Universitat de Girona
Facultat de Medicina

EFFECTS OF CANNABIDIOL AS AN ADJUNCTIVE THERAPY IN PATIENTS WITH A FIRST EPISODE OF PSYCHOSIS

A PROSPECTIVE RANDOMIZED CONTROLLED CLINICAL TRIAL

FINAL DEGREE PROJECT

HOSPITAL SANTA CATERINA, PARC HOSPITALARI MARTÍ I JULIÀ

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1 ABBREVIATIONS

2-AG: 2-Arachidonyl Glycerol

AEA: Anandamide

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios

AMPc: Cyclic Adenosine Monophosphate

AMS: Amisulpride

ATP: Adenosine Triphosphate

CBD: Cannabidiol

CBN: Cannabinol

CBR1: Cannabinoid Receptor Type 1

CBR2: Cannabinoid Receptor Type 2

CEIC: Comitè d'Ètica d'Investigació Clínica

CHR: Clinical High Risk

CIBERSAM: Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM)

CNS: Central Nervous System

CSF: Cerebrospinal Fluid

DA: Dopamine

DAGL: Diacylglycerol Lipases

DSM-5: Diagnostic and Statistical Manual of Mental Disorders

DUI: Duration of Untreated Illness

DUP: Duration of Untreated Psychosis

EC: Endocannabinoid

eCBS: Endocannabinoid System

EIPP: Equips d'Intervenció Precoç a la Psicosi

FAAH: Fatty Acid Amide Hydrolase

FDA: Food and Drug Administration

FEP: First Episodes of Psychosis

Glu: Glutamate

HSC: Hospital Santa Caterina

IAS: Institut d'Assistència Sanitària

IQ: Intelligence Quotient

K: Potassium

MAPK: Mitogen-Activated Protein Kinase

MCCB: MATRICS Consensus Cognitive Battery

MGL: Monoacylglycerol Lipase

PANSS: Positive and Negative Syndrome Scale

PHIMJ: Parc Hospitalari Martí i Julià

PKA: Protein Kinase A

PLB: Placebo

PsD: Psychotic Disorders

SAS: Simpson-Angus Scale

SCZ: Schizophrenia

THC: Δ-9 Tetrahydrocannabinol

UHA: Unitat d'Hospitalització d`Aguts

WAIS-IV: Wechsler Adult Intelligence Scale Fourth Edition

XSMA: Xarxa de Salut Mental i Addicions

2 ABSTRACT

BACKROUND: People suffering from psychosis exhibit a wide variety of symptoms, such as hallucinations or delusions, which lead to feel fear, distress and isolation. In our environment the annual incidence of FEP is about 31.6/100,000 in population aged ≥ 15 years. Also, it causes damage to family members and friends, who feel powerless in this situation and may have to carry the emotional and physical burden of care. In recent years there has been controversy in the role of two of the main components of cannabis sativa plant in psychotic disorders: THC and CBD. Several studies done last years have been proved that CBD can have antipsychotic properties based on the capacity to directly inhibit the reuptake of anandamide and also reduce endocannabinoids degradation by blocking fatty acid amide hydrolase function. The result of this is an increasing level of anandamide that it is studied that can alleviate psychotic symptoms.

OBJECTIVE: The main objective of this study is to determine the efficacy of the CBD using them as an adjunctive therapy in standard antipsychotic treatment with Risperidone in patients who are diagnosed with a first episode of psychosis, compared to those patients who only receive the standard treatment. Secondary objectives will be assessing the neuroprotective effects of CBD treatment in the cognitive impairments associated with FEP and also, the treatment tolerance and side effects of each group.

STUDY DESIGN: The study will be a prospective, double-blind, randomized and controlled 6-week clinical trial. It study will be carried out in the *Xarxa de Salut Mental i addicions* (XSMA) in the Girona region.

INTERVENTIONS AND METHODS: Subjects of the study will be those patients over 18 years old newly diagnosed with a first episode of psychosis considering the diagnosis criteria of DSM-V. Candidate patients will be selected as they are admitted to the *Unitat d'Hospitalització d'Aguts* (UHA) of *Parc Hospitalari Marti i Julià* (PHMIJ). They will randomly divide in two groups: group 1 (n = 87), patients will be treated with a low dose of an antipsychotic atypical (Risperidone) plus concomitant cannabidiol (CBD); in group 2 (n = 87), patients will receive the same antipsychotic plus concomitant placebo treatment instead of cannabidiol. Psychotic symptoms will be assessed using the Positive and Negative Syndrome Scale (PANSS) at baseline and biweekly. In addition, the cognitive performance will be evaluated by the MATRICS Consensus Cognitive Battery (MCCB) at baseline and at end of 6 weeks of treatment.

KEY WORDS: Psychosis, FEP, cannabidiol, psychotic symptoms, cognition.

3 INTRODUCTION

3.1 FIRST EPISODE OF PSYCHOSIS

3.1.1 Psychotic disorders

3.1.1.1 Definition and diagnosis

"Psychotic episode" is a generic term that can evolve to different disorders or none. The evolution after several months or sometimes years after the psychotic episode is what will determine the specific diagnostic of the psychotic episode. Psychosis affects each person differently and it is not always helpful to name or label the disease during the initial stages. "Diagnosing" means determining the nature of a disease based on the patient's symptoms, and the diagnosis will depend on both the factors that have caused the disease and the length of time these symptoms last. However, it is important to be familiar with some of the terms commonly used in the diagnosis of different types of psychosis (1).

According to the DSM-V, schizophrenia and other psychotic disorders (PsD) are defined by abnormalities in one or more of the following five domains (2,3):

- **Delusions:** fixed false beliefs; they are based on incorrect (false) inferences about reality external to, or about, oneself and maintained firmly (fixed) despite the presentation of evidence. The types of delusions commonly occurring in individuals with psychotic disorders are: persecutory; grandiose; religious; referential; thought control; mind being read; somatic.
- **Hallucinations:** defined as a sensory perception in the absence of somatic stimulus and described according to the sensory domain in which it occurs (eg. visual, auditory, tactile, olfactory, gustatory, nociceptive, thermoreceptive, proprioceptive, equilibiroceptive); may be unformed (ie. nonspecific sensory perceptions within sensory domain) or formed (ie. people, objects, voices making comments or commands). Hallucinations may occur with or without insight into their hallucinatory nature.
- **Disorganized thinking (speech):** formal thought disorder that it can appears in different forms: form of derailment (individual who changes the subject to another constantly), tangentiality (the answers given are unrelated to the question asked), or incoherence (speech being nearly incomprehensible).

- **Grossly disorganized or abnormal motor behaviour (including catatonia):** difficulty in goal-directed behaviour, unpredictable agitation or silliness, social disinhibition or behaviours that are bizarre to onlookers.
- **Negative symptoms:** defined as a diminished emotional expression, aboulia, anhedonia, apathy, poverty of language and thought, thought blocks, affective blunting, social withdrawal and carelessness.

Disorders along the schizophrenia spectrum differ from one another by the type, number, complexity, severity and duration of the psychotic symptoms and its specific DSM-V criteria(2). Thus, the term schizophrenia spectrum and other psychotic disorders include the following disorders: Schizotypal (personality) disorder; Delusional disorder; Brief psychotic disorder; Schizophreniform disorder; Schizophrenia; Schizoaffective disorder; Substance/Medication-induced psychotic disorder; Psychotic disorder due to another medical condition**;** Other specified schizophrenia and other psychotic disorders; Other specified schizophrenia and other psychotic disorders (3).

3.1.2 First Episode of Psychosis (FEP)

3.1.2.1 Definition, clinic and diagnosis of FEP

In the scientific literature there are many different definitions of the first psychotic episodes. One of the definitions agreed between different clinicians is included in the “Guía Clínica y Terapéutica para Primeros Episodios Psicóticos en la infancia y la adolescencia” carried out by the *Centro de Investigación Biomédica en Red de Salud Mental* (CIBERSAM) in 2015 (4): "A first psychotic episode consists in the presence, for the first time, of psychotic symptoms, defined as the existence or clinical suspicion (by behavioural disorganization, catatonia, etc.) of delusions and/or hallucinations, regardless of the type of evolution of the symptoms".

Patients suffering these symptoms can experience fear, distress, and isolation. Many of these patients are also at greater risk to themselves and others. The family and carers witnessing this psychosis may experience fear, guilt, and often carry the emotional and physical burden of care (5). In addition, this behaviour change can be quite abrupt and appear in a week or two, or it can be more progressive and appear over months or years until it is already very evident. Often the person who undergoes these changes is not aware of it (1). Also, the are common mental health problems (including anxiety and depression) and coexisting substance misuse may also be present in psychosis and first episode of psychosis (6).

Each person will have a unique experience and combination of symptoms. Core clinical symptoms are usually divided into positive symptoms, so called because they are added experiences, and negative symptoms, so called because something is reduced. In the following table there are the symptoms previously explained in the PsD classified (7):

Positive symptoms	Negative symptoms
Hallucinations	Poverty of language and thought
Delusions	Emotional apathy
Disorganized behaviour	Lack of drive
	Social withdrawal
	Self-neglect

Table 1. *Positive and negative symptoms.*

The Positive and Negative Syndrome Scale (PANSS) is the most common used measure for the assessment of symptoms in schizophrenic patients. Although, there exists some FEP studies that have used the PANSS in order to assess and classify the psychotic symptoms. As a conclusion of these studies, it is possible to define psychosis as a score ≥4 on PANSS criteria (P1, P3, P5, P6 or G9) for a period of time between more than one week and less than six months (8,9).

It is important to mention, that in patients with a FEP, the psychosocial functioning is a significant predictor of the course and prognosis of the disorder since its deterioration is a precursor of chronic or long-term resistance to treatment (10).

Finally, the life expectancy of subjects with psychosis is shorter than in the general population because there is a risk of violent death, a wide range of physical health problems and a risk of suicide (about 20% carry out at least one attempt during the course of the disease) (6); the risk of it occurring is higher within the first five years (10).

3.1.2.2 Phases of Psychosis

At the onset of psychosis, the patient goes through 4 stages: the premorbid phase, the prodromal phase, the active phase (First Psychotic Episode) and the recovery phase after the First Psychotic Episode. In the following figure it can be seen the order of these phases and also a brief explanation of the symptoms and clinic that the patient goes through (10):

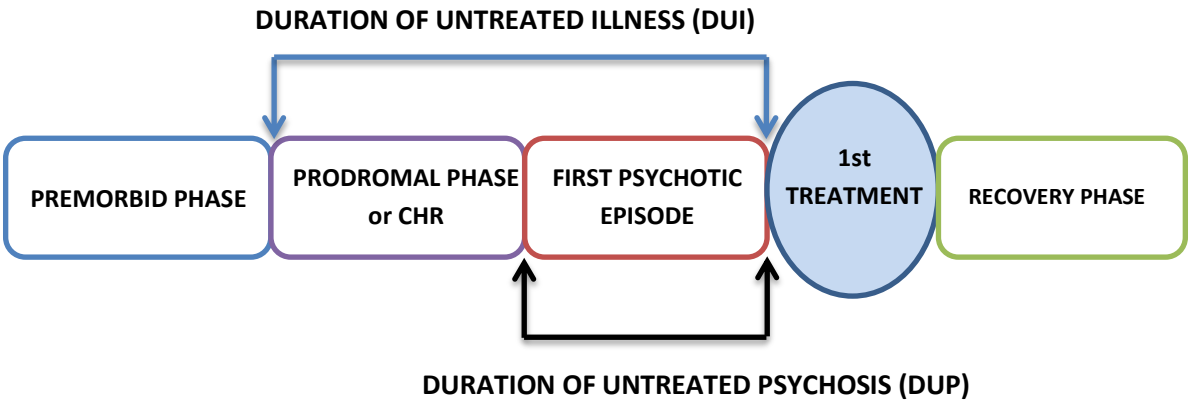

Figure 1. *Phases of Psychosis*. Adapted from (10).

1. PREMORBID PHASE

- Period prior to the appearance of the first prodromal symptom.
- Retrospective evaluation.
- A malfunction in the following areas (sociability, interpersonal relationships, academic performance, environmental adaptation and psychosexual development) is directly associated with:
  - ❖ Earlier onset of psychotic disorder
  - ❖ Worse functional prognosis
  - ❖ Higher cognitive impairment

2. PRODROMAL PHASE or CHR

- Phase of initial non-specific symptoms preceding mental disorder. **Clinical High Risk (CHR)** for psychosis: only a 33-55% of this population will develop a psychosis.
- Retrospective evaluation.
- **Duration of Untreated Illness (DUI):** period of time (between 2 and 5 years) from the initial prodromal phase to the beginning of the treatment of psychotic symptoms.

3. FIRST PSYCHOTIC EPISODE

- First episode may be abrupt (without presenting a CHR) or insidious (presenting an CHR previous).
- **Duration of Untreated Psychosis (DUP)**: period of time between manifestations of first psychotic symptoms until the start of treatment (average of **six months**).
- Shorter duration of DUP has been associated with a reduction in acute psychotic symptoms, a better response to antipsychotic.
- Appearance of positive symptoms:
  - ❖ Hallucinations
  - ❖ Delusions

4. RECOVERY PHASE

- Period of time during which acute symptomatology is controlled and also, a progressive decrease in the intensity of symptoms (**6 months to one year and a half**).
- **70%** of first psychotic episodes cause symptoms and signs to remit completely within **3-4 months** of treatment.
- Recovery after the first episodes will depend on factors such as: age of onset, type of onset of the disease, precipitating factors, socio-occupational support, pharmacological treatment, psychological treatment.
- In this phase exists an increased risk of drug abandonment, relapse and risk of suicide.

According to a first episode of psychosis study at 8 years, the annual incidence of FEP (including all psychosis with psychosis in the context of neurodegenerative diseases as an exception) is about 31.6/100,000 in population aged ≥ 15 years (11).

The subjects who experience a psychotic episode for the first time are usually a heterogeneous group of people; however, they are usually young people, who are at the end of adolescence or at the beginning of adulthood. The primary risk age range is 20 to 35 years. For men, a pronounced peak is observed at the age of 15-24 years. For their part, women become ill 3 to 4 years later than men on average. They have a lower peak than men at the age of 15-29 and a second lower peak, around the age of menopause (45-49 years) (10). If we compare genres, schizophrenia spectrum psychoses show higher incidence in males, while in affective psychoses the incidence is indistinguishable between males and females (11).

It is important to mention that substance-induced psychotic disorder (especially the one caused by cannabis) it is usually seen used on this group of patients (11) and also is related to the appearance of FEP and development of psychosis (1). In addition, up to 25% of psychotic patients report prior and/or current substance abuse (11).

3.1.2.3 Ethiopathogenic

Regarding the aetiopathogenesis of psychotic disorders, several studies have found that genetic predisposition and environmental factors as well as the hypothesis of dopamine and other neurotransmitters have a leading role in the development of psychosis (12).

- **Genetic predisposition:**

Although there is a lot research to be done, several have shown that people who suffer episodes of psychosis are born with a marked predisposition (4). It has been seen that there is a clear component of the pathology that is inherited and also, has more relevance than the environmental factors (12).

- **Environmental factors**

Some studies have shown that exist factors as the date of birth, place of birth and seasonal effects as well as infectious diseases, complications during pregnancy and childbirth, substance abuse and stress that can contribute to the onset of psychosis (12).

In addition, one of the best documented risk factors is obstetric complications and also, in recent years, the consumption of substances and more specifically of cannabis it is associated

with increased risk of psychosis and cognitive impairment (13). Other factors that we find within this group are migration, a history of sexual abuse and head trauma (12).

- **Hypothesis of dopamine and the other neurotransmitters**

According to the studies done, the hypothesis that is considered about the onset of psychosis is that there is an imbalance of a dopaminergic function which causes increase levels of dopamine that would produce the symptoms of psychosis (12). The two dopaminergic pathways that are relevant in this process are:

- **Mesolimbic pathway:** projected from the ventral segmental area from the mesencephalon to some limbic areas such as the Accumbens, which is part of the reward circuit. The elevation of dopamine in this zone produces the positive symptoms of psychosis.
- **Mesocortical pathway:** projected from the ventral tegmental area to the ventromedial and dorsolateral prefrontal cortex. This path is associated with the regulation of emotion and affectivity, so a deficit in this route produce the negative symptoms and also the cognitive (12,14). The proof of this is that all antipsychotics have the property of blocking the D2 type dopaminergic receptors and in consequence are effective against delusions and hallucinations but have less effect on cognitive and motivational disability (15). In addition, it has been studied that there exist other neurotransmitters that are involved such as glutamate and serotonin (16).

3.1.2.4 Therapeutic management of a FEP

In several FEP studies it has been a main conclusion that an early intervention and treatment are crucial to potentially achieving better clinical outcomes and to alleviating the psychological impact on patients and their families (4). In addition, FEP interventions for short-term outcome in terms of adherence to and retention in treatment as well as to aspects of social and community functioning and satisfaction with life (17).

The first five years of psychosis that is described as a critical period is the most important time for recognition and treatment. Services for early intervention should be easily accessible, non-threatening and non-stigmatising. Effective treatment is based on (18,19):

- **Successful engagement and the development of trust** between patients, their families and the mental health professionals assisting them.

- **Psychosocial interventions:** they provide a humane basis for acute and continuing care, prevention or resolution of the secondary consequences of psychosis and the promotion of recovery.
- **Antipsychotic medication:** considered effective and it is recommended by evidence based research in the treatment of first episode of psychosis (18).

3.1.2.5 Psychopharmacology and intervention in a first psychotic episode

The antipsychotics are essential in the acute phase of all psychotic episodes, and they are also often necessary in the maintenance phase to prevent relapses (4). There are many types of antipsychotics that are effective in reducing the psychotic symptoms which we can group into two main categories (15): classic antipsychotics and atypical or second generation antipsychotics.

All antipsychotics have the property of blocking dopamine receptors of subtype D2, but both groups differ in their affinity profile for other receptors. Classical antipsychotics, based on hyperdopaminergic theories (12), act by blocking the D2 dopamine receptor of the mesolimbic pathway. Today new receptors have been discovered where to act and this is where we have the appearance of atypical drugs. They act blocking D2 receptor and also, they have the mechanism of action by blocking 5HT receptor and inhibit serotonergic hyperactivity. They could be classified their profile blockers as (15):

- D2 and 5HT receptor blockers: risperidone, paliperidone, sertindole, ziprasidone.
- Multiple receptor blockers: clozapine, olanzapine, quetipine.
- Partial D2 agonists: aripriprazole and amisulpride.

The blocking of these receptors on the different pathways of the central nervous system produces different effects, both on a therapeutic level (effect antipsychotic) as in the form of adverse effects. The main differences in adverse effects between classic and atypical antipsychotics in the different pathways are:

In the mesocortical pathway of the frontal lobe, there is a dopamine deficit that is aggravated by D2 blockade (common effect of the antipsychotics drugs), but the atypical antipsychotics also act blocking 5HT-2A and this implies a release of dopamine in this region which causes less worsening of negative symptoms. In addition, the low affinity for D2 receptors of these drugs and their rapid dissociation from the receptor, decrease the extrapyramidal effects and also the levels of prolactin are lower respects the patients with classical antipsychotics. The extrapyramidal symptoms include (20):

- Dyskinesias and dystonic reactions
- Parkinsonism
- Akinesia
- Akathisia
- Neuroleptic malignant syndrome

In patients starting treatment for the first time, most clinical guidelines recommend choice of an atypical antipsychotic other than clozapine and olanzapine, because of its higher risk of metabolic syndrome (21).

The treatment of the first psychotic episode and recovery or critical period phases is comparable to the acute and stabilisation phase of schizophrenia respectively, with the sole exception that in these early stages of psychosis the diagnosis of schizophrenia is not yet established. We can classify in three phases: acute, stabilisation and stable. The aim in the acute (or crisis) phase is to decrease severe positive psychotic symptoms; this is followed by a stabilisation (or post-crisis) phase, during which the intensity of psychotic symptoms is reduced positive and then negative symptoms may become more evident.

In several studies it has been proved that in first episode of psychosis lower doses of an atypical antipsychotic are effectiveness to decrease the symptoms associated with psychoses and also have a better safety profile (22,23) than the classic ones. In concrete, in this clinical trial we will use Risperidone at low dose (4mg/day) taking into account a study that was conducted in patients with a first psychotic episode in this doses and experience a decrease of a 59% in the PANSS total scores (24).

3.2 CANNABINOIDS

3.2.1 Generalities

Cannabinoids are chemicals compounds that, regardless of their origin and structure, bind to the cannabinoid receptors of the body and brain. The cannabinoids can act like an agonist or inverse agonist and the specific bind with the cannabinoid receptor type 1 (CBR1) and type 2 (CBR2) have the action of modulate the neuro-immuno-endocrine function.

They are classified in (25,26):

- **Phytocannabinoids:** appear in nature in the species *Cannabis Sativa* plant. There are approximately 140 phytocannabinoids. The main ones are: Δ-9 tetrahydrocannabinol

(THC), cannabidiol (CBD), and cannabinol (CBN). THC in its neutral form is the responsible for the psychoactive effects of this plant.

- **Endocannabinoids:** synthesized on demand and released immediately to the outside of the cell and these with the cannabinoid receptors (CB1 and CB2) form the endocannabinoid system (eCBS).

  Endocannabinoids are compounds derived from polyunsaturated fatty acids of which the most important are the two arachidonic acid derivatives, anandamide (AEA) and 2-arachidonyl glycerol (2-AG). Despite the similarities in their chemical structure, both ligands are synthesized and degraded by different enzymatic pathways. In addition, the three enzymes responsible for its biosynthesis are phospholipase D and diacylglycerol lipases (DAGL) and their hydrolytic inactivation: fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL) (27). In differents studies it has been proved that CBD decreases fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) (28).

- **Synthetic cannabinoids:** chemical compounds that are designed in laboratories and act on the same receptors as THC, CB1 and CB2, in a more powerful way since they have more affinity.

It is known the action of THC as a partial agonist in the endogenous cannabinoid receptors CB1 and CB2 (29). As a result of this specific binding is associated with analgesia, relaxation and enjoyment but also, an acute dose can cause unpleasant effects such as anxiety, psychotic symptoms, depression, apathy and impairment of memory (30).

Cannabidiol (CBD) is the main non-psychotropic phytocannabinoid present in the Cannabis sativa plant (31). In contrast of THC, CBD has a low affinity for CB1 receptors and its molecular mechanism of action it is been studied recently (30). Despite this characteristic, CBD appears to reduce the efficacy of THC and other agonists at CB1 and CB2 receptors. CBDs pharmacological profile includes: 5-HT1A receptor activation, suppression of immunoactivation-induced tryptophan degradation, activation of TRPV1 vanilloid receptors and act as partial agonist at dopamine D2 receptors (32). The CBD can have anticonvulsant, sedative, anxiolytic and antipsychotic effects (32). Finally, CBD affects synaptic plasticity and facilitates neurogenesis (33).

3.2.2 Pharmacokinetics of CBD

The **table 2** summarizes the different pharmacokinetics of CBD (26)**:**

ABSORPTION	-VERY LIPOSOLUBLE -LARGE DISTRIBUTION VOLUME→**32L/KG** -ORAL ROUTE OF ADM LIMITED: VARIABLE, DEPENDS ON CBD INTAKE→**BIOAVAILABILITY OF 13-19%** -POSSIBLE ROUTE OF ADMINISTRATION TRANSCUTANEOUS
HALF LIFE	**18-32h**
METABOLISM	HEPATIC: CYP3A and CYP2C (strong inhibitor of CYP1A, CYP3A4, CYP2C and CYP2D)
ELIMINATION	FAECAL ROUTE

Table 2. *Pharmacokinetics of CBD.* Adapted from (26).

3.2.3 Endocannabinoid System (eCBS)

As discussed above, cannabinoids have a pharmacological effect on certain membrane receptors. Today, two cannabinoid receptors are known: CB1 and CB2. Both belong to the family of G-protein coupled receptors characterized by the presence of seven transmembrane domains. More details of the action and location of these receptors:

- **CB1:** located in peripheral organs and in the CNS, being the most abundant G-protein-coupled receptor in the brain. The highest density of the receptor is found in the basal ganglia, cerebellum and hippocampus. The CB1 receptor is present at the peripheral level in the spleen and tonsils, heart, prostate, uterus, ovaries and at the presynaptic level, in sympathetic nerve terminals. Other peripheral locations of the CB1 receptor are adipose tissue, muscle, liver, gastrointestinal tract and pancreas.

  In general, the distribution of the CB1 receptor is closely linked to the pharmacological effects produced by cannabinoids. For example, the high density of this receptor in the basal ganglia correlates with the effect of cannabinoids on locomotive activity, and in hippocampal and cortical areas on learning, memory and its anticonvulsant effect. Finally, there is a low density of CB1 receptors in the brain stem, area that is responsible for cardiovascular and pulmonary functions, which allow justifying the low toxicity and lethality of marijuana (25).
- **CB2:** Located in cells of spleen, tonsils and other tissues and peripheral organs such as the heart, endothelium, bone, liver and pancreas. However, its activation has not been

observed to produce psychoactive effects and appears to be responsible for the immunomodulatory properties of marijuana (27).

Both receptors couple to inhibitory G_i/G_o proteins and have the ability to activate several signal transduction mechanisms to inhibit voltage-gated calcium channels and adenylyl cyclase as well as activate potassium channels and MAP kinase (34).

As we can see in the **Figure 1** the two main routes that are described are: firstly, there is an inhibition of the conversion of ATP to AMPc catalysed by an enzyme and which causes a decrease of this messenger inside the cell. The AMPc allows phosphorylating a protein called protein kinase or PKA and subsequently, activating the cascade of MAP kinase (MAPK) (25). Also cannabinoids increase nitric oxide production (35).

Another action of cannabinoid receptors are voltage sensitive calcium channels; inhibitory G protein blocks these channels leading to an accumulation of intracellular calcium and decrease the expulsion of substances, as occurs in the release of neurotransmitters by the presynaptic neuron (36). In the same way, the blocking of this channel allows the release of potassium (K) to the exterior and causes a decrease of the electrical excitability of the cell (26).

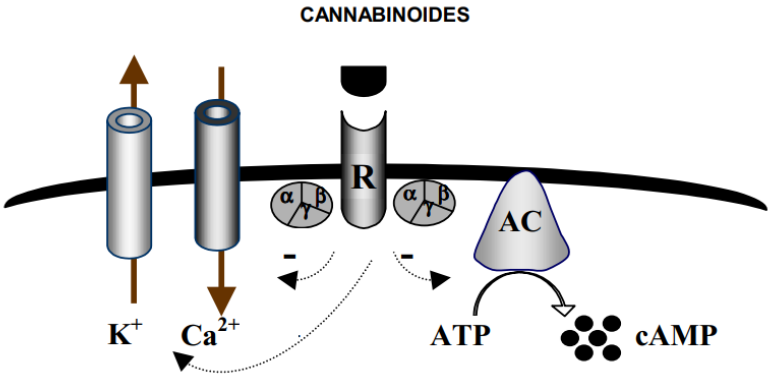

Figure 2. *Physiological Mechanism of Cannabinoid Receptors (25).*

3.2.4 Cannabinoids functions

Cannabinoids have shown that they have a wide variety of biological and physiological actions that allow us to think of a pharmacological application of these substances for different pathologies. Some of the responses that occur at the cannabinoid and receptor junction are(25):

- Changes in temporal perception (overestimation of elapsed time) and recent memory.
- Feeling of euphoria, sedation and relaxation.

- Analgesic and anti-inflammatory activity.
- Orexigenic and antiemetic activity (37).
- Actions on muscle tone and motor coordination (ataxia, muscle weakness).
- Decrease in intraocular pressure.
- Hypothermia.
- Actions on the respiratory system (bronchodilation).
- Cardiovascular effects (hypotension and tachycardia).
- Neuroendocrine effects (decreased release of different sex hormones, and increases in the release of hormones related to the stress response).
- Immunomodulatory effects (low dose immunostimulation and high dose immunosuppression).
- Antiproliferative and antitumor effects.

If we talk about mental health, the possible therapeutic uses of CBD that have been studied in mental disorders are (26):

- Attenuation of the psychoactive effects of THC: possible addiction treatment.
- Antiepileptic and anticonvulsant.
- Anxiolytic.
- Neuroprotective effect.
- Antipsychotic.

The mechanism of action of CBD is very promising for future therapeutic applications in the field of neurological and mental disorders. Additional evidence needs to be obtained in double-blind, randomized clinical trials for possible application in the treatment of addictive disorders, psychosis, anxiety and chronic pain.

A number of medicinal products have been authorised for marketing, containing cannabinoids; the most mentioned are the following (38):

- **Marinol and Syndros®** (active ingredient: dronabinol): is indicated for anorexia associated with loss of weight in patients with acquired immunodeficiency syndrome (AIDS) and nausea and vomiting associated with cancer chemotherapy, usually after the failure of the previous treatments.
- **Cesamet and Canemes®** (active ingredient: nabilone): indicated for nausea and vomiting associated with chemotherapy, usually after failure of pre-treatments.

- **Sativex®** (active ingredient: nabiximol): a medicine containing quantities approximately equal amounts of THC and CBD from two cannabis extracts. This product, which is sprayed on the inside of the cheek or under the tongue, is authorised for the treatment of muscular spasticity secondary to sclerosis.
- **Epidiolex®** (active ingredient: CBD): oral solution of CBD indicated for treatment of crises associated with Lennox-Gastaut syndrome or Dravet and Tuberous Sclerosis(39).

3.3 CANNABINOIDS AND PSYCHOSIS

In recent years there has been controversy in the role of two of the main components of cannabis sativa plant in psychotic disorders: THC and CBD. THC has been shown to cause an increased risk of psychotic disturbances, while cannabidiol may have a neuroprotective function and may even decrease the effect of THC (26).

Several studies have been suggested that heavy cannabis use may precipitate psychosis (40) and can experience more positive and less negative symptoms, compared with those who never used cannabis or used low-potency types (33,34). There is evidence that daily use of cannabis and the use of high-potency cannabis is related with an increased odds of developing non affective psychotic disorders, especially for those with a pre-existing vulnerability and elevated familial risk for psychosis (43). Up to 64% of individuals who have experienced a FEP have used cannabis, and 30% of these have a cannabis use disorder (42). However, a recent study that used completed cognitive test battery assessing verbal memory, verbal fluency and attention and interviewing about the history of substance use, has shown that there wasn't indication that cannabis use was associated with cognitive impairments in people diagnosed with FEP.

This discussion has been mainly associated with studies, initially, control cases (44) or case series (45), in which they demonstrated that the administration of cannabidiol in fairly high doses of 1500mg/day and 1280mg/day were able to decrease psychotic symptoms.

Subsequently, clinical, double-blind, randomized studies have been conducted. In the **table 3** we can see the three most relevant studies made in recent years that provide information on the relationship between CBD as antipsychotic treatment. The most commented of these three is the study carried out by Leweke et al (46) (2012) since it is the only study carried out so far that observes the effect of CBD as monotherapy. In it, psychotic symptoms are compared in 4 weeks in patients with schizophrenia (SCZ), one group with CBD and another with Amisulpride.

The results showed that the CBD had a similar efficacy as the treatment with Amisulpride and also had a higher safety profile.

The other two clinical trials that have been conducted have used CBD as an adjuvant. The study by McGuire et al(47) (2018) compared for 6 weeks two groups that already had antipsychotic treatment, CBD was added in one and the other placebo. Cannabidiol was shown to be more effective than placebo in terms of decreased symptoms and motor speed. And in the study of Boggs et al (2018) (48) it was proposed similar than the previous but without having the same results.

Study	N	CBD dosage	Duration	Treatment arms	Results
Leweke et al (46) (2012)	39	800 mg/day of CBD	4 weeks	CBD AMS	CBD=AMS for PANSS overall, positive, negative symptoms CBD<AMS for extrapyramidal symptoms, weight gain, prolactin elevation
McGuire et al (47) (2017)	88	1000 mg/day of CBD	6 weeks	CBD+antipsychotic PLB+antipsychotic	CBD>PLB for positive symptoms, motor speed
Boggs et al (48) (2018)	36	600 mg/day of CBD	6 weeks	CBD+antipsychotic PLB+antipsychotic	CBD=PLB in cognition impairments (MATRICS) CBD>PLB for positive symptoms

Table 3. *Rabdomized controlled trials with CBD in SCZ.* Adapted from (26).

The potential antipsychotic properties of CBD are to directly inhibit the reuptake of anandamide, an endocannabinoid that exhibits neurogenic and anti-inflammatory activity. Moreover, CBD can also reduce endocannabinoids degradation by blocking fatty acid amide hydrolase function (49), as we can see in the **Figure 3**. This action produce an increasing level of anandamide that it is studied that can alleviate psychotic symptoms (46). In addition, there studies that hypothesised that CBD may exert its antipsychotic action through a partial agonist activity on dopamine D2 receptors, similarly to the atypical antipsychotic aripiprazole (50).

Some researchers suggest the presence of abnormalities in the endocannabinoid system in SCZ and psychotic disorders. Previous studies have shown that cerebrospinal fluid (CSF) from

schizophrenic patients and in first episode of psychosis (FEP) contains higher levels of the endogenous cannabinoid anandamide, suggesting that they may play a role in psychosis homeostasis (51), than does CSF from healthy volunteers (52,53). In addition, the levels of anandamide in blood and CSF are inversely related with the presence of psychotic symptoms in FEP and in SCZ (54).

Also, there are studies that used immunodetection methods that reported a decrease of CBR1 receptor (CB1R) in patients with SCZ or acute psychotic episode (55,56). Also, several groups have found an increase (57) and no changes (58) in the density of CBR1 in the superior temporal gyrus.

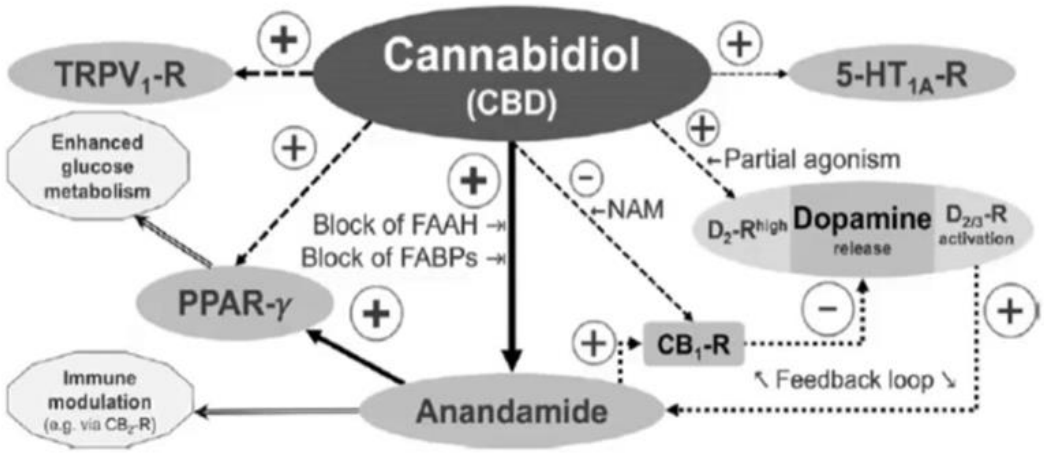

Figure 3. *Action of CBD in the physiological routes*(26).

As we commented, the studies have shown low levels of endocannabinoids, such as anandamide, in the brain in patients with psychosis. And also this authors hypothesize that CBD can increase this levels and alleviate positive symptoms. In the **Figure 4** we see that endocannabinoids acts as an inhibitory molecule in the presynaptic neuron and regulate the release of glutamate. Consequently, there is a decrease in the severity of symptoms related to psychotic disorders due to stabilise dopamine levels that are released by the postsynaptic neuron (18,44).

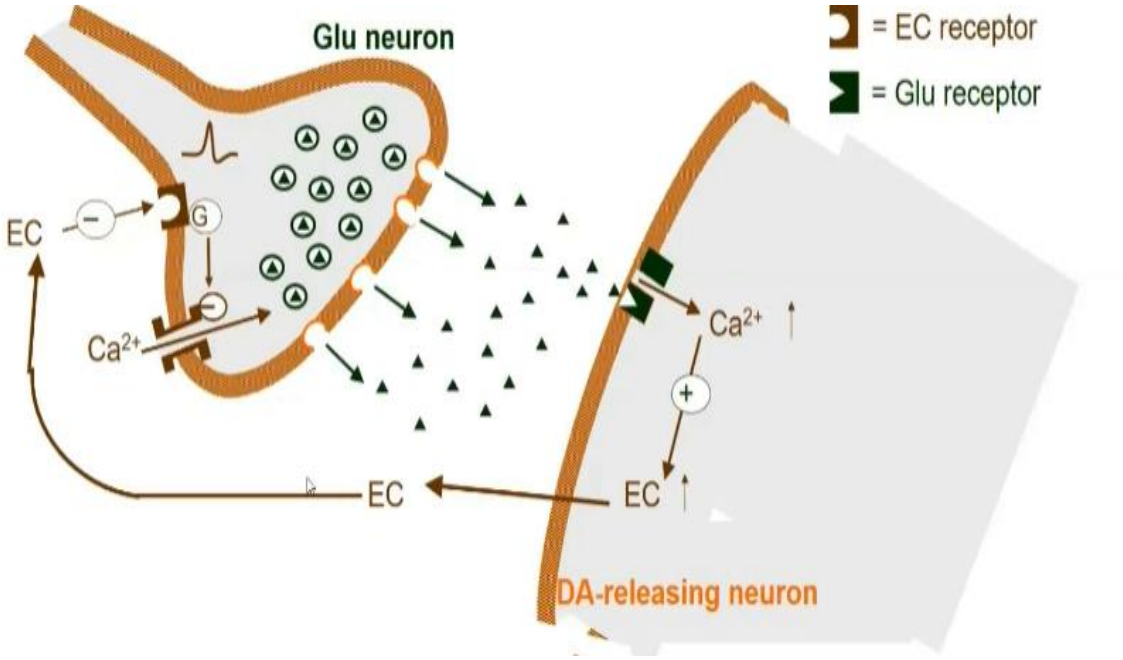

Figure 4. *Physiology of endocannabinoids in presynaptic and postsynaptic neurons* (26).

Finally, the cognitive impairments associated with psychosis are independent of phase of the illness and also the hypothesis that it is considered about that is that manipulation of endocannabinoid function via CB1R antagonism/inverse agonism or modulating endocannabinoid levels might offer a novel target for this cognitive impairments.

The study done by Boggs et al (2018) aimed to examine the effects of adjunctive CBD with antipsychotic treatment on cognition in patients with chronic schizophrenia using the MATRICS Consensus Cognitive Battery (MCCB). The conclusion of the study was that adjunctive CBD was not more effective than placebo in treating cognitive impairments associated with schizophrenia and that future studies should assess if CBD treatment earlier in the course of illness is beneficial (48).

4 JUSTIFICATION

Patients suffering of psychosis experiment in a very short time many sensations as delusions and hallucinations that can that evidently condition their daily life and put at risk their integrity and others. The people with psychotic disorders experience fear, distress and isolation (5).

The data is overwhelming, according to a first episode of psychosis study at 8 years, the annual incidence of FEP in our environment is about 31.6/100,000 in population aged ≥ 15 years (11). In addition to the direct cost of living, it causes damage to family members and friends, who feel powerless in this situation and may have to carry the emotional and physical burden of care, generating anxiety, depression and feelings of guilt for an incomprehensible fact for them (4,17).

Moreover, in recent years there has been controversy in the role of two of the main components of cannabis sativa plant in psychotic disorders: THC and CBD (26). There are many epidemiological studies that show that cannabis use may precipitate psychosis (40) and can experience more psychotic symptoms compared with those who never used cannabis (33,34), especially for those with a pre-existing vulnerability (43) and elevated familial risk for psychosis.

On the other hand, several studies done last years have been proved that CBD can have antipsychotic properties based on the capacity to directly inhibit the reuptake of anandamide and also reduce endocannabinoids degradation by blocking fatty acid amide hydrolase function (49). It is seen that in patients with psychosis there are higher levels of anandamide in the cerebrospespinal fluid (CSF) (51,52,53).

The result of this is an increasing level of anandamide that it is studied that can alleviate psychotic symptoms (46,54). It is also possible, although further studies are needed, to act as a partial agonist activity on dopamine D2 receptors (50) and CBR1.

Currently, there is no published clinical trial that use cannabidiol as an adjunctive therapy with antipsychotic medication in patients with a first episode of psychosis. However, in 2018 McGuire et al (47) compared for 6 weeks two groups that already had antipsychotic treatment with a diagnostic of chronic schizophrenia and add CBD to compare with placebo. The conclusions of the study were that cannabidiol was shown to be more effective than placebo in terms of decreased symptoms and motor speed.

That is why my objective in this prospective, double-blind, randomized and controlled 6-week clinical trial is to evaluate the positive and negative symptoms in patients diagnosed with a FEP by adding in a low dose of Risperidone a stable dose of CBD, compared to those who only receive the antipsychotic plus placebo. This study will provide information and data on a different and novel management of patients with FEP as we know that an early intervention and treatment are crucial to potentially achieving better clinical outcomes, and to alleviating the psychological impact on patients and their families (4).

5 HYPOTHESIS

The patients diagnosed with a first episode of psychosis undergoing adjuvant therapy with cannabidiol (CBD) with standard antipsychotic treatment will have a higher improvement of the positive and negative symptoms and less cognitive impairment than those patients who only have antipsychotic treatment.

6 OBJECTIVES

6.1 MAIN OBJECTIVE

- The main objective of this study is to determine the efficacy of the CBD using them as an adjunctive therapy in standard antipsychotic treatment in patients who are diagnosed with a first episode of psychosis.

6.2 SECONDARY OBJECTIVES

- To assess the neuroprotective effects of CBD treatment in the cognitive impairments associated with first episodes of psychosis in patients diagnosed of early psychosis.
- To assess the treatment tolerance and side effects in patients who are diagnosed with a first episode of psychosis in treatment with CBD.

7 METHODOLOGY

7.1 STUDY DESIGN

The best design to confirm or reject our hypothesis, taking into account that the aim of the study is to compare two treatments in first episode of psychosis; is a prospective, double-blind, randomized and controlled 6-week clinical trial.

The study will be carried out in the *Xarxa de Salut Mental I addicions* (XSMA) in the Girona region (ANNEX 1).

7.2 STUDY POPULATION

The target population of the study will be patients diagnosed with FEP considering the diagnosis criteria of DSM-V.

The psychiatrists of the *Equips d'Intervenció Precoç a la Psiscosi* (EIPP) or the *Unitat d'Hospitalització d'Aguts* (UHA) of *Parc Hospitalari Marti i Julià* (PHMIJ) will select the patients that are hospitalized with a FEP to enter in this 6-week clinical trial as long as they meet the inclusion criteria and none of the exclusion criteria.

7.3 INCLUSION CRITERIA

Patients must meet all the following inclusion criteria in order to participate in the clinical trial; the psychiatrist will verify all these items:

- Patients with first episodes of psychosis considering the criteria of the DSM-V that happen in the community of Girona and are hospitalized.
- Patients aged 18-40 years.
- Capacity to understand and sign the informed consent to be a part of the clinical.

7.4 EXCLUSION CRITERIA

Patients who meet any of these following criteria will be excluded from the trial:

- Patients who have associated affective disorders established by DSM-V criteria.
- Patients suffering from neurological disorders considering the DSM-V criteria.
- Psychosis in the context of a previous diagnosis of neurodegenerative disease.
- Patients diagnosed of cannabis dependence by DSM-V criteria or if the first episode of psychosis is induced by any substance use.

- At screening, patients will be excluded if:
  - PANSS score total <50
  - Low intelligence quotient (IQ) <70
- Patients who are pregnant, lactating or planning pregnancy during or within 3 months.
- Allergy or hypersensitivity reaction to CBD.

7.5 SAMPLE SIZE

Taking into account an international, multicenter, double-blind study that was conducted in patients with a first psychotic episode, we will take as a reference a 59% decrease in the PANSS total scores in patients who took low dose (4mg/day) of Risperidone in a 6-week clinical trial (24). Considering also that CBD as and adjunctive therapy in patients with chronic schizophrenia has achieved a 20% improvement in PANSS total scores in same doses (47), we are taking the following numbers as a reference to calculate the necessary sample size:

Accepting an alpha risk of 0.05 and a beta risk of less than 0.2 in a two-sided test, 87 subjects receiving low doses of Risperidone and placebo and 87 subjects receiving low doses of Risperidone and CBD as an adjuvant treatment are necessary to recognize as statistically significant a relative risk greater than or equal to 1.33, considering a difference equal or greater than 20% as clinically significant. A follow-up loss rate of 5% has been estimated.

These calculations have been made using the application GRANMO develop by Jaume Marrugat.

7.6 SAMPLE SELECTION

The sampling method used in order to recruit the necessary patients will be consecutive non-probabilistic. This sampling consists on selecting patients diagnosed with FEP, who meet the inclusion and exclusion criteria, as they are admitted to *Unitat d'Hospitalització d'Aguts* (UHA) of *Parc Hospitalari Marti i Julià* (PHMIJ).

The participants will be informed and received an information sheet (ANNEX 2) about the clinical trial. Those who want to be a part of the study it will be necessary to read and sign the informed consent (ANNEX 3). Only if these steps are correctly done the individual will participate in the study.

7.7 ESTIMATED TIME OF RECRUITMENT

Our study population will be first episodes of psychosis. According to the data of FEP incidence in our environment, which is 31.6 per 100,000 inhabitants (11) the annual incidence of FEP in Girona region will be 241 cases a year, taking into account that there are 765.554 inhabitants in this province (59). So, as we have calculated a total of 174 patients required to reach statistical significance, we estimate that about 12 months will be needed in order to find the necessary sample, taking into account that some patients might refuse to participate in the study and some others would not meet the inclusion criteria.

7.8 RABDOMIZING AND MASKING

In order to avoid a confusion bias it will be necessary to use a software SPSS to randomize the patients participating in the study. This program will assign the individuals that will take the two different treatments in a first episode of psychosis randomly. The randomization will be made by the pharmacy staff not directly involved in the study when the patients are hospitalized and during the first 24h in the *Unitat d'Hospitalització d'Aguts* (UHA) of *Parc Hospitalari Marti I Julià* (PHMIJ). This study will be double-blind randomized clinical trial as the investigators and psychiatrist of the study will be unaware of the assigned intervention until the study completion as the solution will be administered by the nurses and assistants.

7.9 STUDY VARIABLES

7.9.1 Independent variables

- Treatment: Placebo or Cannabidiol (CBD)

This is a qualitative dichotomous variable. The group 1 will take Risperidone and CBD, and the group 2 will take Risperidone and placebo. The solution dosage and interventions are detailed in the data collection and procedures section of the protocol.

7.9.2 Dependent variables

- ***Primary efficacy outcome*:** Positive and Negative symptoms in patients diagnosed of FEP

This is the primary dependent variable because is the main objective of the study. To assess this objective we will use the PANSS (ANNEX 4).

As the main objective of the study is to see the improvement of the psychotic symptomatology in the two groups of patients (group 1 and group 2), we have set as a goal an equal or greater

improvement of 20% in the PANSS total scores of group 1 respect group 2. As we will explain in the procedure, this variable will be measured at baseline, week 2, week 4 and week 6.

- ***Secondary efficacy outcome*****:** Cognitive function associated in patients diagnosed of FEP

As a secondary objective, this study aimed to see the effects of CBD adjunctive therapy in cognition in patients diagnosed with FEP. To asses this objective we will use The MATRICS™ Consensus Cognitive Battery (MCCB™).

As we will explain above in Data collection and Procedures, this variable will be determined at baseline and at the end of the clinical.

Treatment tolerance and side effects

It will be assessed using a single question that will ask: "How do you feel about the possible side effects that you have suffered or have been suffering recently associated with the treatment?". In the study it will be classified in four groups depending on the answers of the individuals: very bad, bad, fairly well and well.

Also, it is documented in previous clinical trials that in a few individuals the use of CBD as the doses that will be add, can produce gastrointestinal disorders as nauseas, vomits and diarrhoea. These adverse effects will be evaluated in the data collection sheet.

In addition, all the extrapyramidal symptoms associated with the antipsychotic medication that have been explained previously, will be measured with the Simpson-Angus Scale (SAS) (60) (ANNEX 5) and will be compared in the two different groups.

Every undesired effect must be assessed as serious or not serious. The *Agencia Española del Medicamento y Productos Sanitario* (AEMPS) understood as serious those situations that:

- Provoke death.
- They threaten the patient's life.
- Provoke your hospitalization, or prolong it.
- They cause work or school disability.
- Induce congenital defects.
- Be clinically relevant.

7.9.3 Covariates

The following covariates have been chosen in order to describe the sample and assess the correct randomization of both groups:

Covariate	Type	Measure instrument	Categories or values
Age	Continuous quantitative variable	Clinical examination	18 - 24 25 - 40
Gender	Dichotomous nominal qualitative variable	Clinical examination	Male Female
Intelligence quotient (IQ)	Continuous quantitative variable	Clinical examination	<85 ≥85
Education years	Continuous quantitative variable	Clinical examination	<5 5-10 ≥10
Labour situation	Nominal qualitative variable	Clinical examination	Student Unemployed Employed Work absence for illness
Smoking status	Dichotomous nominal qualitative variable	Clinical examination	Yes No
History of mental illness	Dichotomous nominal qualitative variable	Clinical examination	Yes No
Cannabis use	Nominal qualitative variable	Clinical examination	Never Only once/twice lifetime Few times a year Once/twice monthly More than once a week
Alcohol use	Nominal qualitative variable	Clinical examination	Never Only once/twice lifetime Few times a year Once/twice monthly More than once a week

Table 4. *Covariates in the study.*

7.10 MEASURING INSTRUMENTS

7.10.1 Positive and Negative Syndrome Scale (PANSS)

This scale is considered a useful test to assess severity of symptoms and monitoring of response to treatment. It is a test consisting of 30 items that are scored from 1-absent to 7-considerable presence. It is composed of 4 subscales (61):

1. PANSS-P-Positive (7 items).
2. PANSS-N-Negative (7 items).
3. PANSS-PG-General Psychopathology (16 items).
4. PANSS-C-Compound (Subtract positive negative symptoms).

Development of the interview:

- The patient is encouraged to talk about his illness and his vital situation.
- Evaluation of exposed symptoms.
- Existence and severity of symptoms.
- Assess areas in which the patient has been reluctant throughout the interview, evaluating the patient's conceptual organization.

7.10.2 The MATRICS™ Consensus Cognitive Battery (MCCB™)

The cognitive assessment battery consists of 10 instruments to evaluate patients with schizophrenia, although these tests can also be used to evaluate general cognitive functioning or the presence of other pathologies such as dementia.

The tests included in the MCCB grouped by cognitive domains are 7 (62):

1. **Processing speed:** BACS coding and symbol subtest; Trail Making Test (TMT), part A; Semantic verbal fluency: animals.
2. **Attention/surveillance:** Continuous Performance Test-Identical Pairs (CPT-IP).
3. **Working memory:** spatial span of the Wechsler-III memory scale (WMS®-III); Letter-Number Span (LNS).
4. **Learning and verbal memory:** Hopkins Verbal Learning Test-Revised (HVLT-R ™).
5. **Learning and visual memory:** Brief Visuospatial Memory Test-Revised (BVMT-R ™).
6. **Reasoning and problem solving:** Neuropsychological Assessment Battery (NAB®) maze subtest.
7. **Social Cognition:** Emotional Control of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT ™).

Tests Included in the MCCB		
Cognitive domain	**Test**	**Description**
Speed of Processing	Brief Assessment of Cognition in Schizophrenia (BACS): Symbol-Coding	Timed paper-and-pencil test in which respondent uses a key to write digits that correspond to nonsense symbols
	Category Fluency: Animal Naming	Oral test in which respondent names as many animals as possible in 1 minute
	Trail Making Test: Part A	Timed paper-and-pencil test in which respondent draws a line to connect consecutively numbered circles placed irregularly on a sheet of paper
Attention/Vigilance	Continuous Performance Test—Identical Pairs (CPT-IP)	Computer-administered measure of sustained attention in which respondent presses a response button to consecutive matching numbers
Working Memory (nonverbal)	Wechsler Memory Scale®–3rd Ed. (WMS®-III): Spatial Span	Using a board on which 10 cubes are irregularly spaced, respondent taps cubes in same (or reverse) sequence as test administrator
(verbal)	Letter-Number Span	Orally administered test in which respondent mentally reorders strings of numbers and letters and repeats them to administrator
Verbal Learning	Hopkins Verbal Learning Test–Revised™ (HVLT-R™)	Orally administered test in which a list of 12 words from three taxonomic categories is presented and the respondent is asked to recall as many of the words as possible after each of three learning trials
Visual Learning	Brief Visuospatial Memory Test–Revised™ (BVMT-R™)	Test that involves reproducing six geometric figures from memory
Reasoning and Problem Solving	Neuropsychological Assessment Battery® (NAB®): Mazes	Seven timed paper-and-pencil mazes of increasing difficulty that measure foresight and planning
Social Cognition	Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT™): Managing Emotions	Paper-and-pencil multiple-choice test that assesses how people manage their emotions

Table 5. *Tests included in the MCCB and the description of the tests (63)*.

7.10.3 Wechsler Adult Intelligence Scale (WAIS-IV)

The Wechsler scales are composite, verbal and performance scales, made up of precise tests, called "subtests". On the one hand, they are heterogeneous inter-test scales, since they measure different functions and therefore different factors in each of them; on the other hand, they are homogeneous intratest scales, because each sub-test measures a single factor in its entirety. It is a test of maximum performance, in which the items have correct answers and a certain score is obtained for them (64).

WAIS-IV was developed to provide the most advanced measure of cognitive ability and results when addressing the changing clinical landscape. It is a core battery of 10 unique subtests focuses on four specific domains of intelligence (65):

- Verbal comprehension
- Perceptual reasoning
- Working memory
- Processing speed

7.11 DATA COLLECTION AND PROCEDURES

7.11.1 Admission and hospitalisation at UHA

All the patients with a FEP will be treated firstly by the Emergency services and the EIPP from the different areas of Girona: *EIPP Gironès-Pla de l`Estany, EIPP Garrotxa-Ripollès, EIPP Selva interior, EIPP Selva Marítima, EIPP Garrotxa Ripollès, EIPP Alt Empordà and EIPP Baix Empordà*. Then they will be admitted to *Unitat d'Hospitalització d'Aguts* (UHA) of *Parc Hospitalari Marti i Julià* (PHMIJ). In order to avoid the loss of communication and to avoid mistakes as much as possible, it is extremely important a good coordination between the different services. This will be possible thanks to the database model that XSMA works with.

Once there, it will be necessary to be a part of the study that the patient meet all the inclusion and none of the exclusion criteria to participate. Also, the patient must accept and give written consent after reading the information sheet (ANNEX 2). If the patient sign the informed consent document (ANNEX 3), their data would be entered in the data base by one of the investigators. The patient will be assigned an identification number in the database in order to preserve their personal data. It will be collected with de data sheet (ANNEX 6) the following parameters: age, gender, intelligence quotient, education years, labour situation, smoking status, history of mental illness, cannabis use and alcohol use. The intelligence quotient it will be measured with the Wechsler Adult Intelligence Scale IV (WAIS-IV).

7.11.2 First visit

The randomization will be done by the pharmacy staff, which will prepare the treatment for group 1 and group 2. During the 6-week clinical trial, the medication will be administered by the nurses and auxiliary according the randomization done previously. The main psychiatrist will not know which treatment is being taken for the patients in the trial. The pharmacological therapy is represented in the following table:

	GROUP 1	GROUP 2
MORNING 8:00h	2mg Risperidone* 5mL of a 100mg/mL oral solution of CBD	2mg Risperidone* 5mL of an oral solution of PLB
EVENING 20:00h	2mg Risperidone* 5mL of a 100mg/mL oral solution of CBD	2mg Risperidone* 5mL of an oral solution of PLB

Table 6. *Dosage of Risperidone and CBD during the day.*

**an extra dose of 2mg of Risperidone is accepted in the trial, maximum doses a day of 6mg.*

From this first visit, the patient will begin an oral dose of 4 mg Risperidone (twice a day a dose of 2mg) during 6 weeks. In the case of patients of group 1, they will receive a total dose of 1000mg/day of CBD (10 mL of a 100 mg/mL oral solution). CBD will be given every day, a 500mg dose twice a day (morning and evening) during the 6-week trial. If, on the contrary, the patient enters in the "non-cbd group", the patient will be taking a placebo along with the antipsychotic treatment. The placebo used in this study will be a product with the same characteristics, shape, image and measures as the cannabidiol format, so it will be practically indistinguishable for the patients and all the researcher team involved in the study.

This guideline is based on evidence of the efficacy and effectiveness of CBD in clinical trials as and adjunctive therapy in patients with chronic schizophrenia in the same doses as we are taking in this trial (47).

At baseline, as at the end of the 6-week trial, the psychiatrist will be in charge of doing to every patient in the study the MATRICS™ Consensus Cognitive Battery (MCCB™) and PANSS and collect in the data sheet. Also it will be necessary to do a blood test that includes blood count, biochemistry, liver profile and renal function.

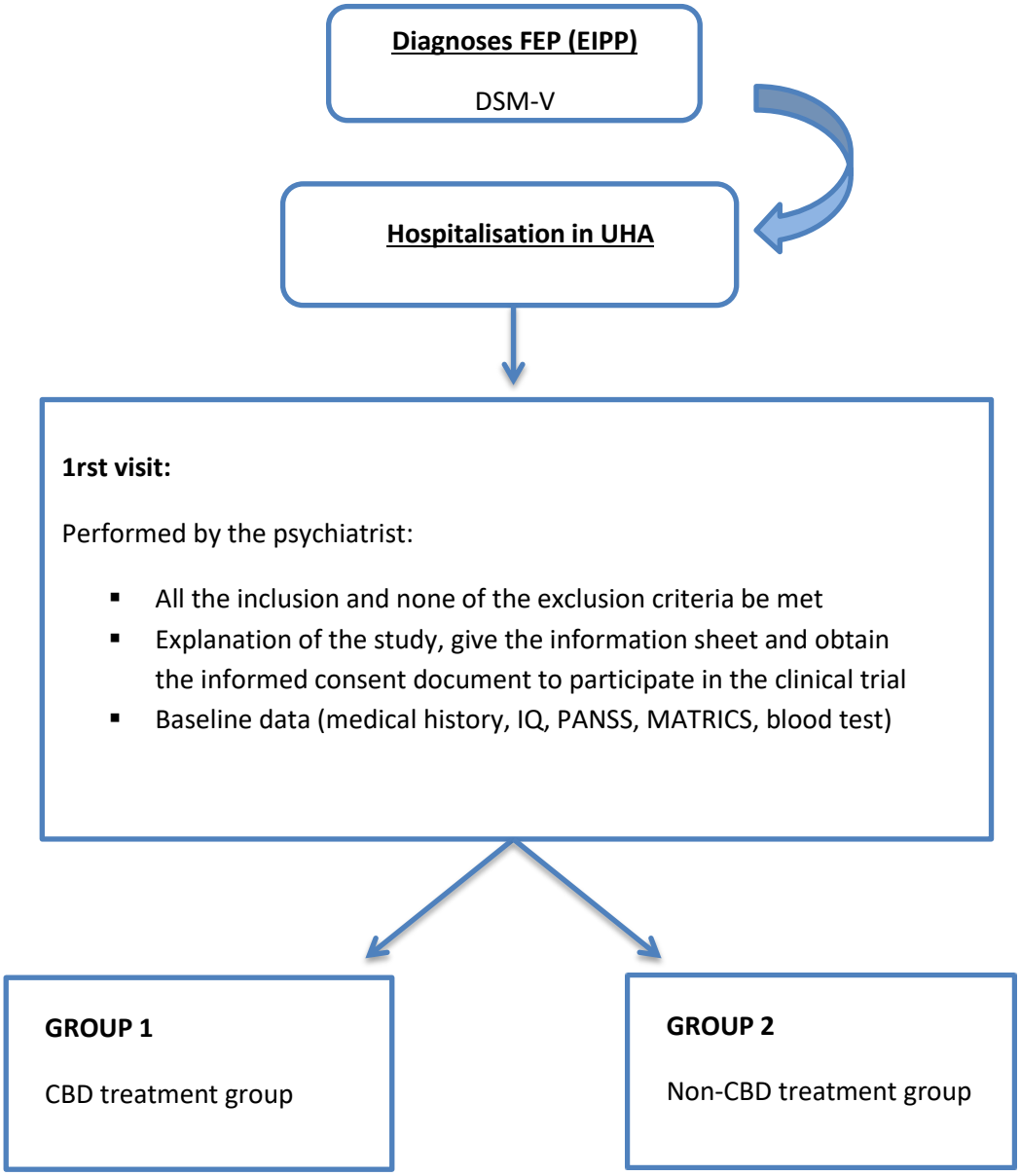

Figure 5. *Flow chart of therapeutic management.*

7.11.3 Subsequent visits: Data collection and follow up

During the treatment, patients will have follow-up visits with the main psychiatrist, in which the patient's condition and the possible unwanted effects during the entire cannabinoid treatment will be evaluated bi-weekly as it is described below. At baseline, week 2, week 4 and week 6 the psychiatrist will do the PANSS to the patients and take the notes in the data sheet.

Also, it will be necessary to do a blood test that includes blood count, biochemistry, liver profile and renal function every two weeks. At each visit, adverse events would be reported,

notify the extra medication that may have been given and also if an increase in medication has been necessary; treatment tolerance will be asked to the patient. In week 6, it will be done by the main psychiatrist the MATRICS™ Consensus Cognitive Battery (MCCB™) to compare cognition with the results at baseline.

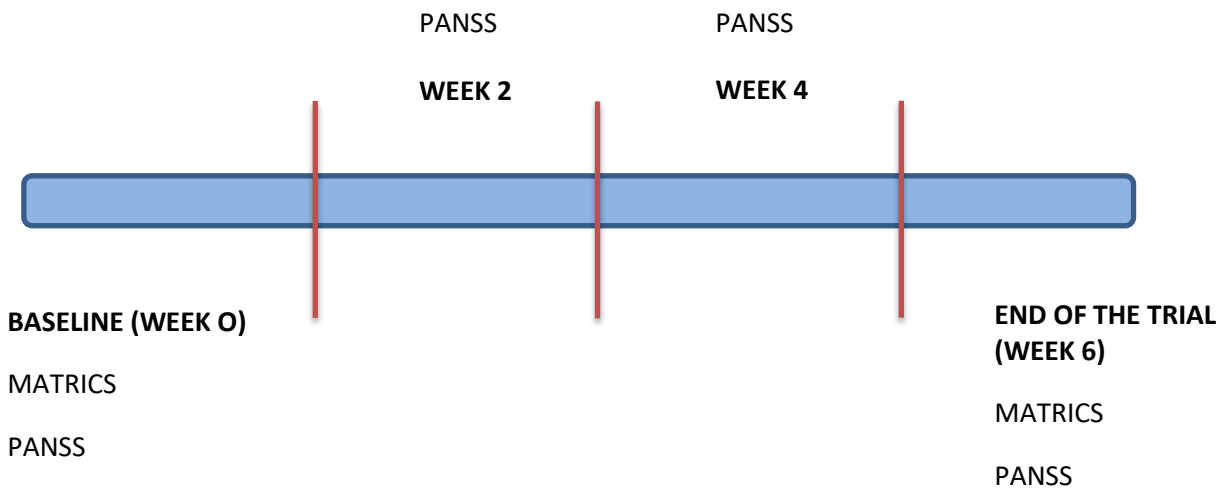

Figure 6. *Diagram of the tests to be carried out in the study.*

All this information will be collected through the data collection sheet and registered in the study data base. All the adverse effects experimented by the patient will be notified according to *AEMPS.*

8 STATISTICAL ANALYSIS

8.1 DESCRIPTIVE ANALYSIS

The results will be expressed as percentages for categorical variables and as mean +/- SD for continuous variables, assuming a normal distribution. If is not possible to assume a normal distribution, median and interquartile range will be computed.

8.2 BIVARIATE ANALYSIS

Baseline characteristics among study groups will be compared by means of bivariate analyses in order to check the random distribution of the covariates. We will use the Fisher's exact test or the Pearson's chi-square test for study group comparisons of categorical variables, and we will use the analysis of variance for comparison of continuous data.

8.3 MULTIVARIATE ANALYSIS

The primary efficacy variable, the change from baseline to week 6 in the PANSS score, will be analyzed with the use of a mixed-model repeated measures analysis, with the change from baseline in the PANSS score at each scheduled visit at week 2, 4 and 6 after baseline as the dependent variable. The model for the fixed effects will include terms for three effects: age, sex, and site of recruitment. Each secondary efficacy outcome will be assessed in a similar way with a repeated measures analysis. In order to avoid the bias related to the non-random loss of the study participants, the efficacy analyses will be conducted on the basis of the intention-to-treat principle, and will involve patients who had outcome measurements both at baseline and at least one measurement after the baseline assessment. We will use the last observation carried forward as a method for imputing data with dropouts.

All statistical analyses will be conducted using STATA 16 SE (STATA Corp. College Station, TX, USA), and we will employ an alpha level for statistical significance of 0.05 (two-tailed).

9 ETHICAL AND LEGAL ASPECTS

Before carrying out the study, the protocol will be presented to the Clinical Research Ethics Committee (CEIC) for evaluation and approval of the protocol. Any input and contributions said from the committee will be introduced in the study. Once the CEIC approves the trial, it will be necessary to ask for permission to the director of the center Hospital Santa Caterina (HSC) to start the study in the *Unitat d'Hospitalització d'Aguts* (UHA). In addition, the study will need to pass the authorization of the AEMPS, as it involves the administration and comparison of drugs.

In addition, it will be necessary to purchase civil insurance, since the centers civil liability policies are not enough.

It is important, as this study needs personal and collect data of the patients, it will be necessary to ensure the confidentiality and proper treatment of the patient data. With the aim of fulfilling this duty, all the personal information of the patient will be randomized and coded with a number and only the investigators will have access to it in case of needing it. The regulations that ensure the information explained are summarized in the following laws and decrees:

- *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de derechos digitales (BOE núm. 294, de 6 de diciembre de 2018).*
- *Real decreto-ley 5/2018, de 27 de julio, de medidas urgentes para la adaptación del Derecho español a la normativa de la Unión Europea en materia de protección de datos*.
- *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.*
- *Registro Español de Estudios Clínicos (BOE núm. 307, de 24 de diciembre de 2015).*
- *Ley 14/2007 de 3 de julio, de investigación biomédica (BOE núm. 159, de 4 de julio de 2007).*

Finally, the study will be carried out in compliance with the ethical principles established by The World Medical Association in the *Declaration of Helsinki,* signed in 1964 and last revised in October 2013 which ensures that the following principles are respected and followed: autonomy, nonmaleficence, beneficence and justice.

10 STUDY LIMITATIONS

There are some limitations that may interfere with the results of this study. They should therefore be considered:

Cannabidiol

Despite the CBD has been proved in several studies and the theoretical evidence states that it has not psychotropic effects, it can cause some adverse effects in patients as gastrointestinal disorders, insomnia, nauseas and headache. In addition, those patients such as pregnant women or planning pregnancy; patients with neurological disorders or neurodegenerative disease as well of this patients who their FEP was induced by cannabis do not meet the inclusion criteria and cannot benefit from the drug. Consequently, we will not be able to extrapolate these results to these types of FEP patients who do not enter into the study.

Knowing the controversy that exists today with cannabinoids, it is important that the patients receive all the necessary information so that he/she can decide for sure about the participation in the study. It must be explained to them that it is a drug that comes from marijuana and that unlike THC it has been found not to induce psychosis. It should also be noted that at these same doses, clinical trials have already been carried out on schizophrenic patients with a clear improvement in their psychotic symptoms and without relevant adverse effects. By following these steps we do not think it is a big limitation for the study.

Participants selection

In our study there might be a certain risk of selection bias regarding patients are selected according to their access to the XSMA, which would imply a selection bias because a part of the population in our region of study would not be a part of the clinical trial. However, in this study an attempt has been made to include all diagnostic categories (usually based on schizophrenia) associated with psychosis, with the objective to increase the representativeness of the sample.

Data collection

In order to avoid or diminish the risk of information bias (detection and realization bias), the study is conducted on a double-blind clinical trial as the patients and the investigators do not known the treatment that are in each group of participants. In addition, the objectives

described in the study are specific and not subject to subactive interpretation, and the variables determined are evaluated with validated external scales.

Cofounding factors

Regarding to cofounding factors, it is possible confusion bias that we hopefully minimize by establishing covariates and randomizing the sample. Also, in the statistical analysis of the results and interpretation it will be considered.

Sample size

In relation to the sample size, a calculator has been used to obtain a statistically significant sample size to see an increase equal to or greater than 20% in the reduction of symptomatology in patients with a first psychotic episode. Our thoughts are that the result of the 174 patients and the 12 month recall time is a great and significant sample size.

Losses during the study

Taking into account studies already carried out using CBD as a therapy in psychotic patients, the loss of patients during the clinical trial was minimal. As our study is a 6-week clinical trial we do not think it will be necessary, considering the low risk of loss, an active replacement of patients. In addition, we have calculated a sample size with a 5% loss of patients, which we consider sufficient based clinical trials done and the studies made in recent years.

Budget

Even if the study is carried out in a hospital and the material and equipment is already included, the CBD must be bought externally and the price is high at present. For this reason we think that it would be necessary to have a financing or agreement with a pharmaceutical distributor of this product in order to carry out the clinical trial. Below it has been explained different solutions to this concern.

11 WORK PLAN AND CHRONOGRAM

The sequence of the different activities in this prospective, double-blind, randomized and controlled clinical trial will be done in the following sequence:

STAGE 0: Elaboration of the protocol design, primary research and coordination (3 months).

- In this first phase, it will be done a bibliographic research and elaboration of the protocol.
- Then the project will be presented to the research team with the objective of standardize the data collection and the procedure of the protocol in the different centres: *UHA, EIPP Gironès-Pla de l`Estany, EIPP Garrotxa-Ripollès, EIPP Selva interior, EIPP Selva Marítima, EIPP Garrotxa Ripollès, EIPP Alt Empordà and EIPP Baix Empordà*.
- The main psychiatrists of the each center will be responsible to inform the rest of the professionals that participate in the study in order to ensure a good transfer of information.

STAGE I: Ethical and legal approval (1 month).

- Presentation to the Comité d'Etica d'Investigación Clínica (CEIC) of the clinical trial protocol to receive the approval and be allowed to implement the study.
- Contracting an insurance.

STAGE II: Data collection (12 months).

- The patients with FEP will be proposed to participate in the project by the referring of the UHA or the different EIPPs. The participants would have to give the consent to be a part of the trial after they received all the information about the study and signed the informed consent.
- After the patients are hospitalized, they will be during 6-week in the UHA and the main psychiatrist will do the first visit and the follow-up visits every two weeks. All the data will be collect in the data collection sheet and introduced in the database.

STAGE III: Data analysis (1 month).

- All the data collected during the previous phase will be analyzed by an experienced and formed statistical following the statistical plan of the protocol.

STAGE IV: Interpretation of the results and elaboration of the discussion and conclusion of the clinical trial (2 months).

STAGE V: Publication and dissemination phase (3 months).

- Publication of the study and subsequently distribution of this into journal articles, reports, or conference presentations.
- Presentation in several congresses such as the *Congreso Nacional de Psiquiatría, International College of Neuropsychopharmacology* (CINP) or *Congreso de Patología Dual.*

	2021												2022									
Stages:	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT
STAGE 0:																						
Bibliographic research																						
Protocol elaboration																						
Present the protocol to the different services																						
STAGE I:																						
CEIC approval																						
Hospital direction approval																						
Contracting an insurance																						
STAGE II:																						
Formation																						
Data collection and follow-up visits																						
STAGE III:																						
Data analysis																						
STAGE IV:																						
Interpretation of the results																						
Elaboration of the discussion and conclusions																						
STAGE V:																						
Publication of the study																						
Dissemination and presentation in congresses																						

Table 6. *Chronogram.*

12 BUDGET

Item	Cost per unit Cost per hour	Quantity	Total
STAFF			
Qualified Statistician	50€/hour	50 hours	2.500€
Research team	-	-	0€
INSURANCE			
Trial policy	20.000€/trial	1	20.000€
SCALE' COPYRIGHT			
PANSS	-	-	0€
SAS	-	-	0€
WAIS-IV	1.355,8€/kit	1	1.355,8€
MATRICS	1.275€/kit	1	1.275€
MATERIAL			
Risperidone	-	-	0€
Cannabidiol (CBD)*	10 mL of CBD 100mg/mL: 54,95€/unit	87 patients (x42 days)= 3654 units	200.787,3€
Printing copies	0,06€/unit	180	10,8€
CONFERENCES (3 investigators)			
Inscription	500€/inscription	1	500€
Travelling	300€/person	3	900€
Accomodation	200€/person	3	600€
PUBLICATION AND DISSEMINATION			
Publication in open access journal	2.550€/publication	1	2.550€
TOTAL			**230.478,9€**

The budget doesn`t include equipment such as computers, blood test and material that are already available in the different services that are a part of the study. Also, the psychiatrist and personnel that participate in the study will not receive financial compensation.

As this is a non-commercial study, it will be not necessary the authorization of a clinical trial by the AEMPs.

*In the Fleasibility section the high price of this product has been justified in relation to the therapeutic utility it may have in the future.

13 FEASIBILITY

We consider that this study is feasible and available to carry out for the following reasons described:

Firstly, the XSMA of the IAS is the public network of the Girona region which takes care of the mental health of the inhabitants of this region (765,554 inhabitants). The functions of this network and activity in the care of the inhabitants of this region are based on community care as well as hospital care. The centres and teams that make up this group are in constant contact with the aim of having a good coordination for a better efficiency of the services.

As it is explained in the sample selection, the study participants will be selected by the Emergency services and the EIPP from the different areas of Girona. When these patients are diagnosed with a FEP, they will be admitted and hospitalized into the UHA. This will allow obtaining the entire necessary sample to make the study. In order to avoid mistakes as much as possible and information loss, team work and good communication between the different professionals involved in the study will be essential. The database model that XSMA works with will facilitate this whole process described above.

In addition, the entire team of professionals (psychiatrists, nurses, paramedics...) working for the IAS will combine their daily clinical practice with the participation in the study without financial reward. Also, all the necessary data needed for this clinical trial will be obtained across the medical equipment and resources that are used in hospital practice on a routine basis.

Since this study is a prospective, randomized, double-blinded and controlled 6-week clinical trial, a long follow-up will not be necessary and also, this design of the study allows reducing the risk of biases that may appear during the study.

As for the budget, we think it could be the main feasibility concern in the study. Objectively and externally, the cost of this 6-week clinical trial may seem excessive. Even so, we believe that it is a very innovative opportunity to seek solutions for a pathology that is currently very limiting for the patient and the family. The future of this product, the CBD, may have great potential for the management of psychosis in the coming years and this study may allow us to provide more information and safety on this drug which is still discovering its beneficial effects in different pathologies. It may be the beginning of a new form of treatment in psychosis that will help to determine whether it can reduce the symptoms early on and also the effect on the

cognition impairments associated with psychosis and consequently to improve the quality of life of the patient. Furthermore, as mentioned above, there are no relevant adverse effects that are susceptible to clinical worsening compared to those that we know antipsychotics produce.

In addition, we believe that various resources can help us solve this problem as:

- Firstly, ask for non-commercial clinical trial grant to *Programa de Promoción de la Investigación Biomédica y en Ciencias de la Salud del Instituto Carlos III.*
- Secondly, ask for a grant to *La Fundación CANNA,* non-profit initiative of the company CANNA España Fertilizantes SL, which provides financial support to various congresses, initiatives and clinical studies dedicated to the advancement of research into the medicinal use of cannabinoids.
- Thridly, we could also use the international medical cannabis companies that have been authorised to manufacture and distribute this product in Spain, such as *Aurora Cannabis, Linneo Health or Canopy Growth* (in Spain acquired Cáñamos y Fibras Naturales SL, Cafina).
- Finally, if it is not possible to obtain a grant from these institutions and companies to carry out the clinical trial, we could resort to financing a pharmaceutical company such as GW Pharmaceuticals, Pharmabinoid or MGC Pharma.

14 PROJECT IMPACT AND FUTURE PERSPECTIVES

The subject of the cannabinoids and psychosis has generated controversy in recent years on the basis of epidemiological studies and clinical trials. This study will provide new evidence and a better insight into the impact of the CBD as an adjunctive therapy in patients with FEP, allowing to observe improvement in symptomatology and cognition in these type of patients.

Furthermore, more and more studies are being carried out to see how far this product can go therapeutically, and it has already been approved by international organizations such as the FDA for use in certain pathologies; this study could provide more information for who knows, in the recent years it could be a potential new treatment for psychosis**.**

In addition, at the time of the present protocol, there is no study comparing treatment with CBD added to an antipsychotic drug in patients who have suffered a first psychotic episode with patients not taking it. So, in our opinion, it would be a great advance in the treatment of the first psychotic episodes and also, an incentive for the study of this drug to take advantage of all the therapeutic possibilities it may have and we still don't know.

15 CONFLICTS OF INTEREST

The authors declare no conflict of interests

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17 ANNEXES

ANNEX 1: XARXA DE SALUT MENTAL I ADDICCIONS (XSMA)

The Xarxa de Salut Mental i Addicions (XSMA) of the Institute d`Assistència Sanitaria (IAS) is the public network of the Girona regions specialized in mental health care for the reference population (765.554 inhabitants).

This network has a total or partial hospitalization services, located in PHMIJ (Salt) and also community care services.

Concerning to hospital care, we find:

- **Unitat de ReferÈncia en Psiquiatria infantil i juvenil (URPIJ):** Is a unit for people under 18 years old; specialized in acute episodes in situations of crisis. It has 10 beds.
- **Unitat d`Hospitalització d`Aguts (UHA):** This unit is for people over 18 years old who have had a crisis situation, which due to its severity require an intensive short – term treatment. It has 42 beds.

For community care, we have:

- **Equips d`Intervenció Precoç en la Psicosi (EIPP):** The objective of this unit is to detect early those people who present a psychosis or risk of developing it, in addition to carrying out a comprehensive treatment depending on the needs of the person.
- **Centres de Salut Mental Infant i Juvenil (CSMIJ):** Offer specialized attention to infants and adolescents from 0 to 18 years old with mental health problems and/or addictions. Children and adolescents who, due to the complexity of their disorder, need more specialized attention that cannot be resolved from the primary care centers. Treatment includes family members while coordination with the school and other services involved.
- **Centres de Salut Mental d`Adults:** They are a free public service that offers specialized attention to people over 18 years old with psychiatric pathology and/or behavioral disorders, from a multidisciplinary and community perspective.

These organizations are at: Selva interior and Selva marítima, Ripollés, La Garrotxa, Baix empordà, Alt Empordà, Gironès-Pla de l`Estany.

ANNEX 2: INFORMATION SHEET

FULL D'INFORMACIÓ PER AL PACIENT:

Títol de l'estudi:

EFFECTS OF CANNABIDIOL AS AN ADJUNCTIVE THERAPY IN PATIENTS WITH A FIRST EPISODE OF PSYCHOSIS

Benvolgut/da,

Aquest document té la finalitat d'informar i proveir tota la informació necessària per a que vostè pugui decidir de manera totalment voluntària la seva participació en l'assaig clínic que es realitzarà a la Unitat d'Hospitalització d'Aguts (UHA) del Parc Hospitalari Marti i Julià (PHMIJ) de Salt (Girona).

La seva participació a l'estudi, com ja s'ha esmentat, és voluntària i sense ànim de lucre, i la no participació en aquest no suposarà ningun canvi en la pràctica clínica per part del seu metge en relació a l'assistència mèdica, el seu tractament i control posterior.

Objectiu de l'estudi

Actualment, la incidència d'un primer episodi psicòtic en el nostre ambient és elevada (31.6 de cada 100,000 habitants). Som coneixedors de les limitacions que suposa aquesta malaltia cap al malalt, que pot experimentar sentiments com ara: por, confusió, malestar, desorientació,... així com per la família que ho pateix i que molts cops han de carregar amb tot el pes assistencial d'aquesta persona.

L'objectiu d'aquest estudi és demostrar que afegint una solució oral de Cannabidiol (CBD) dos cops al dia, sense efectes psicotròpics com elS que es coneixen de la droga cànnabis, hi hagi una disminució en la simptomatologia pròpia de la psicosis. De manera secundària, també es pretén avaluar si existeix una milloria en el dèficit cognitiu que s'ha vist que es produeix associat a l'episodi psicòtic.

Procediment i activitats de l'estudi

Si vostè, un cop llegit aquest document, decideix participar en aquest estudi el psiquiatra del centre li explicarà que rebrà el tractament que segons l'evidència científica i la pràctica clínica diària s'ha vist que es efectiva en un cas de primer episodi psicòtic com és el fàrmac Risperidona, a dosis baixes. A aquest tractament serà al mateix per tots els participants a l'estudi amb l'única diferència que aleatòriament vostè serà inclòs en un grup 1 o 2. En el grup

1, el tractament consistirà en Risperidona i una solució oral de CBD; en el grup 2, el tractament consistirà en Risperidona i una solució oral d'una substància inactiva. Ni vostè ni els professionals i equip sanitari del centre sabran quin medicament o quin grup li ha tocat. Així, ens assegurem un correcte funcionament. És important que tingui clar que en cap moment es prioritzarà a un grup que a un altre, ni tindran un seguiment diferent.

Un cop el psiquiatra asseguri que compleix tots els criteris d'inclusió i cap criteri d'exclusió, vostè entrarà a formar part d'aquest assaig clínic de 6 setmanes de duració. Vostè haurà d'estar ingressat a l'Hospital santa Caterina en l'UHA fins que així ho determini el psiquiatra. Finalment, en acabar aquest període, es realitzarà una anàlisi de les dades obtingudes per part d'un estadístic. Totes aquestes dades es posaran a la seva disposició i el seu psiquiatra li explicarà detalladament.

En el cas que vostè es negui a participar a l'estudi no se li assignarà cap d'aquestes dues solucions però si que rebrà el tractament antipsicòtic determinat pel psiquiatra responsable del seu cas.

Aspectes legals

L'estudi ha estat aprovat pel Comitè d'Ètica d'Investigació Clínica (CEIC) de l'Hospital Santa Caterina de Salt (Girona).

Totes les dades obtingudes i proporcionades pels pacients seran tractades de manera curosa i seran totalment confidencials. D'acord a la *Llei Orgànica 3/2018, de 5 de Desembre, de Protecció de Dades Personals i garantia de Drets Digitals* vostè disposarà del seu dret d'accés i cancel·lació d'aquestes dades. Tota la informació que es tingui amb la finalitat de recerca serà emmagatzemada en la base de dades i cada pacient rebrà un codi numèric per identificar-lo i preservar així, la seva identitat.

El promotor de l'estudi disposa d'una pòlissa d'assegurança que s'ajusta a la legislació vigent i que li permetrà tenir una compensació econòmica en cas de detriment de la salut que pugui originar-se a conseqüència de participar en l'assaig clínic fet que, segons el nostre coneixement, és molt poc probable.

Els investigadors que participen en l'assaig clínic no obtindran cap benefici econòmic de l'estudi. De la mateixa manera, vostè no rebrà remuneració pel fet de formar part d'aquest, així com no li suposarà cap despesa. Els medicaments que es faran servir en l'estudi no hauran de ser pagats per vostè.

Canvi d'opinió

La participació és totalment voluntària i està en el seu dret de revocar el consentiment de participació en l`estudi en qualsevol moment sense ser necessari i obligat donar explicacions o justificar la causa.

Més informació

En cas que tingui qualsevol dubte o vulgui rebre més informació sobre l'estudi pot preguntar al psiquiatra que porti el seu cas, contactar amb l'Unitat d'Hospitalització d'Aguts (UHA), així com pot consultar altres professionals sanitaris per a qualsevol dubte que presenti.

HOJA DE INFORMACIÓN PARA EL PACIENTE

Título del estudio:

EFFECTS OF CANNABIDIOL AS AN ADJUNCTIVE THERAPY IN PATIENTS WITH A FIRST EPISODE OF PSYCHOSIS

Estimado / a,

Este documento tiene la finalidad de informar y proveer toda la información necesaria para que usted pueda decidir de manera totalmente voluntaria su participación en el ensayo clínico que se realizará en la Unidad de Hospitalización de Agudos (UHA) del Parc Hospitalari Marti i Julià (PHMIJ) de Salt (Girona).

Su participación en el estudio, como ya se ha mencionado, es voluntaria y sin ánimo de lucro, y la no participación en este no supondrá ningún cambio en la práctica clínica por parte de su médico en relación a la asistencia médica, su tratamiento y control posterior.

Objetivo del estudio

Actualmente, la incidencia de un primer episodio psicótico en nuestro ambiente es elevada (31.6 de cada 100,000 habitantes). Somos conocedores de las limitaciones que supone esta enfermedad hacia el enfermo, que puede experimentar sentimientos como: miedo, confusión, malestar, desorientación,… así como para la familia que lo sufre y que muchas veces tienen que cargar con todo el peso asistencial de esta persona.

El objetivo de este estudio es demostrar que añadiendo una solución oral de Cannabidiol (CBD) dos veces al día, sin efectos psicotrópicos como el que se conocen de la droga cannabis, haya una disminución en la sintomatología propia de la psicosis. De manera secundaria, también se pretende evaluar si existe una mejoría en el déficit cognitivo que se ha visto que se produce asociado al episodio psicótico.

Procedimiento y actividades del estudio

Si usted, una vez leído este documento, decide participar en este estudio el psiquiatra del centro le explicará que recibirá el tratamiento que según la evidencia científica y la práctica clínica diaria se ha visto que es efectiva en un caso de primer episodio psicótico como es el fármaco Risperidona, a dosis bajas. A este tratamiento será el mismo para todos los participantes en el estudio con la única diferencia que aleatoriamente usted será incluido en un grupo 1 o 2. En el grupo 1, el tratamiento consistirá en Risperidona y una solución oral de

CBD; en el grupo 2, el tratamiento consistirá en Risperidona y una solución oral de una sustancia inactiva. Ni usted ni los profesionales y equipo sanitario del centro sabrán qué medicamento o qué grupo le ha tocado. Así, nos aseguramos un correcto funcionamiento. Es importante que tenga claro que en ningún momento se priorizará a un grupo que a otro, ni tendrán un seguimiento diferente.

Una vez el psiquiatra asegure que cumple todos los criterios de inclusión y ningún criterio de exclusión, usted entrará a formar parte de este ensayo clínico de 6 semanas de duración. Usted deberá estar ingresado en el Hospital Santa Caterina en la UHA hasta que así lo determine el psiquiatra. Finalmente, al terminar este periodo, se realizará un análisis de los datos obtenidos por parte de un estadístico. Todos estos datos se pondrán a su disposición y su psiquiatra le explicará detalladamente.

En caso de que usted se niegue a participar en el estudio no se le asignará ninguna de estas dos soluciones pero sí que recibirá el tratamiento antipsicótico determinado por el psiquiatra responsable de su caso.

Aspectos legales

El estudio ha sido aprobado por el Comité de Ética de Investigación Clínica (CEIC) del Hospital Santa Caterina de Salt (Girona).

Todos los datos obtenidos y proporcionados por los pacientes serán tratados de manera cuidadosa y serán totalmente confidenciales. De acuerdo a la *Ley Orgánica 3/2018, de 5 de Diciembre, de Protección de Datos Personales y garantía de Derechos Digitales* usted dispondrá de su derecho de acceso y cancelación de estos datos. Toda la información que se tenga con el fin de investigación será almacenada en la base de datos y cada paciente recibirá un código numérico para identificarlo y preservar así, su identidad.

El promotor del estudio dispone de una póliza de seguro que se ajusta a la legislación vigente y que le permitirá tener una compensación económica en caso de detrimento de la salud que pueda originarse a consecuencia de participar en el ensayo clínico que, según nuestro conocimiento, es muy poco probable.

Los investigadores que participan en el ensayo clínico no obtendrán ningún beneficio económico del estudio. Del mismo modo, usted no recibirá remuneración por el hecho de formar parte de este, así como no le supondrá ningún gasto. Los medicamentos que se utilizarán en el estudio no deberán ser pagados por usted.

Cambio de opinión

La participación es totalmente voluntaria y está en su derecho de revocar el consentimiento de participación en el estudio en cualquier momento sin ser necesario y obligado dar explicaciones o justificar la causa.

Más información

En caso de que tenga cualquier duda o quiera recibir más información sobre el estudio puede preguntar al psiquiatra que lleve su caso, contactar con la Unidad de Hospitalización de Agudos (UHA), así como puede consultar otros profesionales sanitarios para cualquier duda que presente.

ANNEX 3: INFORMED CONSENT

CONSENTIMENT INFORMAT

Títol del estudi:

EFFECTS OF CANNABIDIOL AS AN ADJUNCTIVE THERAPY IN PATIENTS WITH A FIRST EPISODE OF PSYCHOSIS

Jo (Nom i cognoms)_____, amb DNI/NIF _____, amb data de naixement_____, accepto participar en aquest estudi de manera voluntària i confirmo que:

- He llegit la fulla informativa sobre l'estudi que se m`ha entregat i he pogut realizar totes les preguntes corresponents per poder resoldre dubtes que m'han sorgit.
- He rebut tota la informació necessària sobre l'estudi i he entès la informació que se m'ha donat sobre la meva participación en aquest.
- He estat correctament informat/da pel Dr./Dra. _____ de les implicacions i finalitats de l'estudi.
- Entenc que la meva participació és voluntària i que estic en el meu dret de revocar el meu consentiment de participació en l`estudi, sense ser necessari i obligat donar explicacións o justificar la causa.
- Entenc que es respectarà la confidencialitat de les dades proporcionades i que s'utilitzaran amb finalitats purament d'investigació médica.

Firma del participant: Firma de l'investigador/a:

_____, _____ de _____ del 20____.

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo (nom i cognoms)_____, revoco el document prèviament firmat en el qual acceptava participar en l'estudi i decideixo no continuar en aquest.

Firma del participant:

_____, _____ de _____ del 20____.

CONSENTIMIENTO INFORMADO

Título del estudio:

EFFECTS OF CANNABIDIOL AS AN ADJUNCTIVE THERAPY IN PATIENTS WITH A FIRST EPISODE OF PSYCHOSIS

Yo (Nombre y apellidos),_____, con DNI / NIF _____, con fecha de nacimiento _____, acepto participar en este estudio de manera voluntaria y confirmo que:

- He leído la hoja informativa sobre el estudio que se me ha entregado y he podido realizar todas las preguntas correspondientes para poder resolver dudas que me han surgido.
- He recibido toda la información necesaria sobre el estudio y he entendido la información que se me ha dado sobre mi participación en este.
- He sido correctamente informado / a por Dr./Dra. _____ de las implicaciones y finalidades del estudio.
- Entiendo que mi participación es voluntaria y que estoy en mi derecho de revocar mi consentimiento de participación en el estudio, sin ser necesario y obligado dar explicaciones o justificar la causa.
- Entiendo que se respetará la confidencialidad de los datos proporcionados y que se utilizarán con fines puramente de investigación médica.

Firma del participante: Firma del investigador / a:

_____, _____ de _____ del 20____.

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO

Yo (nombre y apellidos), _____, revoco el documento previamente firmado en el que aceptaba participar en el estudio y decido no continuar en este.

Firma del participante:

_____, _____ de _____ del 20____.

ANNEX 4: POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS)

1. Delirios	1	2	3	4	5	6	7
2. Desorganización conceptual	1	2	3	4	5	6	7
3. Alucinaciones	1	2	3	4	5	6	7
4. Excitación	1	2	3	4	5	6	7
5. Grandiosidad	1	2	3	4	5	6	7
6. Suspicacia/perjuicio	1	2	3	4	5	6	7
7. Hostilidad	1	2	3	4	5	6	7
Escala positiva (PANSS-P)	*Puntuación directa:*				*Percentil:*		
1. Embotamiento afectivo	1	2	3	4	5	6	7
2. Retraimiento emocional	1	2	3	4	5	6	7
3. Contacto pobre	1	2	3	4	5	6	7
4. Retraimiento social	1	2	3	4	5	6	7
5. Pensamiento abstracto	1	2	3	4	5	6	7
6. Fluidez de la conversación	1	2	3	4	5	6	7
7. Pensamiento estereotipado	1	2	3	4	5	6	7
Escala negativa (PANSS-N)	*Puntuación directa:*				*Percentil:*		
	1	2	3	4	5	6	7
Escala compuesta (PANSS-C)	*Puntuación directa:*				*Percentil:*		
1. Preocupación somática	1	2	3	4	5	6	7
2. Ansiedad	1	2	3	4	5	6	7
3. Sentimientos de culpa	1	2	3	4	5	6	7
4. Tensión motora	1	2	3	4	5	6	7
5. Manierismos/posturas	1	2	3	4	5	6	7
6. Depresión	1	2	3	4	5	6	7
7. Enlentecimiento motor	1	2	3	4	5	6	7
8. Falta de colaboración	1	2	3	4	5	6	7
9. Pensamientos inusuales	1	2	3	4	5	6	7
10. Desorientación	1	2	3	4	5	6	7
11. Atención deficiente	1	2	3	4	5	6	7
12. Ausencia de *insight*	1	2	3	4	5	6	7
13. Trastornos de la volición	1	2	3	4	5	6	7
14. Control deficiente de los impulsos	1	2	3	4	5	6	7
15. Ensimismamiento	1	2	3	4	5	6	7
16. Evitación social activa	1	2	3	4	5	6	7
Psicopatología general (PANSS-PG)	*Puntuación directa:*				*Percentil:*		
	1	2	3	4	5	6	7

ANNEX 5: SIMPSON ANGUS SCALE (SAS)

Instrucciones: Esta escala consiste en una lista de 10 síntomas, cada uno de los cuales debe ser clasificado en una escala de 5 grados de gravedad. Para cada síntoma, por favor, marque el grado que mejor describe el estado actual del paciente.

1. **Forma de andar.** Se examina al paciente mientras camina en la habitación: su paso, el braceo, su postura general, todo ello constituye la base para una puntuación global en este parámetro
   0. Normal
   1. Leve disminución en el braceo mientras el paciente camina
   2. Obvia disminución en el braceo que sugiere rigidez de los hombros
   3. Paso rígido con braceo escaso o inexistente
   4. Paso rígido con los brazos ligeramente pronados; o bien paso en actitud encorvada arrastrando los pies, con propulsión y retropulsión
   9. No clasificable

2. **Caída de los brazos.** El paciente y el examinador suben los brazos hasta la altura del hombro y los dejan caer a los lados. En un sujeto normal, se escucha un fuerte palmetazo al golpear los brazos los lados del tronco. En el paciente con síndrome de Parkinson severo, los brazos caen muy lentamente
   0. Caída libre normal con palmetazo audible y rebote
   1. Caída enlentecida ligeramente con contacto menos audible y poco rebote
   2. Caída enlentecida, sin rebote
   3. Enlentecimiento marcado, sin ningún palmetazo
   4. Los brazos caen como contra resistencia; como a través de pegamento
   9. No clasificable

3. **Movimiento de los hombros.** Se flexionan los brazos del sujeto en ángulo recto a nivel del codo y son agarrados sucesivamente por el examinador que agarra una mano y aprieta con la otra el codo del paciente. Se empuja la parte superior del brazo del paciente de un lado para otro rotando externamente el húmero. Se estima y se valora el grado de resistencia desde la normalidad a la rigidez extrema. Se repite el procedimiento con una mano, palpando la cápsula articular mientras tiene lugar la rotación
   0. Normal
   1. Ligera rigidez y resistencia
   2. Rigidez y resistencia moderadas
   3. Rigidez marcada con dificultad para el movimiento pasivo
   4. Rigidez extrema casi con la articulación congelada
   9. No clasificable

4. **Rigidez de los codos.** Se flexionan las articulaciones de los codos en ángulo recto por separado, flexionándolas y extendiéndolas pasivamente, observando el bíceps del sujeto y palpándolo simultáneamente. Se clasifica la resistencia al procedimiento
   0. Normal
   1. Ligera rigidez y resistencia
   2. Rigidez y resistencia moderadas
   3. Rigidez marcada con dificultad para el movimiento pasivo
   4. Rigidez extrema casi con la articulación congelada
   9. No clasificable

5. **Rigidez de la muñeca.** El examinador sostiene la muñeca con una mano y los dedos con la otra mano, extendiendo y flexionando la muñeca, y moviéndola en dirección cubital y radial o dejando que caiga la muñeca extendida por su propio peso, o bien agarrando el brazo por encima de la muñeca moviéndola de un lado a otro. Una escala de «1» sería una mano que se extiende fácilmente, cae suelta, o se mueve arriba y abajo fácilmente
   0. Normal
   1. Ligera rigidez y resistencia
   2. Rigidez y resistencia moderadas
   3. Rigidez marcada con dificultad para el movimiento pasivo
   4. Rigidez extrema casi con una muñeca congelada
   9. No clasificable

ANNEX 6: DATA COLLECTION SHEET

EIPP:_____ CODI PARTICIPANT:__ __ __ __ Data: __/__/____

Nª Història clínica: _____ Dr. Dra. responsable: _____

DADES PERSONALS I ANTECEDENTS DEL PARTICIPANT:

Edat: _____

Gènere: Home ☐ Dona ☐

Quoficient intel·lectual (IQ): _____

Anys de formació acadèmica: <5 ☐ 5-10 ☐ ≥10 ☐

Situació laboral: Estudiant ☐ Atur ☐ Actiu ☐ Absència laboral per malaltia ☐

Història d'antecedents de malaltia mental: Sí ☐ No ☐

ANTECEDENTS TÒXICS

De les següents substàncies que apareixen a continuació, quin és el consum que en té?

TABAC: Mai ☐ Només una vegada / dues vegades a la vida ☐

Poques vegades a l'any ☐ Un cop / dues vegades al mes ☐

Més d'una vegada a la semana ☐

CANNABIS: Mai ☐ Només una vegada / dues vegades a la vida ☐

Poques vegades a l'any ☐ Un cop / dues vegades al mes ☐

Més d'una vegada a la semana ☐

ALCOHOL: Mai ☐ Només una vegada / dues vegades a la vida ☐

Poques vegades a l'any ☐ Un cop / dues vegades al mes ☐

Més d'una vegada a la semana ☐

DADES VISITA: SEMANA_____ (0,2,4,6)

- **Positive and Negative Syndrome Scale (PANSS)**

  - PANSS-P-Positive: _____
  - PANSS-N-Negative: _____
  - PANSS-PG-General Psychopathology: _____

  - PANSS puntuació TOTAL: _____

- ***MATRICS™ Consensus Cognitive Battery (MCCB™)*** puntuació TOTAL: _____

Tolerància al tractament:

-Com se sent sobre els possibles efectes secundaris que ha patit o està patint recentment associats al tractament? Molt malament ☐ Malament ☐ Bastant bé ☐ Bé ☐

-Ha patit algun dels següents símptomes escrits: diarrea, vòmits, nàusees, insomni o somnolència. Si l'ha resposta és afirmativa indiqui quin d'aquests: Sí ☐ : _____

No ☐

-Símptomes extrapiramidals: Simpson-Angus scale puntuació: _____

MEDICACIÓ EXTRA ADMINISTRADA

S'ha donat dosis extra de Risperidona? Sí ☐ No ☐

Si la resposta és afirmativa, quants cops des de la darrera visita? _____

Altres complicacions:

_____

_____

_____

_____

_____