community service or by other hospitals from the area.
- *Acute unit*: Provided with 42 beds.
- *Acute unit for children and adolescents*: With 10 beds.
- *Detoxification unit*: Having 4 beds.

2. Dual pathology unit: Available to treat patients with several mental disorders concomitant with substance abuse disorder.

3. Rehabilitation service:

- *Sub – acute unit*: For the admission and treatment of people with severe mental disorders.
- *Medium and Long stay unit*: For people from the old psychiatric who have not been possible to externalize.

4. Til·lers

- *Adult day hospital and Children day hospital*: Both providing psychosocial interventions for severe mental disorders. Is an intermediate treatment place, for people discharged from hospitalization in need of a more intensive intervention than the offered at the Mental Health Center.

It is important to outline that day hospital is a service included in the “Community attention”, but, due to infrastructural issues, it is located in the hospital precinct.

- *Intellectual disability services.*

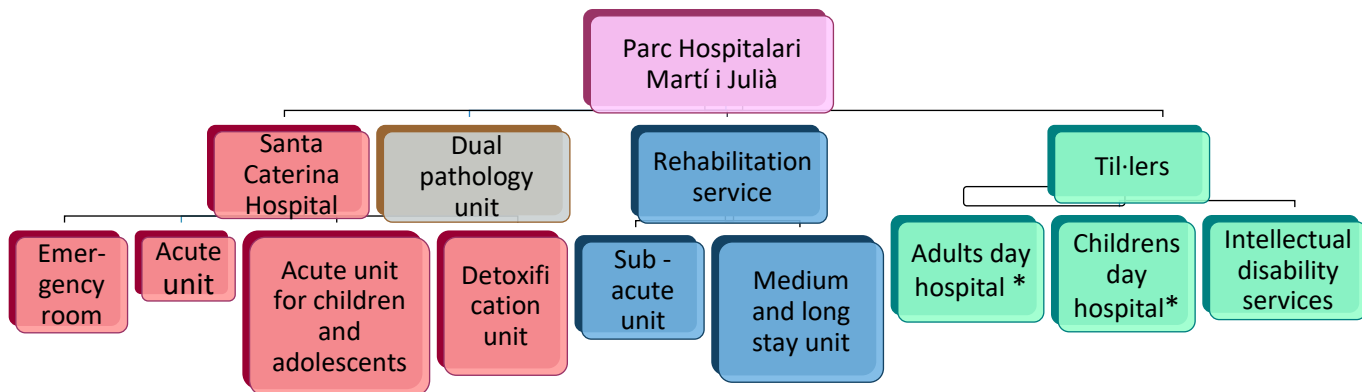


Figure 1: Hospital Attention services. *Source: Author*

*Included in the community attention services.

Community attention

Organized in seven areas: Alt Empordà, Baix Empordà, Gironès – Pla de l’Estany, La Garrotxa, Ripollès, La Selva Interior and La Selva Marítima.

1. Mental Health Center for adults and for children and adolescents: Its function is to attend patients derived from primary care services, as well as patients discharged from hospital or in rehabilitation programs. Regarding severe mental illnesses such as Schizophrenia, each patient has his/her reference psychiatrist, and the different psychosocial interventions available are offered in here, to both the patient and the family.
2. Psychosocial Rehabilitation Center: Working together with the Mental Health Center, Psychosocial Rehabilitation Center offers a range of programs going from social skills training, psychoeducation, cognitive rehabilitation and daily activities to family interventions.
3. Drug – Dependence Center: Present in all areas except La Selva interior, which are relocated to Gironès – Pla de l’Estany center.

4. Supported flats: For people suffering a severe mental illness a shared flat program can be offered, with regular external visits and support.

5. Residence "La Maçana": Only available in Girona, it offers a place with continuous support but trying to normalize as much as possible the daily living, adapting the person with a severe mental illness to live in a less dependent place, which can go from other support living services to their own home.

6. Early psychosis intervention program: Available in two areas: Gironès – Pla de l'Estany and La Selva Marítima. For an integrated treatment of people with a high risk mental status or with a first episode of psychosis ranging from 16 to 35 years old.

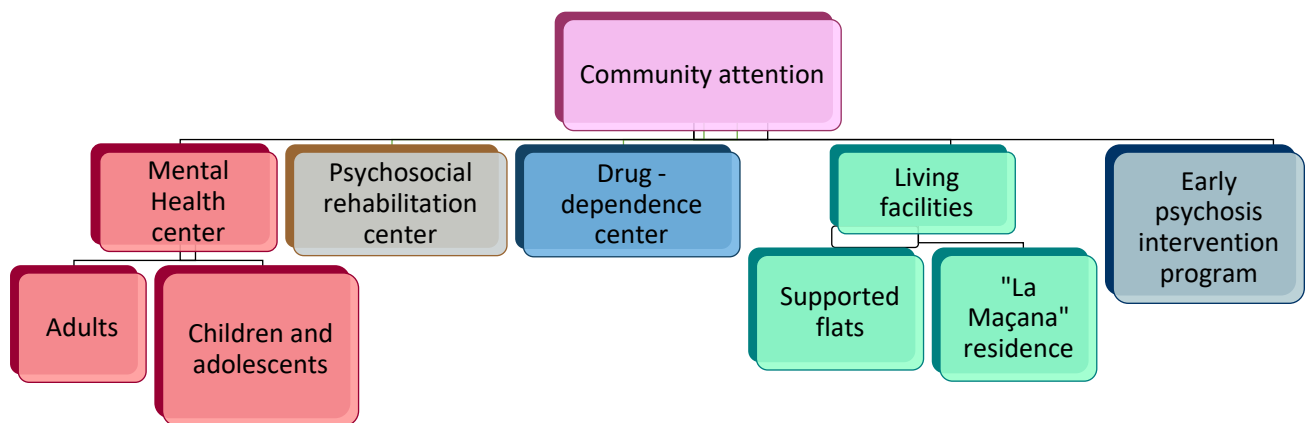


Figure 2: Community Attention services. *Source: Author*

Other services attached to XSM

1. Supported employment- Drissa Foundation: Drissa is a private foundation aiming to provide reinsertion into the working world for people suffering a severe mental illness. It offers the following programs:

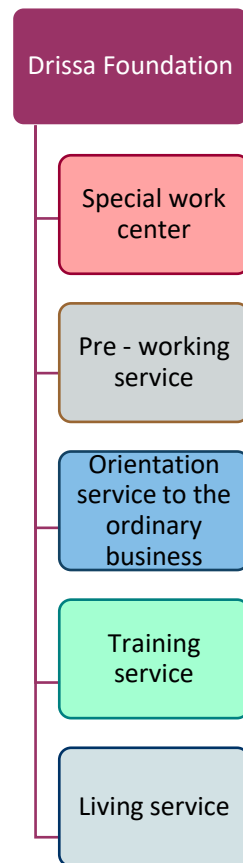


Figure 3: Drissa Foundation services. *Source: Author*

2. Tutelar foundation: Addressed to people who have been incapacitated, providing tutelar charge to help with several aspects in the day to day life.

Appendix 4

Criteria for the diagnosis of a severe mental illness

For the diagnosis of a severe mental illness, according to the National Institute of Mental Health (NIMH), the following criteria are required (28):

1. Diagnosis of a psychotic disorder according to the ICD – 10 criteria (in that case, it must be schizophrenia).
2. Presence of the disease during 2 or more years, or a severe and progressive deterioration of the functioning during the last 6 months (with a high risk of developing a chronic disease).
3. Presence of disability, producing important limitations in personal, functional, social and familiar functioning, defined as a GAF scale inferior to 70.

Appendix 5

Psychosocial and other resources interventions

Cognitive Behavioral Therapy: The main aspects addressed will be:

- Monitoring and acceptance of the patients' thoughts, feelings and actions.
- Promotion of rational or adaptive pathways to solve conflicts and stress reduction strategies.
- Development of a new comprehension of the patients' experiences.

CBT is highly recommended since the onset of an acute episode of schizophrenia, and should be continued during the stabilization phase, especially in those whose symptomatology have not responded to pharmacological treatment. It should be approximately 4 – 9 months in duration (4,29).

In patients hospitalized the therapy will be performed twice a week. In patients linked with the Day Hospital the intervention will be conducted once a week. In patients attending to the Mental Health Center, the intervention will be conducted monthly. A group therapy will be conducted every two weeks. The intervention will be applied by a psychologist.

Cognitive Rehabilitation: Using the strategies of restauration and compensation mentioned, according to the patients' needs. Cognitive rehabilitation will be conducted by a psychologist during a period of 4 - 9 months, two times a week at hospitalization, once a week at day hospital and monthly at the Mental Health Center.

Social Skills Training: In order to acquire the behavior needed to achieve an adequate social interaction, independent living and other outcomes needed to community functioning, different modules will be treated: free – time abilities, basic communication abilities, friendship and couple relationships, work basic abilities, medication use, symptomatology management, substance abuse management and prevention and community reincorporation.

Those modules will be treated using a role playing model in group sessions, as well as the positive reinforcement technique and feed – backs.

Since the stabilization of the acute phase, social skills training will be attended from 4 to 9 months. It is important to conduct this intervention together with a psychoeducation program. Social skills training will be conducted twice a week at hospitalization, once a week at day

hospital and monthly at the Mental Health Center. A psychologist together with a nurse will conduct the activity.

Psychoeducation: Psychoeducation is an intervention aiming to provide specific information and knowledge about the disease and about different techniques to confront the problems than can arise from it.

The general structure of the intervention will be:

1. Brief explanation of the state and feelings of the participants.
2. Summary of the aspects treated in the previous session.
3. List and immersion in the main aspects of the present session.
4. Manifest of the actual feelings of each participant after the session.

Psychoeducation can be done individually and in groups, being preferred the last option. It can be started after the acute symptoms remission, during a period of 9 months. At the hospital, psychoeducation will be conducted three times a week. In patients going to the day hospital, once a week. At the Mental Health Center, psychoeducation will be performed monthly. Together with the psychologist, an expert – user, a person who has the disease and is currently in a stable phase due to treatment, will conduct the intervention, also providing information from personal experiences.

Family Intervention: This intervention is based on the building of a strong alliance with the family and the caregivers of the person affected with schizophrenia. Its aim is to provide information about the disease, help families to manage the stress caused by the situation and to manage the adversities and conduct problems that can appear during the course of the disease. Family interventions can be conducted individually in the form of a behavioral family therapy (BFT) or in a relatives group (RG).

Since the acute episode, and during a period from 9 months to 2 years, depending on the needs, a behavioral family therapy will be conducted by a psychologist and a psychiatrist once a week, in the hospitalization period, in those patients with family support, focusing mainly in the Expressed Emotion. At the Mental Health Center, individual family interventions will be attended once a month.

Families will be also included at a relatives group, having a session every two weeks and completing a 10 session program

Assertive Community Treatment: Assertive community treatment will include visits at home or at the supervised living place with revision and education in difficulties experienced in

medication use or daily living in those patients at high risk of disengagement from the XSM. Visits will be done once a week by a nurse and an occupational therapist, being reduced progressively according to the patients' progress.

Supported Employment: This intervention will be included once the patient has gone through the acute phase, and will be provided by the Drissa foundation. For patients without a job measures to achieve immediate incorporation in the labor market will be conducted, such as Pre – working service, orientation service to the ordinary business and training service. A special work center is also available, providing special jobs for people who have attended the services mentioned. For those with a job the support will be mostly focused in the maintenance of the work place (**See Appendix 3**).

Living Resources: depending on the situation of the participant, several types of living supports are available:

- **Autonomic living:** the patient lives independently, only with individualized following from external resources when needed and arranged visits.
- **Domiciliary help:** intervention in the patient's home, living alone or with relatives, providing help in day to day activities and self – care. A nurse together with an occupational therapist will visit the patient once a week, diminishing the visits according to the patients' evolution to one every two weeks, and finally, to a monthly visit.
- **Protected living:** consisting in a flat with 4 – 6 places with professional support and assessment in the daily living activities and integration. Nurses will provide daily assistance. The Drissa foundation also offers a total of six protected flats for those patients included in the foundation project.
- **Residence:** with assistance 24 hours a day. For people with severe mental illness who are not prepared to live independently. "Llar Residència La Maçana" is the residence available in Girona.

In patients hospitalized in a Sub – acute unit, before providing any living resource, the project *Pis Escola* will be attended. Its objective is to provide the necessary skills and information to be able to start living out of the hospital, combining self – care, productivity and free time, as well as to foment a healthy and active lifestyle and identify and solve dangerous situations at home (42). *Pis escola* will be performed in 5 hour sessions twice a week for a period of three weeks by an occupational therapist and a nurse.

Appendix 6

Global Assessment of Functioning Scale

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health - illness. Do not include impairment in functioning due to physical (or environmental) limitations.

Note: Use intermediate codes when appropriate e.g: 45, 72, 68.

| | |
|--------|--|
| 100-91 | Superior functioning in a wide range of activities, life problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms. |
| 90-81 | Absent or minimal symptoms (e.g., mild anxiety before an exam), good functioning in all areas, interested and involved in a wide range of activities. Socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g. an occasional argument with family members). |
| 80-71 | If symptoms are present, they are transient and expectable reactions to psychosocial stressors (e.g., difficulty concentrating after family argument); no more than slight impairment in social, occupational or school functioning (e.g., temporarily failing behind in schoolwork). |
| 70-61 | Some mild symptoms (e.g. depressed mood and mild insomnia) OR some difficulty in social, occupational, or school functioning (e.g., occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships. |
| 60-51 | Moderate symptoms (e.g., flat affect and circumstantial speech, occasional panic attacks) OR moderate difficulty in social, occupational, or school functioning (e.g., few friends, conflicts with peers or co-workers). |
| 50-41 | Serious symptoms (e.g. suicidal ideation, severe obsessional rituals, frequent shoplifting) OR any serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job). |
| 40-31 | Some impairment in reality testing or communication (e.g., speech is at times illogical, obscure, or irrelevant) OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school). |
| 30-21 | Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) OR inability to function in almost all areas (e.g., stays in bed all day; no job, home, or friends). |
| 20-11 | Some danger of hurting self or others (e.g., suicide attempts without clear expectation of death; frequently violent; manic excitement) OR occasionally fails to maintain minimal personal hygiene (e.g., smears feces) OR gross impairment in communication (e.g., largely incoherent or mute). |
| 10-1 | Persistent danger of severely hurting self or others (e.g., recurrent violence) OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death. |
| 0 | Inadequate information. |

Appendix 7

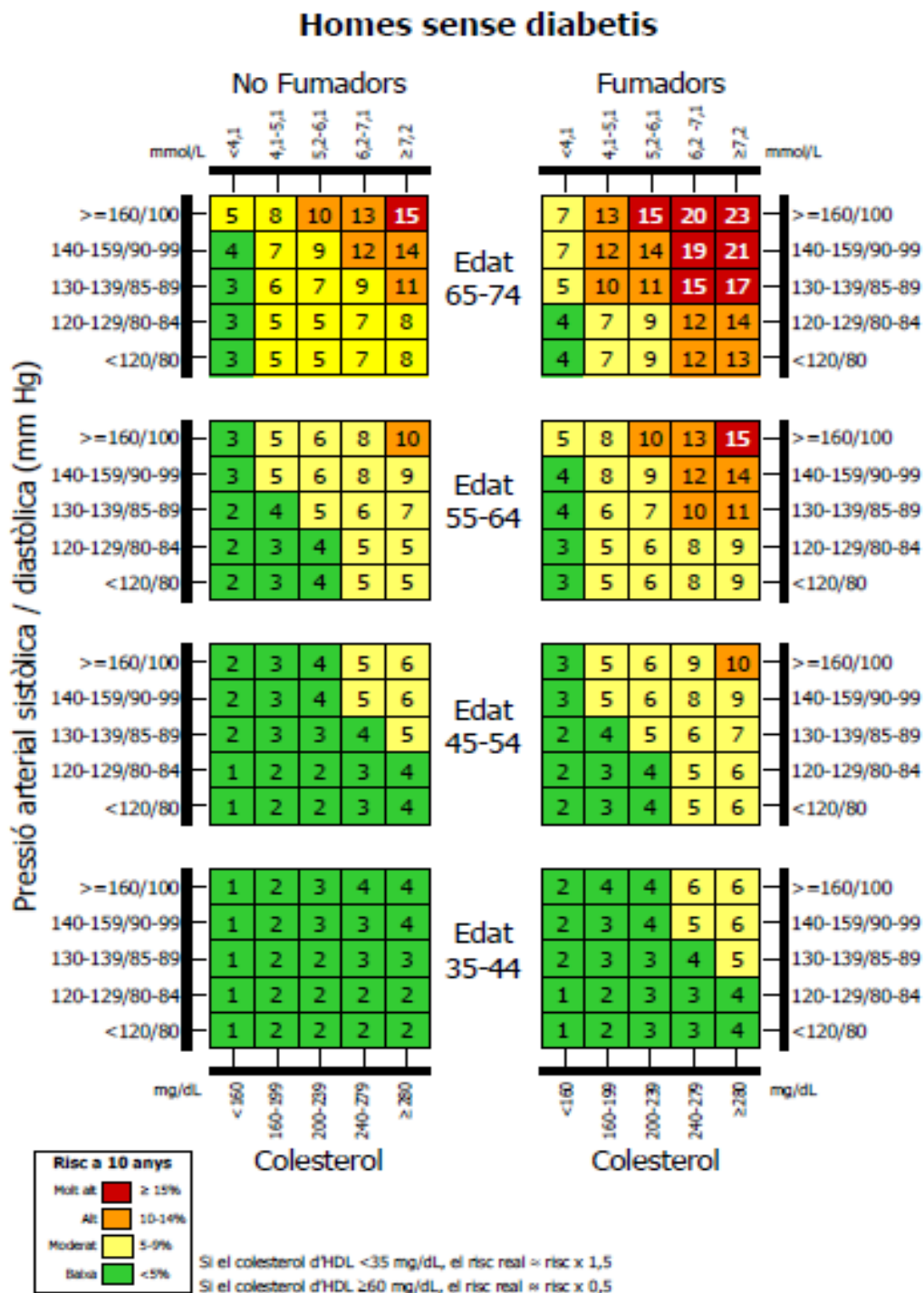
Bioequivalences of the different antipsychotics

| Antipsychotic | 1 mg/d olanzapine equivalent |
|------------------------|-------------------------------------|
| Chlorpromazine | 26.6 mg/d |
| Flupentixol | 0.8 md/d |
| Flupentixol depot | 2.66 mg/week |
| Fluphenazine | 0.53 md/d |
| Fluphenazine depot | 1.33 mg/week |
| Haloperidol | 0.53 mg/d |
| Haloperidol depot | 3.99 mg/week |
| Perphenazine | 2.66 mg/d |
| Pimozide | 0.53 mg/d |
| Pipotiazine depot | 2.66 mg/week |
| Sulpiride | 20 mg/d |
| Trifluoperazine | 1.33 mg/d |
| Zuclopenthixol | 6.65 mg/d |
| Zuclopenthixol depot | 26.6 mg/d |
| Aripiprazole | 1.33 mg/d |
| Aripiprazole Depot | 26.6 mg/month |
| Asenapine | 1.33 mg/d |
| Clozapine | 40 mg/d |
| Iloperidone | 1.07 mg/d |
| Lurasidone | 5.33 mg/d |
| Olanzapine | 1 mg/d |
| Paliperidone | 0.4 md/d |
| Paliperidone palmitate | 10 mg/month |
| Quetiapine | 20 mg/d |
| Risperidone | 0.27 mg/d |
| Risperidone LAI | 5 mg/2 weeks |
| Sertindole | 1.60 mg/d |
| Ziprasidone | 5.33 mg/d |

Calculated from data obtained from “Dose equivalents for second generation antipsychotics: The minimum effective dose method” (60), “The Maudsley Prescribing Guidelines in Psychiatry” (71) and “International consensus study of antipsychotic dosing” (72)

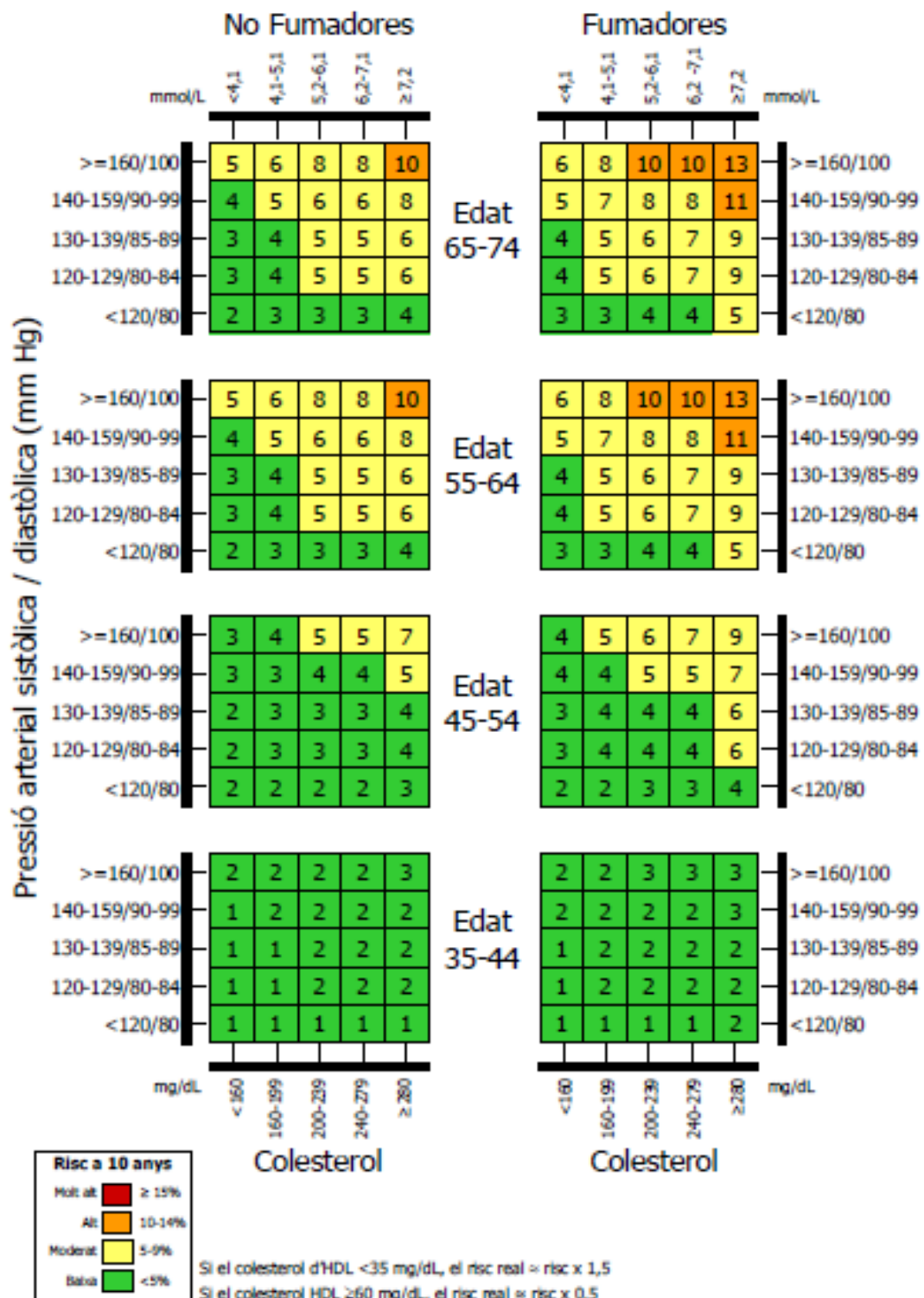
Appendix 8

REGICOR scale for the determination of the 10 – year cardiovascular risk factor



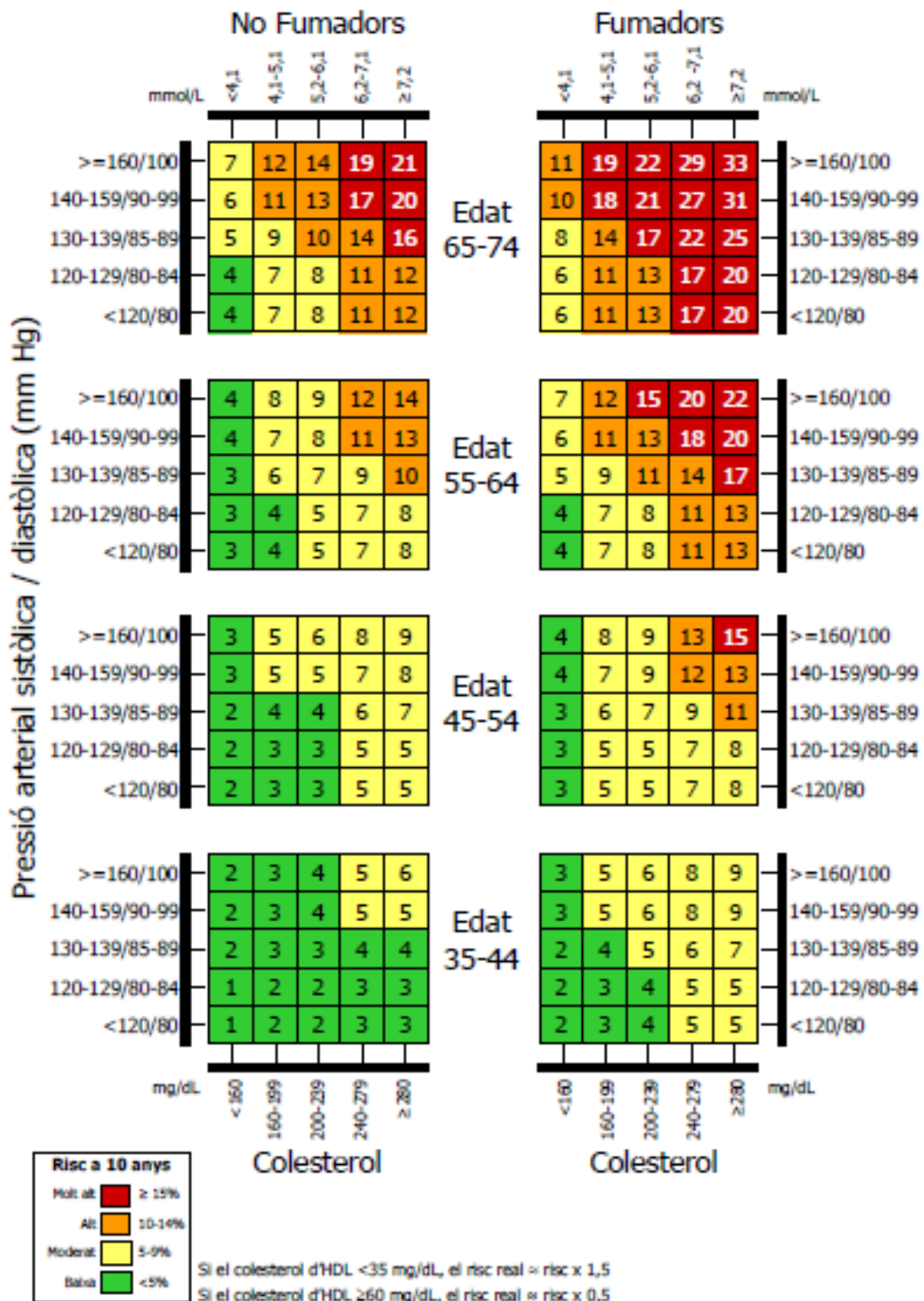
Original from "Taules per al càlcul del risc coronari en 10 anys: Adaptació de les taules de Framingham a la població de Catalunya" (73)

Dones sense diabetis



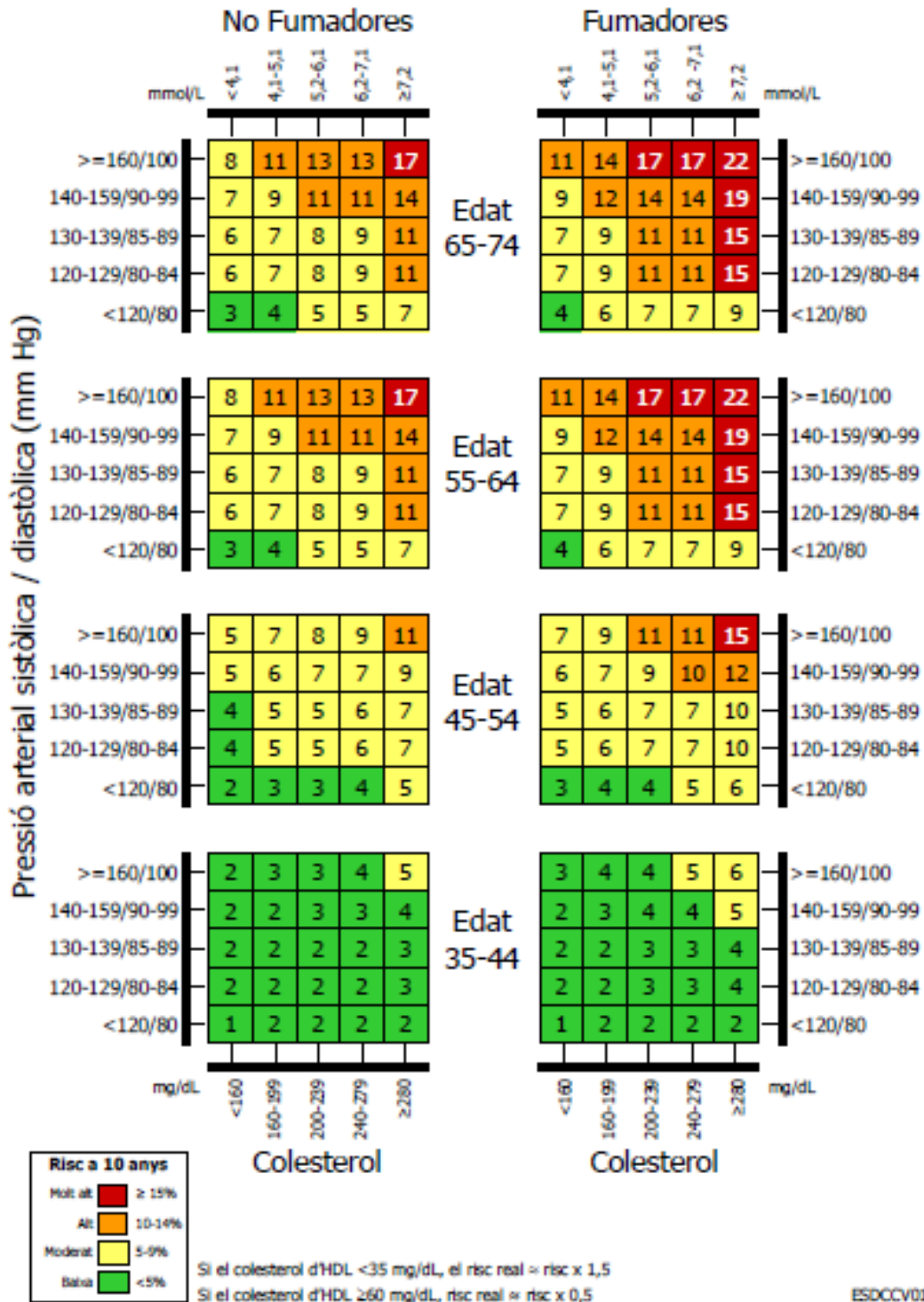
Original from "Taules per al càlcul del risc coronari en 10 anys: Adaptació de les taules de Framingham a la població de Catalunya" (73)

Homes amb diabetis



Original from "Taules per al càlcul del risc coronari en 10 anys: Adaptació de les taules de Framingham a la població de Catalunya" (73)

Dones amb diabetis



Original from "Taules per al càlcul del risc coronari en 10 anys: Adaptació de les taules de Framingham a la població de Catalunya" (73)

Appendix 9

Involvement Evaluation Questionnaire - European Version

The following questions are about the financial cost to you and your household, as a result of your relative/friend's mental health problems

Have you, during the past four weeks, had to incur extra expenses on behalf of your relative friend?

| | YES | NO |
|---|-----|----|
| Professional help for your relative/friend | | |
| Damage caused by your relative/friend | | |
| Large expenditures incurred by your relative/friend | | |
| Relative/friend's travel expenses | | |
| Medicine for your relative/friend | | |
| Paying off debts incurred by your relative/friend | | |
| Other expenses | | |

If you add up all the extra expenses which you have incurred on behalf of your relative/friend during the past four weeks, what is the estimated total figure?

| | |
|--|----------------|
| | Less than 25€ |
| | 25 – 50 € |
| | 50 – 125 € |
| | 125 – 250 € |
| | More than 250€ |

Original from "Consequences for caregivers of patients with severe mental illness: the development of the Involvement Evaluation Questionnaire – Appendix II: IEQ - EU" (74)

Appendix 10

Spanish adaptation of the Insight scale Birchwood

| | |
|---------------------------|--------|
| Nombre: | |
| Lugar de administración: | Edad: |
| Diagnóstico del paciente: | Fecha: |

Por favor, lea las siguientes frases atentamente y señale el recuadro que mejor se aplique en su caso

| | Estoy de acuerdo | Estoy en desacuerdo | No lo sé |
|--|------------------|---------------------|----------|
| 1. Algunos de los síntomas fueron producto de mi mente | | | |
| 2. Estoy bien mentalmente | | | |
| 3. No necesito medicación | | | |
| 4. Mi estancia en el hospital fue necesaria | | | |
| 5. El doctor tiene razón al prescribirme medicación | | | |
| 6. No necesito ser visto por un médico o psiquiatra | | | |
| 7. Si alguien dijese que he tenido una enfermedad mental o de los nervios, tendría razón | | | |
| 8. Ninguna de las cosas extrañas que he experimentado son debidas a una enfermedad | | | |

Original adaptation from Camprubí, N. and Almela, A. 2008 (66)

Appendix 11

Case report form

Nº historia clínica:

Fecha:

Participante nº:

Sexo:

Edad:

Estado civil: Soltero Divorciado Casado / en pareja

Nivel educacional: Ninguno Educación primaria Educación secundaria
 Superior

Situación laboral: Empleado Desempleado

Soporte familiar: Sí No

Años desde el diagnóstico de esquizofrenia:

| | Inicio | Semana 6 | Mes 6 | Mes 12 | Mes 18 | Mes 24 |
|-----------------------|--------|----------|-------|--------|--------|--------|
| Puntuación GAF | | | | | | |

| Antipsicótico | Previo al inicio (Si/No) | Inicio | Semana 6 | Mes 6 | Mes 12 | Mes 18 | Mes 24 |
|---------------------------------------|---------------------------------|---------------|-----------------|--------------|---------------|---------------|---------------|
| Tipo | | | | | | | |
| Dosis | | | | | | | |
| Posología | | | | | | | |
| Tratamiento Concomitante. Tipo | | | | | | | |

| Hospitalizaciones | Inicio | Mes 24 |
|--------------------------|---------------|---------------|
| Número | | |
| Duración (media) | | |

| | Inicio | Cambio de tratamiento (si procede) |
|----------------------------------|---------------|---|
| Puntuación escala Insight | | |

Intervención psicosocial Sí No

En caso afirmativo:

| | Terapia familiar | Tratamiento asertivo comunitario | Recursos de vivienda | Recursos laborales |
|-----------------------------|------------------|----------------------------------|----------------------|--------------------|
| Ha asistido | | | | |
| Duración | | | | |
| Otra información de interés | | | | |

| | Terapia cognitivo conductual | Habilidades sociales | Rehabilitación social | Psicoeducación |
|-----------------------------|------------------------------|----------------------|-----------------------|----------------|
| Ha asistido | | | | |
| Duración | | | | |
| Otra información de interés | | | | |

Valoración riesgo cardiovascular y síndrome metabólico

| | Inicio | Semana 6 | Mes 3 | Mes 6 | Mes 12 | Mes 18 | Mes 24 |
|-------------------------------------|--------|----------|-------|-------|--------|--------|--------|
| Hª familiar patología CV | | | | | | | |
| IMC | | | | | | | |
| Circunferencia cintura | | | | | | | |
| Fumador | | | | | | | |
| Presión arterial | | | | | | | |
| Tratamiento antihipertensivo | | | | | | | |
| Diabetes | | | | | | | |
| HDL | | | | | | | |
| Colesterol total | | | | | | | |
| Tratamiento dislipemiente | | | | | | | |
| Hábitos dietéticos | | | | | | | |
| Ejercicio físico | | | | | | | |
| Riesgo CV REGICOR | | | | | | | |
| Síndrome metabólico | | | | | | | |

Valoración de costes

| | Fármaco utilizado / dosis | Coste diario | Días utilización | Coste total |
|------------------------------------|---------------------------|--------------|------------------|-------------|
| Antipsicótico (Para mantenimiento) | | | | |
| Antidepresivo | | | | |
| Ansiolítico | | | | |
| Otra medicación concomitante | | | | |
| Antihipertensivo | | | | |
| Antidiabético | | | | |
| Antidislipemiente | | | | |

| | Coste aproximado por paciente | Número de días de uso del servicio | Coste total |
|---|--|--|-------------|
| Hospitalización por el presente episodio | Agudos: 284.31€ Sub-agudos: 161.12€ | Días en agudos: Días en sub-agudos: | |
| Hospitalizaciones agudas por reingresos | 284.31 € | | |
| Hospitalizaciones sub – agudas por reingresos | 161.12€ | | |
| Consultas urgencias | 136.12€ | | |
| CSM | 96.54€ | | |

| | | | |
|-----------------------------|--|--|--|
| Hospital de día | 67.24€ | | |
| Centro de día | 96.54€ | | |
| Soporte de empleo | | | |
| Recursos de vivienda | Llar residencia : 71.97€ Pis escola: Pis protegit: | | |

| Paciente | Ganancia media teórica diaria | Días perdidos por enfermedad mental | Pérdida económica total |
|-----------------|--------------------------------------|--|--------------------------------|
| Desempleados | 23.59€ | | |
| Empleados | 23.59€ | | |

| Cuidador | Salario mínimo interprofesional diario | Días perdidos por enfermedad mental | Otras pérdidas económicas (Involvement evaluation questionnaire) | Pérdida económica total |
|-----------------|---|--|---|--------------------------------|
| Desempleados | 23.59€ | | | |
| Empleados | 23.59€ | | | |

Appendix 12

Hoja informativa para el participante

Estimado/a:

Agradecemos su interés y participación en el presente estudio llevado a cabo a través de la Red de Salud Mental de la provincia de Girona. Su colaboración es de gran ayuda para poder desarrollar de manera adecuada el proyecto ideado. A continuación le exponemos detalladamente los motivos del presente estudio, así como los detalles que de este necesita conocer. Por favor lea atentamente toda la información, y no dude en consultar cualquier aspecto con la persona que le entrega el presente documento, si lo considera necesario.

¿Por qué se realiza este estudio?

La esquizofrenia es una de las enfermedades mentales más frecuentes e incapacitantes en nuestro medio. Afecta tanto a mayores como a jóvenes, ocasionando una importante discapacidad, con elevados índices de morbi-mortalidad, debido a su curso crónico. Pese a la eficacia demostrada de su tratamiento farmacológico, una parte importante de la sintomatología no responde lo suficiente a este tratamiento. Además, los fármacos antipsicóticos tienen un importante efecto negativo sobre los factores de riesgo cardiovasculares, así como sobre diferentes parámetros metabólicos. Esto empeora la morbi-mortalidad del que sufre dicha enfermedad.

Con el presente estudio se pretende valorar si la realización de un abordaje psicosocial amplio y personalizado permite reducir las dosis de fármacos con las que se encuentran los pacientes, y de esta manera se reducen así los efectos secundarios que de estos surgen. Esto permitiría mejorar la calidad de vida y el pronóstico de los pacientes afectados, además de tener un importante impacto económico sanitario.

¿Por qué debo ser seguido durante dos años?

Es importante valorar las dosis a las que la persona afecta de esquizofrenia se mantiene en una situación estable. Para ello es necesario dejar pasar un periodo considerable de tiempo desde el empeoramiento de la clínica, así como desde el inicio del abordaje psicosocial. Además, es interesante valorar como todo ello afecta a los factores de riesgo cardiovasculares a largo plazo. Por ello un periodo de dos años se ha considerado necesario y suficiente para realizar el estudio.

¿Qué debo hacer al participar en el estudio?

Únicamente deberá atender a las visitas acordadas con los profesionales que le atiendan en el centro en el cual esté siendo tratado, ya sea en la unidad de sub – agudos, en el hospital de día o en su centro de salud mental de referencia. En ellas, inicialmente se le harán un seguido de preguntas relacionadas con sus antecedentes e información personal. En las siguientes, se obtendrán los datos necesarios para calcular el riesgo cardiovascular, así como la presencia del llamado síndrome metabólico. Además, se le proporcionará algún cuestionario a rellenar, tanto a usted como a su familiar cuidador, con fines científicos, siempre explicándole previamente el motivo de dicha prueba, así como su funcionamiento. Las visitas quedan acordadas de la siguiente manera: al día siguiente de la llegada, a la semana 4, semana 6, mes 3, mes 6, mes 12 mes 18 y mes 24. Deberá atender pero con una frecuencia mayor para recibir el tratamiento acordado.

Deberá además cumplir el tratamiento pautado, tanto farmacológico como psicosocial, en el caso de haberlo aceptado, con las pautas estipuladas por los profesionales.

¿Puedo salir perjudicado al participar en el estudio?

No. El presente estudio está diseñado bajo unos principios legales y éticos, garantizando que ningún participante salga perjudicado por el hecho de participar en el estudio.

¿Y si cambio de opinión?

En todo momento podrá cambiar el tratamiento acordado inicialmente. Así, si decide iniciar un abordaje psicosocial íntegro, aun habiéndolo rechazado inicialmente, podrá incorporarse inmediatamente a éste. Lo mismo ocurre en el caso contrario. No obstante, si ha transcurrido más de un mes desde el inicio del estudio, quedará excluido del mismo, sin esto afectar al tratamiento que seguirá recibiendo.

Si usted desea dejar de formar parte del estudio, podrá comunicarlo en cualquier momento, sin esto afectar al tratamiento recibido ni a su seguimiento.

¿Se harán públicos mis datos, una vez acabado el estudio?

No. Sus datos quedan totalmente protegidos por la *Ley Orgánica 15/1999 de 13 de diciembre, de Protección de Datos de Carácter Personal*, siendo su información totalmente confidencial. Los datos médicos necesarios para el estudio serán publicados de manera totalmente anónima.

¿Una vez finalizado el estudio, tendré acceso a los resultados?

Sí. Todos los participantes en el estudio, tendrán derecho a acceder a la información y conclusiones que de este se deriven, así como a una explicación de los datos obtenidos en su persona, siempre que se desee.

Hoja de consentimiento informado

Yo (Nombre y apellidos) _____:

- He leído detalladamente y comprendido toda la información proporcionada acerca de la participación en el presente estudio
- He recibido toda la información necesaria acerca del estudio
- Me ha sido explicada mi participación en el estudio de manera clara
- He podido resolver todas las dudas que tenía respecto el estudio y mi papel en él
- He entendido claramente cuál será mi papel en el estudio, y a qué debo comprometerme en cuanto al cumplimiento de mi tratamiento y visitas
- He comprendido la voluntariedad de mi participación, pudiendo en cualquier momento retirarme del presente estudio, recibiendo independientemente el tratamiento necesario

Con todo ello, acepto participar en el estudio.

Firma y fecha:

Firma del profesional que le atiende:

Full informatiu per al participant

Estimat / estimada :

Agraïm el seu interès i participació al present estudi dut a terme a través de la Xarxa de Salut Mental de la Província de Girona. La seva col·laboració és de gran ajuda per a poder desenvolupar de manera adient el projecte ideat. A continuació li exposarem detalladament els motius del present estudi, així com els detalls que en necessita conèixer. Si us plau llegeixi atentament tota la informació, i no dubti en consultar qualsevol aspecte amb la persona que li entrega el present document, quan ho consideri necessari.

Per què es realitza aquest estudi?

L'esquizofrènia és una de les malalties mentals més freqüents i incapacitants al nostre medi. Afecta tant joves com grans, ocasionant una important discapacitat, amb elevats índex de morbi – mortalitat, degut al seu curs crònic. Tot i la eficàcia demostrada del tractament farmacològic realitzat, una part important de la simptomatologia no respón suficientment al tractament. A més, aquests fàrmacs tenen un important efecte negatiu sobre els factors de risc cardiovasculars, així com sobre diferents paràmetres metabòlics. Això provoca un empitjorament de la morbi-mortalitat patida per la persona afectada.

Amb el present estudi es pretèn valorar si la realització d'un abordatge psicosocial ampli i personalitzat permet reduir les dosis de fàrmac amb les que es troben els pacients, i d'aquesta manera reduir els efectes secundaris que se'n deriven. Això permetria millorar la qualitat de vida i el pronòstic dels pacients afectes, a més de tenir un important impacte sobre l'economia sanitària.

Per què m'han de fer seguiment durant dos anys?

És important valorar les dosis a les que la persona afecta d'esquizofrènia es mantè en una situació estable. Per això és necessari deixar passar un període considerable de temps des de l'empitjorament de la simptomatologia, així com des de l'inici de l'abordatge psicosocial. A més, és interessant valorar com tot això afecta als factors de risc cardiovasculars a llarg termini. Per tot això un període de dos anys s'ha considerat necessari i suficient per a realitzar l'estudi.

Què haig de fer al participar a l'estudi?

Únicament haurà d'assistir a les visites acordades amb els professionals que l'atenen al centre al que està sent tractat, ja sigui la unitat de sub – aguts, l'hospital de dia o el seu centre de salut mental de referència. Durant aquestes visites, inicialment se li faràn unes breus qüestions sobre

els seus antecedents i informació personal. A les següents, s'obtindràn les dades necessàries per a calcular el risc cardiovascular, així com la presència de l'anomenat síndrome metabòlic. A més, se li proporcionarà algun qüestionari a emplenar, tant a vostè com al seu familiar cuidador, amb una finalitat científica, sempre explicant-se prèviament el motiu de la seva realització, així com el seu funcionament. Les visites queden acordades de la següent manera: el dia següent de l'arribada, a la setmana 4, setmana 6, mes 3, mes 6, mes 12, mes 18 i mes 24. No obstant, haurà d'atendre amb una freqüència major per a rebre el tractament pautat.

Haurà a més de comprometre's a complir el tractament pautat, tant farmacològic com psicosocial, en el cas d'haver-lo acceptat, amb les pautes marcades pels professionals.

Puc sortir-ne perjudicat de la meva participació a l'estudi?

No. El present estudi està dissenyat sota uns principis legals i ètics, garantint que cap participant en surti perjudicat pel fet de participar-hi.

I si canvio d'opinió?

En tot moment podrà canviar el tractament acordat inicialment. Així, si decideix iniciar un abordatge psicosocial íntegre, tot i no haver-lo acceptat inicialment, podrà incorporar-se immediatament al tractament. El mateix succeeix en el cas contrari. No obstant, si ha passat més d'un mes des de l'inici de l'estudi, quedarà exclòs d'aquest, no afectant això al tractament que continuarà rebent.

Si en algun moment vostè desitja deixar de formar part de l'estudi, podrà comunicar-ho en qualsevol moment, sense afectar la seva decisió al tractament rebut ni al seu seguiment.

Es faràn públiques les meves dades, un cop acabat l'estudi?

No. Les seves dades queden totalment protegides per la *Ley Orgánica 15/1999 de 13 de diciembre, de Protección de Datos de Carácter Personal*, essent la seva informació totalment confidencial. Les dades mèdiques necessàries per a l'estudi seràn publicades de manera totalment anònima.

Un cop finalitzat l'estudi, tindrè accés als seultats?

Sí. Tots els participants de l'estudi tindran dret a accedir a la informació i conclusions que se'n derivin, així com a una explicació de les dades obtingudes en la seva persona, sempre que així ho desitji.

Full de consentiment informat

Jo (Nom i cognoms) _____ :

- He llegit detalladament i entès tota la informació proporcionada sobre la meva participació a l'estudi
- He rebut tota la informació necessària sobre l'estudi
- M'ha estat explicada la meva participació a l'estudi de manera clara
- He pogut resoldre tots els dubtes que tenia respecte l'estudi
- He entès clarament quin serà el meu paper a l'estudi, i a què m'haig de comprometre quant al compliment del meu tractament i visites.
- He entès la voluntarietat de la meva participació, poguent en qualsevol moment retirar-me del present estudi, rebent independentment el tractament necessàri.

Amb tot això present, accepto participar a l'estudi.

Signatura i data:

Signatura del professional que l'atèn:

