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FACULTY OF MEDICINE

Bipolar patients with alcohol consumption will have more relapses?

A 5 year follow-up study.

END OF TERM PROJECT

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Abstract

Title. Bipolar patients with alcohol consumption will have more relapses? A 5 year follow-up study.

Background. Alcohol use disorder (AUD) occurs at high rates in Bipolar disorder (BD). However, the reasons of this co-occurrence are unknown. It is estimated that 46.2% of bipolar I patients had a lifetime history of AUD. Alcohol is strongly associated with maintaining or developing affective symptoms and could act as course or episode modifier of BD. The association of these two disorders can influence on the onset, the duration, on the progression and on the time of recovery of the episode. It is associated with poor symptomatic, with more hospitalizations and with poor response to the treatment. Also, it increases the psychosocial stress and residual, irritability, depressive and anxiety symptoms. Has influence on sleep and circadian rhythm and increases the risk of morbidity and chronicity of the disorder. All of these factors can lead to more relapses and to a shorter time between episodes. Although BD is one of the most severe chronic mental illnesses and it has been hypothesized that bipolar patients who have an alcohol consumption will have more relapses than those who don't have this alcohol consumption.

Aim. Determine if the bipolar patients who have an alcohol consumption will have more relapses than those who don't have this alcohol consumption, using the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria for depression, mania and mixed features, in order to classify the patients as "relapse" and "no relapse" and determine if patients have a relapse or don't.

Methods. This study will be a prospective cohort study, which will include ninety patients with bipolar disorder, from "Xarxa de Salut Mental" de Girona, using a consecutive sequential sampling. These patients will be followed for 5 years, after being assigned two separate groups, according to their scores in the CAGE questionnaire (≥ 2 o <2) (independent variable). Relapses will be the dependent variable, measured with, the DSM-5 criteria for depression, mania and mixed features at the 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months mark. Frequencies, percentages, mean$\pm$SD, Fisher's exact test, Student's t-test, logistic regression analysis and general lineal model will be performed to analyse and describe the results of the study.

Keywords: bipolar disorder, alcohol consumption, relapse, CAGE questionnaire, DSM-5 criteria depression, DSM-5 criteria mania, DSM-5 criteria mixed features.

Abbreviations:

UDPD Unidad de Patologia Dual y Desintoxicació

AUD Alcohol use disorder

DSM-5 Diagnostic and Statistical Manual of Mental Disorders 5th edition

BD Bipolar disorder

XSM Xarxa de Salut Mental

U.S. United States

SUD Substance use disorder

NICE National Institute for Health Care and Excellence

GGT Gamma glutamyltransferase

CDT Carbohydrate deficit transferrin

ALT Alanine aminotransferase

AST Aspartate aminotransferase

ALDH2 Aldehyde dehydrogenase 2

ECA Epidemiologic Catchment Area

NCS National Comorbidity Study

NLAES National Longitudinal Alcohol Epidemiological Survey

WHO World Health Organization

OR Odds Ratio

HRD-S Hamilton Rating Depression Scale

GABA Gamma Amynobutiric Acid

YMRS Young Mania Rating Scale

PRISM Psychiatric Research Interview for Substance and Mental Disorders

CAS Centre d'Atenció a les Drogodependències

CSM Centre de Salut Mental

IAS Institut d'Assistència Sanitària

CEIC Comité Ético de Investigación Clínica

CRF Case Report Form

GDP Gross Domestic Product

NIH National Institute on Alcohol abuse and Alcoholism

Introduction

Bipolar disorder

Definition

Bipolar disorder (BD) is a psychiatric chronic disorder that causes fluctuations in a person's mood. Bipolar patients have mood disturbances and experience intense and extreme emotional states at different periods of time. These mood episodes are distinguished in maniac episodes, hypomanic episodes, depressive episodes and mixed features. The periods of normal mood are the periods of euthymia (1).

BD also causes changes to a person's energy and function ability (1). Some people, may have a mood instability when they face stressful life events like, work problems, death of a familiar or a close friend, economical problems, divorce or marital separation (…). Grande I. et al. said that when mood swings are striking and persistent and result in notable distress or impairment, there could be an underlying affective disorder (2). These affective disorders, are classified in bipolar I, bipolar II and cyclothymic disorders (1,3).

In figure 1 we can see the possible progression of a BD (2).

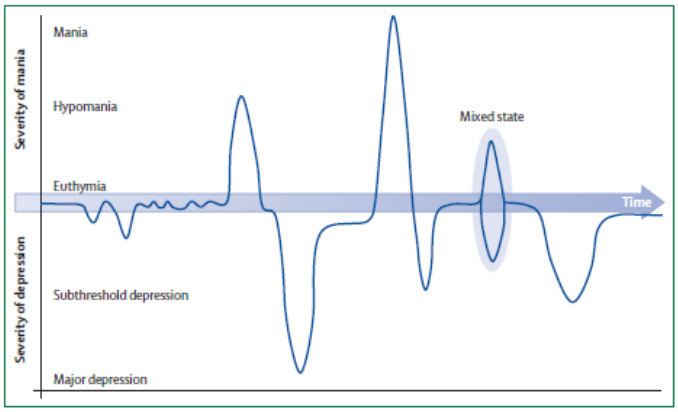

Figure 1 – Life chart showing progression of BD. Adapted from "Seminar Bipolar Disorder" (2)

Epidemiology

According to Grande I. et al., BD is one of the leading causes of disability among young people (2).

This mood disorder affects more than 1% of the population, independently of the ethnic, culture, nationality and socioeconomic status (2).

The prevalence of BD is 2.4% for the BD spectrum and 0.6% for bipolar I disorder. (2,3).

The lifetime male-to-female ratio is 1,1:1. The mixed states, the rapid cycling and the depressive symptoms are more common in females. According to Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), they also have a higher lifetime risk of alcohol use disorder than males and a much greater likelihood of alcohol use disorder than do females in the general population (3).

Diagnostic and Clinical features

The diagnostic of BD can be done with the DSM-5 criteria for BD (Appendix 1). DSM is the standard classification of mental disorders used by mental health professionals in the United States (U.S.) and contains a listing of diagnostic criteria for every psychiatric disorder recognized by the U.S. healthcare system.

According to DSM-5, for the diagnosis of bipolar I disorder, it is necessary to meet the criteria for a maniac episode. The maniac episode may have been preceded by and may be followed by hypomanic or major depressive episodes (3). (Appendix 1)

Mania

The DSM-5 criteria for mania are on appendix (Appendix 1). The main clinical aspects of mania are described on the table 1.

Mania features	
Core mood characteristics All must be present abnormally and persistently	1. Elevated mood 2. Expansive or irritable mood 3. Increased energy or goal-directed activity
Core mood duration	
Total duration, days	7 consecutive days (or nearly every day)
Daily duration	Majority of day
Behavioural characteristics 3 or more must be present during above period (4 if only irritability is present)	• Inflated self-esteem or grandiosity • Decreased need for sleep (e.g. feels rested after only 3 hours of sleep) • More talkative than usual • Flight ideas or racing thoughts • Distractibility • Increase in goal-directed activity (social, work, school, or sexual) • Excessive risk-taking activities with potential painful consequences
Severity causes marked functional impairment	Yes
Psychotic symptoms present?	Yes

Table 1 – Adapted from "Seminar Bipolar Disorder" (2)

Depression

The DSM-5 criteria for a major depressive episode of unipolar and bipolar depression are the same, as is shown in the appendix 1.

The main clinical aspects of depression are described on the table below.

Depression features	
Core mood characteristics All must be present abnormally and persistently	• Depressed mood. A long period felling sad, empty, hopeless or appears tearful by the other's observation. • Loss of interest or pleasure in activities once enjoyed, including the sexual activities.
Core mood duration	
Total duration, days	7 consecutive days (or nearly every day)
Daily duration	Majority of day
Behavioural characteristics	• Changes on the appetite (can have more or less appetite than usual) and on weight (can loss or gain weight) • Psychomotor agitation or retardation • Fatigue or loss energy • Feelings of worthless or excessive or inappropriate guilty (which may be delusional) • Diminish ability to think or problems in concentration, memory or indecisiveness • Recurrent thoughts of death or suicide or suicide attempt
Severity causes marked functional impairment	Yes

Table 2 - Adapted from DSM-5 *Diagnostic and Statistical Manual of Mental Disorders* (3) and "Bipolar disorder in adults" (4)

Mixed features

A patient with mixed features presents episodes of both mania and depression, simultaneous or in rapid sequence (4).

Prognosis

BD has periods of remission and recurrence. The recurrence occurs especially when the treatment adherence is poor (2).

Most studies have shown that depression is the most prevalent mood state (2).

According to Grande I. et al., the polarity of the index episode can predict the polarity of subsequent episodes (2). A depressive onset, suicides attempts and seasonal pattern are related with the depressive polarity. Bipolar I disorder patients frequently have mania polarity. These patients have an early age of onset and are more likely to have a Substance use disorder (SUD) (2).

BD is associated also with neurocognitive deficits. Many studies show poor performance in verbal memory and in executive functions that are related with the severity of the disorder, the presence of psychotic symptoms, more duration of the BD, more maniac episodes and also with subsyndromal depressive symptoms (2).

Medical comorbidities are related with a poor outcome of the disorder. The most common medical conditions that are associated with BD are cardiovascular disorders, diabetes and obesity (2). Comorbidity with other psychiatric disorders, like anxiety, is related with a poor course and prognosis of the disorder (5).

The most common causes of mortality are the circulatory disorders and the suicide. The incidence of suicide is estimated to be 15 times higher than in general population. A non-treated BD is related with a greater risk of suicide. A history of suicide attempt and the episodes of depression are associated with a higher risk of suicide attempts or completions (2,3).

The stressful events in life and the individual's vulnerability to relapse are related with a worse outcome of the disorder (2).

The symptoms of BD have influence on the psychosocial functioning. Levy B et al. report that recurrent mood episodes, residual symptoms between episodes, hospitalizations, comorbidity with SUD and psychosis disrupt the consistency of psychosocial engagement required for functional development (5).

Treatment

The main objectives of BD treatment are to stabilize the symptoms, prevent mood episodes, and maximize family, social and work function.

The goals of treatment for BD are described in the table below.

Goals of BD treatment	
Goal	**Description**
Stabilize	The primary goal is stabilizing mood disturbance: • Mania and/or • Depression
Prevent	Once stability is achieved, relapse prevention is the goal: • Encourage adherence and proactivity, including patient's symptom tracking • Mobilize family and social support
Maximize function	Maximize function(family, social, work) over the long term: • Reassess treatment goals • Mobilize nonpharmacological therapies to address dysfunctional cognitive and behavioural patterns

Table 3 – Adapted from "Practical approaches in the management of bipolar depression: Overcoming challenges and avoiding pitfalls" (6)

There are two pharmacological options for the treatment of BD: monotherapy or combination therapy. The physicians should use monotherapy when is possible to diminish complications such as adverse effects and pharmacological interactions. Studies found that monotherapy was associated with less adverse effects and with a better treatment adherence than combination therapy (6).

The outcome of the disorder depends largely on accurate and timely diagnostic and appropriate treatment. Culpepper et al. report that treatment selection for acute symptomatic management should anticipate the long-term course of the illness. The adverse effects of the treatment should have been taken on account (6).

Mood stabilizers, like lithium, carbamazepine or valproate, and antipsychotics, like quetiapine or olanzapine are considered as the primary evidence-based treatment choices because of demonstrated efficacy and tolerability. Lamotrigine is used, as maintenance therapy, to avoid relapses in depression episodes of BD, as well as atypical antipsychotics (quetiapine) in bipolar depression. Antidepressants shouldn't be used in monotherapy because of their lack of efficacy and risk of induced maniac symptoms (6).

Studies reported that some atypical antipsychotics have adverse effects like metabolic effects and weight gain (2,6).

It's important to ensure that patient has a good treatment adherence because this is associated with the outcome of the disorder. Colom et al. assessed adherence based on patient interview, family member interview, and plasma drug levels, which, according to the National Institute for Health and Care Excellence (NICE) guidelines for BD, should be measured every 3, 6 or 12 months, depending on the drug, how long has been diagnosed the disorder, treatment adherence and other medical conditions. "Good compliance" was demonstrated when all three criteria suggested medication adherence (7,8).

Pharmacological management of bipolar disorder in mania, depression, and maintenance phases					
	Clinical management			**Advantages**	**Disadvantages**
	Mania	**Depression**	**Maintenance**		
Mood stabilizers					
Lamotrigine	- - -	++	+++	Depressive predominant polarity	Slow titration
Lithium	+++	++	+++	Antisuicidal proprieties	Not recommended in renal failure
Carbamazepine	+++	+	++	Effective in BD with non-classic features	CYP450 inducer
Valproate	+++	+	++	Useful in episodes with mixed features	CYP450 inhibitor, not recommended in women at childbearing age
Antipsychotics					
Olanzapine	+++	+++*	++	Rapid efficacy	Severe metabolic syndrome
Quetiapine	+++	+++	+++	Only antipsychotic drug with indications for treatment of acute manic and depressive episodes and maintenance	Sedation
Antidepressants	- -	+	+	Applicable in resistance bipolar depression combined with mood stabilizers	Risk of switch to mania

Table 4 – The table includes some clinically significant adverse effects that can be experienced by some patients which is by no means exhaustive and is not meant as a comparison between different drugs. +++ = very high recommended. ++ = highly recommended. +=recommended. - - = not recommended - - - = not al recommended *Olanzapine plus fluoxetine. Adapted from "Bipolar Seminar"(2)

Alcohol Use Disorder

Definition

According to DSM-5, a cluster of behavioural and physical symptoms defines Alcohol use disorder (AUD). It is defined, specifically, as a problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the DSM-5 criteria for AUD (Appendix 2), occurring within a 12-month period (3).

Epidemiology

According to DSM-5, the prevalence of AUD in U.S. is 8.5% in adults. In Catalonia, a study about detection and prevalence of alcohol use disorder in primary health care, found that 11.7% of patients had an AUD (9).

This disorder is more common in men than in women (12.4% versus 4.9%). The prevalence of AUD it's higher between 18 and 29 years old, with a prevalence of 16.2%. However, women are more vulnerable than men to the physical consequences associated with alcohol (3).

Diagnostic and Clinical features

The diagnostic of AUD can be done with DSM-5 criteria (Appendix 2).

The CAGE questionnaire (Appendix 5), is a short and a quick questionnaire and is one of the most used instruments for diagnosis, in the clinical practice (10). Blood tests for markers can be useful, as well for the diagnosis. It can confirm the veracity of the patient's alcohol history and helps the patient to recognize that alcohol can have serious problems for his health. The most common blood tests markers are, GGT (Gamma glutamyltransferase), CDT (Carbohydrate deficit transferrin) , ALT (Alanine aminotransferase) and AST (Aspartate aminotransferase) (10).

The principal clinical features of AUD are described on the table below.

AUD features	
	AUD
Behaviour	• Alcohol is taken in larger amounts or over a longer period than was intended. • A persistent desire or unsuccessful efforts to cut down or control alcohol use. • A great time is spent in activities to obtain alcohol, use alcohol, or recovery from its effects. • Craving, or a strong desire to use alcohol. • Failure in obligations at work, school, or home. • Continued alcohol use despite having persistent or recurrent social or interpersonal problems • Social, occupational, or recreational activities are given up or reduced • Recurrent alcohol use in situations in which it is physically hazardous. • Alcohol use is continued despite the physical or psychological problems
Period of time	12 months
Tolerance symptoms	• A need for markedly increased amounts of alcohol to achieve intoxication or desired effect. • A markedly diminished effect with continued use of the same amount of alcohol.
Withdrawal symptoms	• The characteristic withdrawal syndrome for alcohol: Autonomic hyperactivity, increased hand tremor, insomnia, nausea or vomiting, transient visual, tactile, or auditory hallucinations or illusions, psychomotor agitation, anxiety and generalized tonic-clonic seizures). • Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

Table 5 – Adapted from DSM-5 *Diagnostic and Statistical Manual of Mental Disorders* (3)

Clinical course and prognosis

The average age of first drink is 15 years old. An early onset of regular drinking is associated with a higher probability of later problems (3,10). According to DSM-5, the period of heaviest drink is between 18 and 22 years old (10). The majority of individuals with AUD were diagnosed before 40 years old (3).

AUD increases the morbidity and the mortality. It can worsen the prognosis of psychiatric conditions like, BD (3,10).

AUD is associated with depressive episodes, anxiety disorders, BD, sleep problems, other SUD's, and suicide risk that are increased in these patients. It is also associated with heart diseases, such as cardiomyopathy and other myopathies, stroke, cancer of oesophagus, stomach, and other parts of the gastrointestinal tract, liver cirrhosis, pancreatitis and other medical conditions. It can cause mild anterograde amnesias, temporary cognitive deficits, sleep problems, and peripheral neuropathy that can be evidenced by muscular weakness, paraesthesia, and decreased peripheral sensation. Low-grade hypertension is one of the most common comorbidities. The gastrointestinal problems, like gastritis, stomach or duodenal ulcers or decrease bone density and production of blood cells are also associated with AUD (3,10).

There are some factors that increase the risk of having an AUD. Between them we can consider the culture toward drinking and intoxication, the availability of alcohol, including the price, the personal experiences with alcohol, the stress levels, and the genetics. Genetics have a strong influence on this disorder, because people with family problems of AUD have an increased risk to have an AUD (3).

This disorder has periods of remission and relapse. After a crisis, it's normal that the individual decide to stop drinking. After this decision, he will have a period of weeks or months, with a controlled drinking or abstinence. However, once alcohol intake resumes, it is highly likely that consumption will rapidly escalate and that severe problems will once again develop (3). The periods of remission are associated with new partners, health problems and a new job (10).

Individuals who have a history of years of severe alcohol problems are more difficult to treat and have more relapses. However, most of the AUD patients don't have so severe problems and they have a much better prognosis (10).

Treatment

The three drugs that have shown effectiveness to treat AUD are, acamprosate, naltrexone and disulfiram.

Naltrexone diminishes the craving and the feelings of reward or pleasure of drinking. Acamprosate increases the time of relapse, decreases the number of drinks per day, or helps to maintain the abstinence. Some studies reported that the combination of acamprosate and naltrexone could be better than acamprosate in monotherapy. Disulfiram was the best drug to ensure compliance, because it inhibits Aldehyde dehydrogenase 2 (ALDH2) so that acetaldehyde increases after drinking and produces nauseas, vomiting, diarrhoea, rapid heart rate, and changes in blood pressure. This makes that patient refuses the alcohol, because of the reported effects that arise when the patient drinks (10).

Dual Diagnosis (relation between AUD and BD)

Definition

Dual diagnosis is a condition in which a patient with a mental disorder, such as the BD, has a coexisting problem of SUD such as alcohol. This term is important in psychiatry because describes a prevalent pathology with some clinical features, diagnostic, prognosis and therapeutic, that are an health problem in developed countries(11,12).

AUD and mood disorders are prevalent in the general population. The co-occurrence of AUD and BD has long been recognized and it occurs in high rates in BD. The causes of this AUD and BD, co-occurrence are unknown (13,14). Salloum IM. et al said that this comorbidity is a "dual diagnosis" and creates a serious challenge in terms of establishing an accurate diagnosis and providing appropriate treatment interventions (15). This co-occurrence is adversely associated with the outcome. This dual-pathology patients have more frequent and prolonged mood episodes, a poor treatment adherence and quality of life and an increased risk of suicide. They will have more recurrences and hospitalizations and a higher risk to develop mixed states. These patients also have a poor symptomatic and functional recovery (16,17).

On BD patients, alcohol will have important effects on mood. When a bipolar patient is being subjected to lithium treatment and drinks alcohol, he will be intoxicated for a large period of time.

The effects of alcohol on mood during mania and hypomania are little known. Studies report that during the maniac phase of BD, patients have increased the alcohol consumption. These patients reported that use alcohol to relieve the affective symptoms (13).

Epidemiology

Many epidemiological studies observe a strong association between BD and AUD.

Comorbidity of mood and AUD in the community:

The epidemiological literature, present differences in the prevalence of AUD and mood disorders. According to the literature, depression is the most common comorbid disorder between alcoholics, with 6% having bipolar depression.

The ECA (Epidemiologic Catchment Area), the NCS (National Comorbidity Study) and the NLAES (National Longitudinal Alcohol Epidemiological Survey) are studies that provide information on the prevalence of comorbid AUD's and mood disorders. All of these three studies found that AUD's were more prevalent in men and mood disorders were more prevalent in women (13).

According to ECA study, 46.2% of bipolar I patients had a lifetime history of AUD(17). Mood disorders were present in 13.4% of individuals with alcohol abuse or dependence, with an OR (Odds Ratio) of 1.9. The 21.8% of individuals with a lifetime mood disorder also had a lifetime AUD. This study also found that BD was prevalent among alcoholics, with a prevalence of 5.1% and an OR of 5.1. Some investigators suggested an OR of 6.2 for co-occurring mania and alcoholism which, according to Kranzler, Henry R. et al., was higher than that any other axis I diagnosis. Among bipolar I patients, alcohol dependence was present in 31.5% with an OR of 5.5 and alcohol abuse was present in 14.7 % with an OR of 3.0. (13).

The NCS study found that the OR for a lifetime diagnosis of mania among patients who had an alcohol abuse and dependence was 2.5 and 12.1, respectively. The OR for a lifetime diagnosis of depression among patients who had an alcohol abuse and dependence was 2.4 and 7.1, respectively (13).

The NLAES epidemiological study shows, a high OR for the comorbidity of AUD and major depressive disorder. Also, conclude that the risk of having an AUD in those individuals

with major depression was higher. The risk of lifetime comorbid major depression and AUD increased with the age (13).

World Health Organization (WHO) done a study in America, Asia and Europe by WHO and confirmed the elevated rates of dual pathology among bipolar subjects (18).

OR of Lifetime Prevalence of Alcohol –Use Disorders and Mood Disorders in Community Samples		
	ECA*	NCS
Alcohol abuse	5.5	2.5 (mania) 2.4 (depression)
Alcohol dependence	3.0	12.1 (mania) 7.1 (depression)

*ECA: OR of bipolar I disorder patients

Table 6 - Adapted from "Dual Diagnose and Treatment"(13)

Comorbidity of mood and AUD in clinical samples

ECA study reveals that the number of comorbid non-substance diagnoses in patients with AUD, is correlated with the frequency with which they seek the treatment for psychiatric and medical problems. In fact, according to ECA study data, 55% of those individuals with an AUD, seeking treatment in a mental health or substance abuse setting had a comorbid non-substance use diagnosis, compared with only 24.4% who had not sought the treatment (13).

The rates of alcoholism found in patients treated for BD, are between 1.9% and 4%. Some studies found higher rates that range 5% to 58%. Kranzler, Henry R. et al said that an overlap between the effects of heavy drinking and hypomanic or maniac symptoms presents a diagnostic challenge (13). When alcohol is taken in larger amounts, a tolerance to alcohol can be developed or the activity in a maniac episode can be increased. Grandiosity, irritability or expansiveness, can be symptoms of a maniac episode or symptoms of an alcoholic intoxication. Alcohol withdrawal and hypomanic and maniac episodes have also, symptoms in common. These symptoms can be, insomnia, psychomotor agitation or anxiety. According to, Kranzler, Henry R. et al further complicating this distinction is the observation that alcohol use may precipitate a bipolar disorder that persists independent of the alcohol use (13).

The co-occurrence of depression and alcoholism is important. When this co-occurrence exists, there is an impairment in function and the suicide behavior is higher. Authors found different prevalences of depression among alcoholics in treatment. There are many factors like, the diagnostic criteria employed, the temporal association to drinking or withdrawal, the temporal focus of the diagnosis (current/lifetime) or primary/secondary and finally, the nature of the treatment (treatment for substance abuse or for mental health). These factors, will influence on the prevalence of depression among alcoholics in treatment. For example, using clinical criteria, investigators found that 8.6 % of their sample was diagnosed as depressed. In contrast, using rating scales for depression like, the Hamilton Rating Depression Scale (HRS-D), the prevalence found was 28%. Another important variables that should have been taking in account are, sex and the family history of depression. Kranzler, Henry R. et al report that among patients hospitalized for alcoholism treatment, 14% of males and 39% of females were diagnosed as having a comorbid depressive disorder. (13) Family history of depression is another important factor to take in account, because the risk of depression among alcoholics is greater than in nonalcoholics. Kranzler, Henry R. et al also report that furthermore differences exist in the prevalence of depression among alcoholics in treatment compared with their untreated alcoholic relatives, supporting the notion that comorbidity may result in a greater likelihood of seeking treatment (13).

Lifetime prevalence of mood disorders among alcoholics in three clinical samples				
	No. of patients	Any lifetime diagnosis (%)	Major depression (%)	Mania (%)
Powell et al. (1982)	565	63	42	20
Hesselbrock et al (1985)	321	76	38	4
Ross et al. (1988)	370	82	26	2

Table 7 – Adapted from "Dual Diagnosis and Treatment".(13)

Pathophysiology

Kindling/sensitization models

For conceptualizing the mechanisms that are responsible for the recurrence and the progression of BD, some authors proposed the behavioral sensitization and electrophysiological kindling models (15).

Salloum et al. reported that these two models have similar mechanisms: the threshold effect in which mild alterations ultimately may result in full-blown episodes, maximum disturbances occurring earlier in each of the repeated episodes, the potential importance of both genetic and early environment stress, and increased vulnerability associated with early age of onset. The psychosocial stressors are important on precipitate early episodes. The later episodes often develop spontaneously. This is similar to electrophysiological kindling, because the repeated subictal stimulation may result in a spontaneous seizure (15).

Kindling and sensitization have been reported in alcohol effects. The severity of alcohol withdrawal symptoms are related with the intensity and the duration of the alcohol consumption. The repeated episodes of alcohol withdrawal will result on a physical dependence and in a more severe alcohol withdrawal seizures (15).

Alcohol withdrawal and bipolar disorder are localized in different neuroanatomical substrates. Bipolar disorder is linked with limbic kindling and alcohol withdrawal seizures may originate from the inferior collicular cortex. It is hypothesized that the simultaneous dysfunction of both neuronal systems, result in a poorer prognosis of patients with comorbid BD and AUD (15).

Neurochemical models

Dopamine, serotonin and GABAergic systems, are neurotransmitter systems that play an important role in the mechanism of mood and BD, in the pathogenesis of this disorder and are involved on the neurobiology of addiction (15).

The mesolimbic and mesocortical dopaminergic system are related with the BD and are important in the "reward-motivation" system. Dopamine has a primary role on reinforcing the effects of alcohol. Serotonergic systems are important modulators for the noradrenergic system that is involved in BD and Salloum IM et al. report that also has importance on modulating effects on the "reward" circuitry involved in the addictions. A low serotonergic function is present on maniac and depressive phase of BD. So, we can say, that serotonin exerts inhibitory effects on noradrenergic system. Salloum IM et al. report that, low central serotoninergic 'tone' may fail to adequately modulate the noradrenergic system, leading to increased noradrenergic output during times of stress or activation. Norepinephrine and dopamine are implicated in the grandiose and euphoric manifestations of mania. GABA (Gamma Amynobutiric Acid) is implicated in mechanisms of kindling, physical dependence, ethanol withdrawal seizures, regulation of mood states, and alcohol reinforcing effects. The endogenous opiate peptides are implicated in mood and addictive disorders and are involved in reinforcing effects of alcohol. However, studies reported that the link between this system and BD has not been strong (15).

This comorbidity can be explained by the common pathophysiological factors. For example, Salloum et al. report that anhedonia, volitional, inhibition, and psychomotor retardation suggests a hypofunction of central dopaminergic circuits (15).

Salloum et al. also reported that a higher-grade reinforcer could still motivate operant behavior even in such a hyporesponsive state. So, people who are likely to depressive states have a higher risk of AUD, because they use the alcohol as highly reinforcing (15).

In mania, the subject can't appreciate the adverse consequences of his actions and has loss of judgement. This can lead to a higher risk of AUD, which is related with the diminution of cognitive self-regulatory or restraint mechanisms (15).

According to Salloum et al., a dysregulation of serotonergic system or in GABAergic neurotransmission could result in a greater likelihood for excitement or behavioural activation to 'overshoot' normal set points. The psychotic, the depressive and mania or mixed symptoms can be the result of the dysregulation of noradrenergic, dopaminergic, and glucocorticoid systems (15).

Pathogenesis

There are many hypothesis to explain the high rate of comorbidity between bipolar disease and alcohol use disorder. Maybe all of them contributed to the phenomenon of the dual pathology.

1. The maniac and hippomania symptoms include the DSM-5 criteria of excessive involvement in pleasure activities that have a high potential for painful consequences (3), each could be interpreted to include AUD, increased rates of AUD in BD might result simply by definition (14,19).
2. Genetics. In one hand some studies have reported a little evidence for a genetic link between bipolar disorder and alcoholism. They found no evidence of independent transmission of BD and alcoholism. On other hand, some studies have found an overlap between vulnerability genes for bipolar disorder and vulnerability genes for AUD (13,15,19).
3. Anxiety. Anxiety disorders are common in individuals with BD, and co-occur more often than expected. Individuals with anxiety are more likely to present an AUD. Epidemiological data says, that the rates of AUD and anxiety disorders in persons with BD are higher than rates of AUD and anxiety disorders in general population (19,20).
4. Common pathophysiology. Both disorders share some pathophysiological mechanisms such as, alterations in neurotransmitters systems, especially in dopamine pathways, adaptation processes in postreceptorial signaling pathways, including the expression of neural genes (19).
5. Social diathesis. Psychosocial dysfunction due to bipolar disorder, unemployment, divorce, marital separation, economical problems and other adverse life situations may favor the marginalization which, in turn, increases the risk of AUD (19).
6. Self-medication. According to this hypothesis, bipolar patients would use alcohol, as a means to alleviate symptoms of the primary disease or adverse effects of drug treatment. This hypothesis is not conceptually clearly in the case of dual bipolar disorder. While it is likely to contribute to the consumption of substances in some patients and in some situations (17,19).
7. Personality characteristics. Individuals with bipolar disorder tend to have high scores on impulsivity and novelty seeking. These are personality traits that have been shown to increase the risk of AUD (19).

Diagnostic

First of all, it is important to do a good anamnesis to register the fluctuations on mood during the times without consumption. To do that, we can use, for example, the HRS-D scales (Appendix 3) and the Young Mania Rating Scale (YMRS) (Appendix 4). The HRS-D is a rating scale for depression. It includes a symptom checklist, with 17 items, to identify if the patient is suffering from a depression and it permits the assessment of depression severity. The YMRS is the most used scale to assess the severity of manic symptoms. It includes a symptom checklist with 11 items, to identify the patient's mania (21,22).

The diagnostic of the dual pathology, is done with the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) interview. This interview is validated in Spanish and according the studies, has a strong reliability and validity (23). According to Hasin DS, the PRISM is a semi-structured diagnostic interview that is designed to deal with the problems of psychiatric diagnosis when subjects/patients drink heavily or use drugs. The PRISM assesses DSM-IV Axis I and Axis II disorders. With this interview, we will be able to differentiate primary disorders, substance-induced disorders and the expected effects of intoxication and withdrawal. The interviewer should be trained on doing this kind of interview. Once he has become familiar with, it takes approximately from 45 minutes to 2 hours to administer. The time required depends on the psychiatric history and the complexity of the substance use, which in this case, it will be in the complexity of alcohol use (24).

Three important characteristics of the PRISM that are specific to comorbidity include:

1. Adding specific rating guidelines throughout the interview, including frequency and duration requirements for symptoms, explicit exclusion criteria, and decision rules for frequent sources of uncertainty (23).
2. Positioning of the alcohol and drug sections of the PRISM near the beginning of the interview, before the mental disorder sections, so that the history of alcohol and drug use is available at the time of beginning the assessment of mental disorders (23).
3. More structured alcohol and drug histories to provide a context for assessing comorbid psychiatric disorders (23).

Clinical and course of the illness

Available studies suggest that alcohol modify the course of BD worsening the prognosis. This dual pathology may progress more rapidly, with more frequent relapses and Salloum IM et al. also report that it has a shorter duration of remission intervals between episodes. A more severe and resistant subtypes of BD like, dysphoric, rapid cycling and with mixed features may be developed due to this dual pathology (15).

Alcohol as course modifier of BD

Alcohol is associated with maintaining or developing affective symptoms such as depressive and maniac symptoms (14).

Salloum IM et al. report that alcohol "appear to hasten recurrent episodes of bipolar disorder, maintaining high levels of inter-episode symptoms, and are associated with treatment-resistance" (15). This dual pathology, is also associated with poor outcomes like a poor compliance and treatment adherence and with higher levels of psychosocial stress. All of these factors will contribute to more recurrences of BD. Alcohol, also have influence on the interval between episodes, which is shorter, on the time to relapse, on the time to recover from an affective episode, which will be longer and increase the residual symptoms. This increases the risk of morbidity and chronicity. The effects of alcohol intoxication and withdrawal will result in sleep

and circadian rhythm disruption and increase the symptoms of irritability, depression and anxiety (15).

On one hand, a number of authors reported that during the maniac episode most patients don't change the alcohol consumption. However, some patients increase their alcohol use on this phase and it's uncommon that the patients decrease the alcohol consumption. On other hand, in depression most of patients don't change their alcohol use, but they could increase or decrease their alcohol use (15).

Salloum IM et al. report that Alcohol could precipitate the initial episode of BD in some individuals at a later age than those without comorbid alcohol. Some investigators reported that bipolar patients with primary alcoholism, have a better prognosis with less mood episodes. According to studies, the bipolar subtypes with more severe course have an increased risk to develop an AUD (14,15).

Alcohol as episode modifier of BD

The alcohol effects can influence on the onset, on the duration, on the progression, and on the phenomenology of the BD episode and modify the presentation of the affective episode (15).

The symptoms of mania, such as hyperactivity and euphoria, or the depressive symptoms may be masked by the symptoms of alcohol intoxication or withdrawal (15).

Salloum IM et al. said that the chronic use of alcohol may causes depressive symptoms of mixed state, and on this way, masks the clinical presentation of the acute maniac episode (15).

The depressive symptoms are higher in women with this comorbidity of BD and AUD, than are in males or non-alcoholic bipolar patients (15).

In this way, we can conclude that comorbid BD and AUD increase the number of symptoms such as, impulsivity, the duration of the BD episodes, and according to Salloum IM et al., increase the abruptness of the onset of the maniac episode from mild hypomania to severe maniac symptoms and alcohol is reported to 'switch' process from depression to mania and/or to a mixed state. Also, the risk of suicidal behaviour in these dual pathology patients is increased (14).

AUD and the age of onset of BD

AUD has an influence on the age of onset, on the course and the outcome of the BD (14).

It has been suggested that patients who have an early age of onset of the disorder have a more severe course of illness that included a development of an AUD. In contrast, the patients with antecedent of AUD had a less severe course of illness because they required the alcoholism to onset the BD (14).

So, an early onset of BD may be a risk factor for developing an AUD (14).

Treatment as determinant factor on the course of BD

Specific aspects of the treatment

It has been commented before that, AUD is associated with poor treatment outcome. Dual patients are difficult to treat. Treat these patients on a specific unit such as the dual pathology unit, is an option that should have been considered. This unit has specialized experts in both fields that provide care and treatment to the most serious and difficult patients. As well as community devices that could attend and follow the less serious patients and those who are in stable phases

of the disorder. Some of them need to be admitted at a dual diagnose unit and do a follow up in "Centre d'Atenció a les Drogodependències" (CAS) and "Centre de Salut Mental" (CSM) (19).

Anticonvulsant mood stabilizers such as valproate are the first treatment choice for patients with BD and AUD. Studies have demonstrated a high tolerability on dual pathology patients. Valproate reduces the alcohol consumption, by reducing alcohol craving and alleviating alcohol withdrawal symptoms. Valproate is effective in stabilize affective symptoms and symptoms of alcohol withdrawal (15,16,19).

The anticonvulsant/antikindling drug carbamazepine has the same potential usefulness as valproate. However, is less tolerated than valproate. Antikindling agents may prevent the relapses and are useful in alleviating the "protracted withdrawal syndromes" like, anxiety, depression, insomnia, electrophysiologic abnormalities, and neuroendocrine changes. This syndrome increases the risk of relapse in the first 3-6 months after acute alcohol withdrawal (15).

Lithium carbonate is a mood stabilizer and has efficacy in the first phases of the disease. When the disease progresses into rapid cycling, mixed and dysphoric subtypes the therapeutic action of lithium is compromised. The anticonvulsants mood stabilizers are more useful on these severe subtypes of the disorder (15).

Studies report that quetiapine may be useful in reducing the depressive symptoms, however it hasn't demonstrated efficacy on the reduction of alcohol consumption (19).

Lamotrigine and aripiprazole can be useful on these patients. The aripiprazole is useful in the acute mania, on prophylaxis of relapses and in alcohol treatment (19).

Naltrexone has improved the alcohol consumption as well as the affective symptoms. It has been also reported that, for the treatment of alcohol comorbidity, the best way is to associate the naltrexone to valproate, because has more efficacy than the monotherapy of valproate (19).

The acamprosate and the topiramate have also demonstrated efficacy in this kind of patients (19).

Antidepressants increase the risk of inducing mania or accelerating cycle frequency (15,19).

Justification

BD is a chronic disorder characterised by fluctuations in energy and mood, from euphoria to severe depression, interspersed with periods of euthymia. Bipolar disorder represents a significant public health problem, which often goes undiagnosed and untreated for lengthy periods. This delayed diagnosis and treatment can have adverse clinical, functional and economical effects. This disorder often starts in early adulthood, and causes disability in young people. It affects more than 1% of the population in the world (2,6,25).

BD and AUD are closely linked. This co-occurrence it is a relativity common phenomenon and the epidemiological data reported that this dual pathology occurs in high rates. According to literature, AUD is associated more than six times to BD (12,14,15,17,20,26–28).

The epidemiological studies concluded that among bipolar patients the risk of AUD is increased in men and that AUD in them is usually primary. Mood disorders were more prevalent in women and females with major depression have an increased risk of AUD (13).

Many hypotheses suggest that AUD and BD share a common pathogenesis. The genetics, the anxiety disorders, the stressful events in life (unemployment, divorce, economical problems), the common pathophysiology, explained by the kindling/sensitization models, the sensitization oscillation response and the neurochemical models, the personality characteristics like the impulsivity, the use of alcohol as self-medication to alleviate the symptoms of the disorder and finally, the maniac and hippomania symptoms which include the "excessive involvement in pleasure activities that have a high potential for painful consequences", and these activities, could include AUD. Maybe all of them contributed to the phenomenon of the dual pathology (3,13–15,17,19,20)

The CAGE questionnaire is a brief and quickly questionnaire with 4 questions. It's the most used screening instrument, for detecting alcohol consumption in the clinical practice and it has been demonstrated to be useful in psychiatric patients. According to Dhalla S et al., CAGE has demonstrated high test-retest reliability, and adequate correlations with other instruments (29).

We know that the association between BD and AUD can influence on the onset, the duration and in the progression of the episode. It affects the functional and the time of the recovery, it is associated with poor symptomatic, with more hospitalizations and with poor response to the treatment. Also, it increases the psychosocial stress levels and the time between episodes is shorter. It may increase symptoms of irritability, depression, anxiety, residual symptoms and have some influence on sleep and circadian rhythm. Furthermore, this association increases the risk of morbidity and chronicity of the disorder. We may assume that all of these can lead to a more relapses (14,15).

In medical literature, we can find many studies about the impact of AUD in the course and treatment of bipolar disorder. These studies, describe all these factors, that are well commented before, and assume that this factors can lead to more relapses. However, most of studies didn't determine if the bipolar patients who have alcohol consumption have more relapses (depressive, maniac or mixed features relapses) than those who don't have alcohol consumption. This will be the first study done in Girona about this dual pathology. So, the main reason to propose this study is to determine if bipolar patients who have alcohol consumption will have more relapses.

Given the fact that BD is one of the most severe chronic mental illnesses, with high rates of young disability and economical outcomes, and the relationship with AUD has a negative effect on the bipolar patients, it is imperative to investigate if the alcohol consumption in bipolar patients will precipitate more relapses (using, for that, the most commonly used measures: Cage questionnaire and DSM-5 criteria for depression, mania and mixed features).

Hypothesis

Primary hypothesis:

The bipolar patients who have alcohol consumption will have more relapses in 5 years.

Secondary hypothesis:

The mean number of relapses in the last 5 years in alcohol consuming BD is higher.

Objectives

Primary objective:

Determine if bipolar patients with alcohol consumption will have more relapses in 5 years compared to bipolar patients without alcohol consumption.

Secondary objective:

Determine the mean number of relapses in the last 5 years in alcohol consuming BD compared to the mean of those who don't have alcohol consumption.

Methodology

Study design:

Cohort study. Prospective.

Study subjects:

The study subjects will be all the patients that are included in "Xarxa Salut Mental" (XSM) of Girona, with diagnostic of bipolar disease between 2015 and 2020.

Inclusion criteria

- Patients diagnosed of bipolar I disorder according to the DSM-5 criteria
- Ages ≥ 18 and < 65
- Patient has a familiar that could confirm the accuracy of the information about alcohol consumption and treatment for both BD and AUD
- The patient have firmed the informed consent form

Exclusion criteria

- Patients diagnosed of bipolar II and cyclothimic disorder and other bipolar related disorders such as, short-duration hypomanic episodes and major depressive disorder hypomanic episodes with insufficient symptoms and major depressive disorder hypomanic episode without prior major depressive disorder and short-duration cyclothymia, according to DSM-5 criteria
- Intellectual incapacity
- Any diagnosis regarding other psychiatric as schizophrenia, personality disorders, other substance use disorder, a severe somatic or neurological organic disorders as neurodegenerative diseases and cerebral tumours
- Treatment for any other pathology, either somatic, as tumours or neurodegenerative diseases or psychiatric as, schizophrenia or personality disorders

Sample selection

The sampling method will be a consecutive sequential sampling. The subjects admitted to the XSM de Girona that fulfil the above-mentioned criteria will be recruited, as they come to the program's appointments, for a period of 2 years. The Mental Health and Addictions Network of "Institut d'Assistència Sanitària" (IAS) is the public of Girona specializing in mental health care for the reference population (750,000 inhabitants). It has total or partial hospitalization services, located Park Hospital and Julia Martin (Salt) and community care services that are provided through seven mental health centres for adults, seven childhood, six care centres addictions and seven day centres deployed throughout the province of Girona. It also has nine residential floors, two residential homes (for people with severe mental disorders and people with intellectual disability and mental disorder) and two teams of early intervention in psychosis. Psychiatric emergencies are attended St. Catherine's Hospital. Has an agreement with centres of employment, guardians and family associations.

This study will include the patients from the Gironès, Baix Empordà, La Selva Interior, La Selva Maritima, Alt Empordà, Garrotxa and Ripollès sectors. In 2015, 14179 patients were a part of the XSM of Girona. All the potential participants will be given an information sheet and an informed consent and will only be a part of the study after reading and signing said documents.

Sample Size

The sample size and power calculator GRANMO was used to achieve our sample size. Using the POISSON approximation and accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, **43** exposed subjects and **47** in the non-exposed are necessary to recognize as statistically significant a relative risk greater than or equal to 1.6. A proportion in in the non-exposed group has been estimated to be 0.54. It has been anticipated a dropout rate of 20%.

Study variables

Independent Variable

- **Alcohol consumption:** It is defined through the application of CAGE questionnaire. Through the application of this, we will create 2 groups of patients. One contains the patients diagnosed with alcohol consumption resulting in a score equal or greater than 2(≥2) in CAGE questionnaire. The other group contains the patients with no alcohol consumption, scoring less than 2(<2) points in CAGE questionnaire. The CAGE questionnaire and its criteria are explained in "measuring instruments" paragraph. (Appendix 5)

  This is a dichotomous nominal qualitative variable.

Dependent Variable

- **Relapses:** Every 6 months we will revise the patient's clinical history to quantify the alcohol consumption, using the CAGE Questionnaire score. After 5 years of follow-up (with consultations at 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months mark), by applying the DSM-5 criteria we will classify the participants as "relapse" or "no relapse". If a participant has criteria of major depression or mania or mixed features according to DSM-5 criteria (Appendix 1) we will classify him as "relapse". On the other hand, if the participant doesn't have criteria of major depression or mania or mixed features, he'll be classified as "no relapse".

  This is a dichotomous nominal qualitative variable.

- **Mean number of relapses:** To calculate the mean of relapses in the last 5 years in alcohol consuming BD patients, we will revise every patient's clinical history and count how many relapses each patient has. Then, we will use a mean formula in order to calculate the mean of relapses in the last 5 years in alcohol consuming BD.

  This is a quantitative continuous variable.

Co-Variables

- **Alcohol consumption during the study:** As we said before, on the explanation of the dependent variable we will create 2 groups of patients. One contains the patients diagnosed with alcohol consumption resulting in a score equal or greater than 2(≥2) in CAGE questionnaire. The other group contains the patients with no alcohol consumption, scoring less than 2(<2) points in CAGE questionnaire. During the study, a patient could change his alcohol consumption. In this way, the patient, during the period of the study, can change to one group to another. So, it's important to control the alcohol consumption during the study. We will study this co-variable from the second appointment until the eleven appointment, because it's the time that the alcohol consumption can change during the study. This is a dichotomous nominal qualitative variable.

- **Previous problem of alcohol consumption:** To determine if the patient had a previous problem of alcohol consumption, the psychiatric will use the PRISM semi-structured interview. This is a nominal qualitative variable.

- **A traumatic event in the last year**: "at risk of illness" (score >300), "moderate risk of illness" (score between 150 and 299) and "slight risk of illness" (score <150), according to the Holmes and Rahe Stress Scale. A distressing occurrence can be a trigger for the appearance of alcohol consumption, thus, creating a confounding factor in our study. This is a nominal qualitative variable and it will be determined by using the aforementioned scale. (Appendix 6)

- **Age of diagnosis of bipolar disease:** Measured in years. A younger age of onset of BD is related with a poor outcome of BD. This is a discrete quantitative variable and it will be determined in the clinical interview if it's not specified in patient's clinical history.

- **Pharmacological treatment for AUD:** It's important to know if the patient is on treatment for AUD. For that, it's important to ask the patient's if he is on treatment. Then, to ensure that this information is true, his family should confirm the accuracy of the information.
  This is a nominal qualitative variable and it will be determined in the clinical interview and registered in patient's clinical history.

- **Patient's adherence to pharmacological treatment for BD**: It's important to know the patient's adherence to pharmacological treatment because treatment no adherence is predictive of a number of negative outcomes in bipolar patients. The measure of the patient's adherence of pharmacological treatment for BD will be based on the patient's clinical interview, on the patient's family clinical interview and on the plasma drug levels. The plasma drug levels will confirm if the information that patient and his family is true. We will obtain the plasma drug levels by doing an analytic to the patient. This analytic, will be taken every 3 months, and it will be registered in patient's clinical history. The patient has a good compliance, when the criteria suggested medication adherence: the patient and his family confirms to us that he is taking the medication for BD, and, when the plasma drug levels are according to the drug therapeutic levels. The patient

has a bad compliance, when he or his family don't confirm that he is taking the medication properly, and, when the plasma drug levels aren't according to the therapeutic levels.

This is a nominal qualitative variable and it will be determined in the clinical interview and registered in patient's clinical history.

- **Consumption of other substances:** It's important to know if the patient consumes another substances than alcohol, because this can have an influence in our study. These substances can be cocaine, heroin, tobacco, cannabis, caffeine, hallucinogen, inhalants, opioids, sedative, hypnotic or anxiolytic substances, stimulants or other or unknown substances. This is a nominal qualitative variable and it will be determined in the clinical interview.

- **Patient's BD hospitalizations on the last 6 months:** The number of patient's hospitalizations is related with the outcome of BD. A more number of hospitalizations result on a poor outcome of BD. This is a quantitative discrete variable and it will be determinate in the patient's clinical history.

- **Duration of patient's BD hospitalizations on the last 6 months:** Measured in days. The duration of patient's hospitalization is related with the outcome of the BD. A more duration of hospitalization results on a poor outcome of BD. This is a quantitative discrete variable and it will be determinate in the patient's clinical history.

- **Severity of the relapses:** The severity of the relapse is related with the outcome of the BD. A more severe relapse is related with a worse outcome of the BD. The severity of the relapse will be determined by using the YMRS scale, for mania and the HRS-D, for depression. By using the YMRS scale for mania, if patient's score is between 10 to 19 points he has a "mild mania". On other hand, if his score in said scale is > 19 points, the patient will have a "moderate- serious mania". By applying the HRS-D scale for depression, if patient's score is between 7 and 17 points, he will have a "mild depression". On other hand, if patient's score is from 18 to 24 points he will have a "moderate depression" and if his score is between 25 and 52, he will have a "serious depression". The severity of the relapses is registered on patient's clinical history. Every 6 months, the psychiatric will revise the patient's clinical history and determine the severity of his relapses. This is a nominal qualitative variable and it will be determinate in the patient's clinical history.

- **Sociodemographic variables**: These co-variables will be determined in the semi-structured PRISM clinical interview.

    - Gender: "male" or "female". This is a nominal qualitative variable

    - Age: In years. This is a quantitative discrete variable.

    - Education: "less than high school", "high school degree", "college degree" and "graduate degree". This is a nominal qualitative variable.

    - Marital status: "married", "in a partnership", "single", "separated", "divorced" and "widowed". This is a nominal qualitative variable.

- Employment situation: "employed", "unemployed", "student" and "retired". This is a nominal qualitative variable.

Data collection

All the data will be collected in 11 meetings, with 6 months between them, in face-to-face interviews, after the patients' agreement to participate in the study. Interviews will be conducted with patients and his family, to ensure the information acquired is true.

In the first appointment (appointment nº 1), the trained psychiatrist working in this research will be given a Case Report Form (CRF), specially designed for this cohort, in which the measures of the independent and dependent variables as well as the co-variables. (Appendix 8)

This information will then be reflected in a database. The process of filling in the forms will be repeated in follow-up visits at 6, 12, 18, 24, 30, 36, 42, 48, 54, 60 months of the first consultation (appointments nº 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 respectively) along with the entering of the data on said directory. Homogeneity in data collection must be ensured and that's why the only one who can collect and insert the data is the above mentioned trained psychiatrist working in this project.

DATA COLLECTION AND VISITS CHRONOGRAM												
Data collection	Appointments											
	Baseline	1	2	3	4	5	6	7	8	9	10	11
Informed consent form	X											
Sociodemographic data (gender, age, education, marital status, employment situation)		X										
Alcohol consumption during the study			X	X	X	X	X	X	X	X	X	X
Previous problem of alcohol consumption		X										
Traumatic events last year		X		X		X		X		X		X
Age of diagnosis of BD		X										
Pharmacological treatment for AUD		X	X	X	X	X	X	X	X	X	X	X
Patient's adherence to pharmacological treatment for BD		X	X	X	X	X	X	X	X	X	X	X
Consumption of other substances		X	X	X	X	X	X	X	X	X	X	X
Patient's BD hospitalizations on the last 6 months		X	X	X	X	X	X	X	X	X	X	X
Duration of patient's BD hospitalizations on the last 6 months		X	X	X	X	X	X	X	X	X	X	X
Severity of the relapses		X	X	X	X	X	X	X	X	X	X	X

Measuring instruments

- **CAGE questionnaire:** The CAGE questionnaire is a questionnaire with 4 questions. The questions are: Have you ever felt you should cut down on your drinking? ; Have people annoyed you by criticizing your drinking? ; Have you ever felt bad or guilty about your drinking? ; Have you ever had a drink first thing in the morning to steady your nerves or

to get rid of a hangover (eye opener)? .The doctor has to ask these questions to the patient and he has to answer with "yes" or "no". If the patient answer to a question with "yes" his score will be 1. If the patient answer to a question with "no" his score will be 0. A total score of 2 or greater is considered clinically significant. If the patient has a score of 2 or greater (≥2) he has an alcohol consumption. If his score is less than 2 he doesn't have an alcohol consumption. This instrument will be used to study the independent variable. (Appendix 5)

- **DSM-5:** *Diagnostic and Statistical Manual of Mental Disorders* (DSM) is the standard classification of mental disorders used by mental health professionals in the U.S. and contains a listing of diagnostic criteria for every psychiatric disorder recognized by the U.S. healthcare system. DSM is used in both clinical settings (inpatient, outpatient, partial hospital, consultation-liaison, clinic, private practice, and primary care) as well as with community populations. In addition to supplying detailed descriptions of diagnostic criteria, DSM is also a necessary tool for collecting and communicating accurate public health statistics about the diagnosis of psychiatric disorders. This instrument will be used to study the dependent variable "relapses". We will use the DSM-5 criteria for "major depression", "mania" and "hypomania". (Appendix 1)

- **HRS-D:** HRS-D is a rating scale for use in assessing the symptoms of patients diagnosed as suffering from depressive states. It includes a symptom checklist to identify the patient is suffering a depression. The symptoms checklist includes 17 items (1-17 items) that measures, depressed mood (item 1), culpability (item 2), idea of suicide (item 3), initial insomnia (item 4), middle insomnia (item 5), late insomnia (item 6), work and interests (item 7), retardation (item 8), agitation (item 9), psychic anxiety (item 10), somatic anxiety (item 11), gastrointestinal somatic symptoms (item 12), general somatic symptoms (item 13), genital symptoms (item 14), hypochondriasis (item 15), loss of discernment (item 16) an finally loss of weight (item 17). Each item is scored from 0 to 4 (0-4) or from 0 to 2 (0-2). Items 4, 5, 6, 12, 13, 14, 16 and 17 score from 0 to 2 (0-2). Items 1, 2, 3, 7, 8, 9, 10, 11 and 15 score from 0 to 4 (0-4). The score for the patient is obtained by summing the scores of each item, and is based on the evaluation of the last days. It can be expressed in 4 different categories: "no depression", when the score is between 0 and 6 (0-6), "mild depression", when the score is between 7 and 17 points (7-17), "moderate depression" when the score is between 18 and 24 points (18-24) or "serious depression", when the score is between 25 and 52 (25-52) points. This instrument will be used to study the co-variable severity of the relapses. (Appendix 3)

- **YMRS:** The YMRS is the most widely used tool for the assessment of the intensity of manic symptoms. It includes a symptom checklist to identify the patient's mania. The symptoms checklist includes 11 items (1-11 items) that measures, euphoria (item 1), increase of motor activity and energy (item 2), sexual interest (item 3), sleep (item 4), irritability (item 5), speech - rhythm and quantitate (item 6), language and thought disorder (item 7), thought content (item 8), behaviour changed – aggressive (item 9), appearance (item 10), and finally the insight - conscious of the disorder (item 11). For each item there is a score, that ranges from 0 to 4 (0-4) or from 0 to 8 (0-8). Items 1, 2, 3, 4, 8, 10 and 11, are score from 0 to 4. Items 5, 6, 7 and 9 are scored from 0 to 8. The score is based on, the observation of patient's conduct in the interview and on, the patient's subjective report of the last 48 hours. The score for the patient is obtained by summing the scores of each item. It can be expressed in 3 different categories: "hypomania" if the score is less than 10 (<10) points, "mild mania" if the score is between 10 and 19 (10-19) points and "moderate-severe mania" when the score is more than 19 (>19) points. In our study, we will only use the categories of "mild mania" and "moderate-serious mania", because our patients are diagnosed of bipolar I disorder. According to DSM-5 criteria, bipolar I disorder doesn't include hypomania states. So, for that reason

we will only use, this 2 categories. This instrument will be used to study the co-variable severity of the relapses. (Appendix 4)

- **Homes and Rahe Stress Scale:** This scale is used to assess the occurrence of traumatic events and their contribution to a person's well-being and risk of disease. It has been proven as a valid predictor of illness and allows the classification between "at risk of illness", "moderate risk" or "low risk". This instrument will be used to study one of co-variables. (Appendix 6)

A **CRF** will express the data collected. (Appendix 8)

Statistical analysis

Univariant Analysis

Categorical variables, such as the dependent and the independent variables, will be described using frequencies and percentages. The frequencies will be represented in frequency tables and in bar charts.

The variable Mean number of relapses, continuous variable, will be described as mean±SD.

Bivariate Analysis

Comparisons of results for categorical variables will be performed using Fisher's exact test. Then, to compare the Mean number of relapses, a continuous variable, in the last 5 years between the 2 groups: bipolar patients with alcohol consumption and bipolar patients without alcohol consumption it will be performed a Student's t-test.

Multivariate Analysis

Multivariate analysis will be performed using multivariate logistic regression analysis adjusting for the co-variables to assess the relationship between Alcohol consumption and Relapses conditioned on the presence or absence of other features and their contribution.

A descriptive analysis of the variables will be performed using IBM SPSS Statistics version 22.0.0.0. , 2015 (IBM, Armonk, NY, US). The data set will be thoroughly screened prior to commencing analyses, and double-checking all entries and screening for the presence of missing data will ensure the accuracy of the information.

A p value <0.05 will be considered statistically significant.

Multivariate analysis will be performed using general lineal model adjusting for the co-variables to assess the relationship between Alcohol consumption and Mean number of the relapses. In this case Mean of the relapses will be expressed has continuous variable.

A descriptive analysis of the variables will be performed using IBM SPSS Statistics version 22.0.0.0. , 2015 (IBM, Armonk, NY, US). The data set will be thoroughly screened prior to commencing analyses, and double-checking all entries and screening for the presence of missing data will ensure the accuracy of the information.

A p value <0.05 will be considered statistically significant.

Ethical and Legal Considerations

Before carrying out the study, the research protocol will be presented to the ethics committee, "Comité Ético de Investigación Clínica" (CEIC) from IAS de Girona, and, it will be evaluated and approved by CEIC and, it should be accepted by the same committee.

Since it is a prospective study, we will not depart from a previously constructed database. Therefore, we will need the acquiescence of the participants. Before being included, all potential participants will be informed appropriately of the research's purpose and structure by the psychiatrist and will also be given an information sheet that details the information transmitted beforehand and an informed consent form. (Appendix 8). They will be invited to participate voluntarily and will only be a part of the study once and if they sign said form.

Since that our study includes patients who have an alcohol consumption, it's important that psychiatric services recommended to do a specific treatment. This treatment is provided if the patient accepts the treatment. For ensure that patient's is doing the treatment for AUD, the psychiatrist will first ask to the patient and then, family is going to confirm the information that patient has given. Secondly, it is also important, to ensure that every participant is doing the treatment for BD. For that, the doctor will ask to the patient, if he is doing or not the treatment to BD and then, the psychiatrist will ask to patient's family if the information that he giving is true. Finally, every 3 months patient must do an analytic with the plasma drug levels, to ensure that he is doing the treatment for BD. To ensure that all the information is reliable patient's family must accompany him to all the consultations. It's important to stress that all the study's participants will already be under the program of XSM, which allows for a close and, more importantly, unified actuation protocol.

This study guarantees the confidentiality of the patient's data as the CRF will only use the medical record number and not the participant's name. Clinical history, analytics, information, names and surnames will remain anonymous when collecting data from the database and publishing results.

The present project will be conducted according to national and international ethics guidelines and laws:

- Ley Orgánica 15/1999, del 13 de Diciembre, de Protección de Datos de Carácter Personal
- Ley Orgánica 41/2002, del 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica.
- WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, June 1964. Last revision, October 2013.

The investigators of this project declare that there are no conflicts of interests.

Study limitations

Main limitations of this protocol are inherent to follow-up studies. This study will be expensive and time consuming. Due the large duration of a prospective cohort study, there can be differential losses to follow up that can introduce bias: the patient could miss an appointment or his family couldn't assist to the appointment with him. To avoid sample losses one week before each appointment, the participant, as well as, his family will receive a phone call and an email. The day before the appointment, patient and his family will receive a text message that will act them as a reminder.

One of the main limitations of the study is the small sample size. It was used a non-probabilistic consecutive sampling, which, it has its own limitations. This type of sampling is useful for small sample sizes, it is not time consuming and allows for minor changes and adjustments in the initial phases of research. However, it is hardly representative of the entire population. So, it will be difficult to make definitive conclusions about our hypothesis. These results should be considered as preliminary and will be helpful in the case the study is repeated using a randomized probabilistic sampling.

For measure alcohol consumption we will use the CAGE questionnaire. CAGE questionnaire have demonstrated a high test-retest reliability and is one of the most used questionnaires in clinical practice. Also, have shown to be useful in mental health patients. However, is more sensitive than a blood test. A blood test can be very useful in confirm the veracity of the alcohol use history. With a questionnaire there are many factors that can produce a bias: the information that the patient provides may not be reliable, the interviewer might stress or emphasize some questions, which can have some influence on participants' answers and this may produce a bias. To prevent this bias, the patient's family will be present in every appointment and the psychiatrist will be a professional trained in lead with these dual pathology patients.

Each and every participant will be a part of XSM of Girona and, while that assures that the general guidelines are the same, a certain degree of treatment heterogeneity and the experience of stress-like events cannot be avoided. However, these possible limitations were taken into account and that is why "pharmacological treatment of AUD", "pharmacological adherence to BD" and "traumatic events" are co-variables.

It can be difficult to measure the patient's treatment adherence to the bipolar treatment. To avoid this, we will ask to the patient if he is adhering to the BD treatment, then his family is going to confirm this information and the psychiatrist will revise the patient's clinical history in order to confirm this information with the results of plasma drug levels, done by the patient every 3 months. However, if the patient didn't do the analytics every 3 months, we won't be able to confirm if he is adhering to the BD treatment and this may produce a bias.

In our study, patient could change his alcohol consumption during the study. In this way, the patient, during the period of the study, can change from the group of bipolar patients who have an alcohol consumption to the group of bipolar patients who don't have an alcohol consumption. This can be difficult to control and it's because of that "alcohol consumption during the study" is a co-variable.

We also have to take into account the additional biases, the confounding bias. The relationship is difficult to control due to co-variables. This limitation will be minimized by the use of a multivariate analysis.

The reporting (information) bias that commonly occurs in patients who have an alcohol consumption and in bipolar patients. This can lead to an under or overestimation of the symptomatology or alcohol consumption and to a worse treatment compliance. It is to prevent this bias that in this study we will use a one trained and experience psychiatrist in dual pathology. Also, in order to avoid that bias, patient's family will accompany him to the appointments with the objective of contrasting the information and assessing the veracity of the patient's statements, being careful to control, at the same time, the inter-observer variability. Having clear and objective measuring instruments will minimize the inter-observer variability.

The observer/interviewer is another possible bias. In some cases, the interviewer might stress or emphasize some questions, which could lead to an information bias. To avoid this, the psychiatrist will be a trained professional, with no personal links to the participants.

Work plan

The duration of this study will be 5 years and 11 months and it will be divided in 7 stages:

Stage 1. Protocol Design Stage (Principal investigator) – 3 months (September – November 2015)

This stage consisted on literature review, the elaboration of this protocol and its presentation to a group of teachers of "Facultat de Medicina de la Universitat de Girona", as well as the study's proposal to CEIC and its acceptance.

Stage 2. Coordination Stage (Principal investigator, Collaborator investigator) – 2 months (December 2015 – January 2016)

In this phase, organizational and informative meetings will be held between the main investigators and the rest of the research team.

The work team will consist on one investigator, a psychiatrist and one qualified statistician. The psychiatrist must be trained on doing the PRISM interview. The PRISM is a semi-structured diagnostic interview designed to deal with the problems of psychiatric diagnosis when subjects/patients drink heavily or use drugs. The PRISM assesses DSM-IV Axis I and Axis II disorders. With this interview, we will be able to differentiate primary disorders, substance-induced disorders and the expected effects of intoxication and withdrawal.

The main investigators will meet once with the heads of XMS sectors (Gironès-Pla d'Estany, Baix Empordà, Alt Empordà, La Garrotxa-Ripollès, La Selva Maritima and La Selva Interior), with the aim of explaining the study's outline and its inclusion and exclusion criteria. They will, in turn, transmit that information to the other working members of XSM, making sure every doctor can help in the selection of the patients. If the patient had a relapse, it's important that every doctor have registered, in patients' clinical history, the severity of the relapse, by applying the YMRS, for mania and HRS-D, for depression.

Any doubts the personnel might have about the project should be cleared in this stage.

The PRISM interview has already a validated Spanish version, and we are going to use this version in our study. It is important to use this point to translate all the measuring instruments (Cage Questionnaire, Holmes & Rahe Stress Scale, DSM-5 criteria for "mania", "major depression" and "hypomania", YMRS and HRS-D), if not already available in Spanish.

The training of the psychiatrist in PRISM interview and the database's creation will also happen here.

Stage 3. Participants' Recruitment Stage (Collaborator investigator) **-** (24 months – February 2016 – February 2018)

We will screen the patients included in XSM de Girona.

The trained doctors will do the PRISM interview, in order to know if the patient has a dual diagnosis of BD and AUD. The doctor also, passes the YMRS and HRS-D to assess the severity of mania and depression, respectively. After that, they talk with the family, in order to ensure that the information, the patient's is giving to us, about alcohol consumption, AUD and BD treatment, is true.

When is detected consumption in the follow-up, from psychiatric services it is recommended do a specific treatment. It is recommended a treatment for AUD (that it's provided if the patient accepts the treatment), or he is referred to a specialized unit, like the "Unidad de Patologia Dual y Desintoxicació" (UDPD) or CAS.

When a patient that fulfils the inclusion criteria, arrives to its usual consultation, his doctor will introduce the concept of the study, giving them verbal information, the Information

Sheet and the Informed Consent. The same doctor will later contact the main investigators, who will confirm that the patient can be included in the study. The participants' incorporation in the research will be only carried out following the confirmation that they were properly informed about the characteristics of the study and signed the Informed Consent Form.

It is also in this stage that will happen the application of the independent variable, with the objective of creating two groups:

a) Group A: Bipolar patients with the diagnosis of alcohol consumption and a Cage Questionnaire score ≥2

b) Group B: Bipolar patients without the diagnosis of alcohol consumption and a Cage Questionnaire score <2

Both groups will go through the same steps, attending the consultations with their family and answering the questions without disparities between groups.

The patients' recruitment will be carried out to term until the sample size is completed or the end of the 24 months (where, according to the data available, we can predict we will have all the members' needed).

Stage 4. Data Collection Stage (Principal investigator, Collaborator investigator) –60months (February 2016 – February 2021)

This stage will start when the first participant is recruited and will end five years after the last patient is included. The data will be collected in the appointments between the participants, his family and the psychiatrist. The psychiatrist will see the patient and his family at the same time. In order to fill out the CRF, the psychiatric will first ask to the patient questions about the items of the CRF. Then his family must confirm that the information he is giving is true, to avoid the possibility of have wrong information about patient's alcohol consumption, treatment adherence to BD and AUD. The psychiatrist, reaching a consensus, will fill out the CRF. In the case that a consensus cannot be reached, it should be expressed on the 'observations' paragraph of the CRF.

1. **Appointment nº 1:** it will occur after the Informed Consent is signed and after the agreement to participate in the research is done. In this meeting, the patient will be accompanied by his family, will answer the questions reflected in the CRF. Through patient answers the doctor will determine if the patients meet the DSM-5 diagnostic for depression or mania or mixed features and we will know if he had a or not a relapse. The Holmes & Rahe Stress Scale will also be performed here. It will be asked the age of diagnostic of bipolar disease, if he had a previous episode of AUD and sociodemographic data (gender, age, education, marital status and employment situation), which is only going to be asked in this appointment. Then, it's important to ask, if patient takes another substances than alcohol. As well as if patient is or not in treatment for BD and for AUD: first, the physician will ask him and then, his family should confirm this information. Also, to confirm that he is adhering to BD treatment, he should have done an analytic in order to confirm, the plasma drug levels. This analytic must be done every 3 months and it will be registered in the patient's clinical history. The psychiatric has to access the patient's clinical history and confirm that the plasma drug levels are within therapeutic levels.

   After that, the physician has to ask to the patient and his family, if he has been hospitalized on the last 6 months. Then he must confirm this information on patient's clinical history and see the duration of the hospitalization that is also, registered on the patient's clinical history. The physician will also accede to the patient's clinical history to know the severity of patient's relapses on the last 6 months.

2. **Appointment nº 2:** This appointment will occur 6 months after the first appointment. All the mentioned data will be taken, with the exception of the Holmes & Rahe Stress Scale. In this appointment, the psychiatrist has to see if the patient has changed his alcohol consumption during the study. As we said before, there are 2 groups of patient. One contains the patients diagnosed with alcohol consumption resulting in a score equal or greater than 2(≥2) in Cage questionnaire. The other group contains the patients with no alcohol consumption, scoring less than 2(<2) points in Cage questionnaire. During the study, a patient could change his alcohol consumption. In this way, the patient, during the period of the study, can change to one group to another. So, it's important to control the alcohol consumption during the study. The mental health professional has to review the clinical history of the patient and the CRF on the last 6 months and compare the alcohol consumption he had 6 months ago with the alcohol consumption that he has now and register in the patient clinical history and in the CRF, if this alcohol consumption has changed or hasn't changed.

3. **Appointment nº 3:** Will occur 12 months after the first appointment. All the mentioned data will be taken, including the Holmes & Rahe Stress Scale.

4. **Appointment nº 4:** Will occur 18 months after the first appointment. All the mentioned data will be taken, with the exception of the Holmes & Rahe Stress Scale.

5. **Appointment nº 5:** Will occur 24 months after the first appointment. All the mentioned data will be taken, including the Holmes & Rahe Stress Scale.

6. **Appointment nº 6:** Will occur 30 months after the first appointment. All the mentioned data will be taken, with the exception of the Holmes & Rahe Stress Scale.

7. **Appointment nº 7:** Will occur 36 months after the first appointment. All the mentioned data will be taken, including the Holmes & Rahe Stress Scale.

8. **Appointment nº 8:** Will occur 42 months after the first appointment. All the mentioned data will be taken, with the exception of the Holmes & Rahe Stress Scale.

9. **Appointment nº 9:** Will occur 48 months after the first appointment. All the mentioned data will be taken, including the Holmes & Rahe Stress Scale.

10. **Appointment nº 10:** Will occur 54 months after the first appointment. All the mentioned data will be taken, with the exception of the Holmes & Rahe Stress Scale.

11. **Appointment nº 11:** Final appointment. Will occur 60 months after the first appointment. All the mentioned data will be taken, including the Holmes & Rahe Stress Scale.

To avoid sample losses, one week before each appointment, the participant as well as his family will receive a phone call, and an email and the day before the appointment a text message that will act them as a reminder.

After each appointment, the database will be filled and the investigators will have a reunion, either in person or by phone. Some of those reunions will also assess the progress of the study and the data's quality.

The Holmes & Rahe Stress scale will only be assessed in appointments nº 1, 3, 5, 7, 9, and 11.

Stage 5. Data Analysis Stage (Statician, Principal investigator) – 1 month (March 2021)

The statistician will take all the collected data and proceed to analyse it according to the already mentioned methods and using the appropriate software. A univariate, bivariate and multivariate analysis will be used, to examine the contribution of the confounding variables.

Stage 6. Results' Interpretation and Writing Stage (Principal investigator, Collaborator Investigator) – 3 months (April –June 2021)

In this moment, the investigators will receive the analysed data from the statistician and will interpret the results. From these results, they will draft a conclusion and start writing the final article.

Stage 7. Publication and Dissemination Stage (Principal investigator, Collaborate investigator) **–** From July 2021

The main investigators will present the study's results in a prestigious psychiatric publication. The final article will be sent, with the intent of acceptance and publication, to "JAMA Psyquiatry".

The results will be then presented in a national congress: "XXIII Jornadas nacionales de Patología Dual", in Madrid, Spain and in international specialty congress: "XII CONGRESO INTERNACIONAL DE PATOLOGÍA DUAL: Conductas Adictivas y Otros Trastornos Mentales", in Barcelona, Spain

Chronogram

	Personnel	2015				2016		2017		2018		2019	2020	2021			
		Set	Oct	Nov	Dec	Jan	Feb-Dec	Jan-Feb	Mar-Dec	Jan - Fev	Mar - Dec	Jan-Dec	Jan-Dec	Jan-Fev	Mar	Apr -Jun	From July
Stage 1																	
Protocol design and presentation	PI																
Stage 2																	
Team meetings	PI, CI																
Additional meetings	PI,CI																
Psychiatrist training	CI																
Stage 3																	
Patients' recruitment	CI																
Stage 4																	
Appointments 1-11	CI																
Team meetings	PI, CI																
Stage 5																	
Data analysis	ST, PI																
Stage 6																	
Writing	PI, CI																
Stage 7																	
Publication and dissemination	PI, CI																

PI: principal investigator; CI: collaborator investigator; ST: Statician

Available means to develop the study

The new Santa Caterina's Hospital was funded in 2004 and has de proper functions of a general hospital and incorporates hospitalization services in adult psychiatry, teenage psychiatry, psychiatry emergency department and a Detoxification and Dual Pathology unit, UDPD.

The UDPD unit is a free and public service of adult psychiatry. It serves both patients with consumption of toxics, such as those suffering from psychiatric disorders associated with addiction and can cause or consequence a mental illness.

It is a hospital unit aimed to support the CAS patients and patients from mental health centres of the mental health network of Girona.

It has 10 beds (2 singles and 4 doubles). The space unit includes a living area, multipurpose room and outdoor patio.

The UDPD unit count with several professional physicians leaded by Dra. Núria Rigau.

Impact of the study in National Health System

The dual pathology of AUD and BD, is a common phenomenon in the BD patients. This co-occurrence leads to a shorter time between mood episodes, a poor treatment adherence and compliance, a poor symptomatic and functional recovery, a more severe affective episodes and consequently to a more relapses and hospitalizations.

Actually, the causes for this co-occurrence are unknown. Research on the relation between these two comorbidities has increased last years and there are a number of important epidemiological studies done about the prevalence of this dual pathology. However, this relation needs to be well explored and more studies have to be done. In this way, we may understand why this co-occurrence exists. With that we can provide the pharmacological options that have demonstrated better efficacy and tolerability and follow and treat this patients in a specific unit such as the dual pathology unit. This can allow us to implement new strategies and improving the treatment options and the patients may will have benefit with that. This also can increase their quality of life.

BD and AUD are important economic problems for the national health system and this co-occurrence have a worse economic impact. Oleguer Parés-Badell et al. said that the economic cost of diseases is becoming an ever more important determinant for health policies and decision-making and thus solid Spanish specific estimates are needed (30). Currently, and according to "Estrategia en Salud Mental del Sistema Nacional de Salud", the economic repercussions of mental health in Spain are estimated to be around 3005 millions of euros, with the social cost of mental health disorders bordering near 3375 euros per disorder. Psychiatric ailments are the cause of 10.5% of loss of workdays, in temporary disability, and 6.8% years of working life, in permanent disability (31). In Spain, the direct health-care cost of a BD per-patient is 283 euros and the total social costs of alcohol consumption are about 1% of GDP (10000 million euros) (30,32).

By improving these factors, the rates of relapse and would decrease, which would lead a saving of money and resources by the National Health System.

It would be the first study about this dual pathology in Girona.

Budget

		Maximum cost	
Personnel and personnel costs			
Statistician	35€ per hour x 48 hours	1680€	
Psychiatrist training		2715€	
Travelling	1 person x 11 appointments x 90 patients	650€	
Team meetings		500€	
		Subtotal	5545€

		Maximum cost	
Material and Services			
Questionnaires, scales, and informed consent printing	0,30€ p/unit x 39 units per participant x 90 participants	1053€	
		Subtotal	1053€

		Maximum cost	
Publication and dissemination			
Publication		1000€	
Conference			
National			
Inscription fee	520€ x 2 investigators	1040€	
Travelling	100€ x 2 investigators	60€	
Accommodation	660€ x 2 investigators	1320€	
International			
Inscription fee	540€ x 2 investigators	1080€	
Travelling	16€ x 2 investigators	32€	
Accommodation	700€ x 2 investigators	1400€	
		Subtotal	5932€
	Total	**12.530€**	

Before starting the study it is necessary to ensure its financing.

The patients from the Gironès sector will be seen at Parc Hospitalari Marti I Julià, in Salt, which doesn't entail these kinds of costs. For the remaining sectors, there will be efforts of coordination, to minimize the visits to each CSM or CAS (Alt and Baix Empordà, La Selva Interior and Maritima, Garrotxa-Ripollès), and allow that all the participants from the region can be visited within the same displacement.

The investigators and the doctors working for the program will not receive a compensation for their work in this study.

The budget doesn't include material as computers because it's available in any of the CSM or CAS, as well as, the costs of the analytics because are done on CSM or CAS. All of validated questionnaires and scales that will be applied to patients are available in all centres, meaning that their cost is mainly associated with printing expenses.

Software such as SPSS is not included because it is available to the statistician or free of charge. PRISM software is included on the package of psychiatrist training.

REFERENCES

1. American Psychiatric Association. What Are Bipolar Disorders? [Internet]. [cited 2015 Oct 16]. Available from: http://www.psychiatry.org/patients-families/bipolar-disorders/what-are-bipolar-disorders

2. Grande I, Berk M, Birmaher B, Vieta E. Seminar Bipolar disorder. Lancet [Internet]. 2015 [cited 2015 Oct 16];6736(15):1–12. Available from: http://dx.doi.org/10.1016/S0140-6736(15)00241-X

3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.

4. National Institute of Mental Health. Bipolar Disorder in Adults. US Dep Heal Hum Serv [Internet]. 2012 [cited 2015 Nov 4];NIH Public. Available from: http://www.nimh.nih.gov/health/publications/bipolar-disorder-in-adults/index.shtmlcom

5. Levy B, Manove E. Functional outcome in bipolar disorder: the big picture. Depress Res Treat [Internet]. 2012 [cited 2015 Oct 16];1–12. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3180778&tool=pmcentrez&rendertype

6. Culpepper L, Manning JS, McIntyre RS. Practical approaches in the management of bipolar depression: Overcoming challenges and avoiding pitfalls. J Fam Pract. 2015;64(6 Suppl):S1–23.

7. Gaudiano B, LM W, WI M. Improving Treatment Adherence in Bipolar Disorder: A Review of Current Psychosocial Treatment Efficacy and Recommendations for Future Treatment Development. NIH Public Access. 2008;42(2):157–62.

8. Bipolar disorder : assessment and management. London: National Institute for Health and Care Excellence; 2014.

9. Gual LM, Barrio P, Moreno-España J, Martinez A, Ortega L, Manthey J, et al. Detección y prevalencia del trastorno por uso de alcohol en los centros de atención primaria de Cataluña. Atención Primaria. 2015;4–11.

10. Schuckit MA. Alcohol-use disorders. Lancet [Internet]. 2009 [cited 2015 Oct 29];373(9662):492–501. Available from: http://dx.doi.org/10.1016/S0140-6736(09)60009-X

11. Rubio G, López-Muñoz F, Álamo C, Santo-Domingo J. Transtornos psiquiátricos y abuso de sustancias. Madrid: Editorial medica panamericana; 2002.

12. Klimkie A, Klimkie J, Andrzej J. Comorbidity of alcohol dependence with other psychiatric disorders . Part I . Epidemiology of dual diagnosis. 2015;49(2):265–75.

13. Kranzler HR, Rounsaville BJ. Dual Diagnosis and Treatment. Frosh WA, editor. New York: Marcel Dekker; 1998.

14. Salloum IM, Thase ME. Impact of substance abuse on the course and treatment of bipolar disorder. Biol Psychiatry. 2000;2(3 Pt 2):477–85.

15. Salloum IM, Thase ME. Impact of substance use on the course and treatment of bipolar disorder. Bipolar Disord. 2000;2(3 Pt 2):269–80.

16. Reece A. The prevalence and significance of substance use disorders in bipolar type I and II disorder. Subst Abus Treat Prev policy [Internet]. 2007 [cited 2015 Oct 17];2(1):9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2094705/

17. Strakowski SM, DelBello MP, Fleck DE, Adler CM, Anthenelli RM, Keck PE, et al. Effects of co-occurring alcohol abuse on the course of bipolar disorder following a first hospitalization for mania. Arch Gen Psychiatry. 2005;62(8):851–8.

18. Zubrzycki A. Trastorno bipolar. Salud(i)Ciencia. 2011;18(3):290.

19. Szerman N, Goikolea JM, Vieta E. Patologia Dual: Protocolos de intervencion. Trastorno Bipolar. Barcelona: Sociedad Española de Patología Dual; 2012.

20. McElroy SL, Altshuler LL, Suppes T, Keck PE, Frye MA, Denicoff KD, et al. Axis I Psychiatric Comorbidity and Its Relationship to Historical Illness Variables in 288 Patients With Bipolar Disorder. Am J Psychiatry [Internet]. 2001 [cited 2015 Oct 1];158(3):420–6. Available from: http://psychiatryonline.org/doi/abs/10.1176/appi.ajp.158.3.420

21. Colom F, Vieta E, Martínez-Arán A, Garcia-Garcia M, Reinares M, Torrent C, et al. Versión española de una escala de evaluación de la manía: validez y fiabilidad de la Escala de Young. Med Clin (Barc) [Internet]. 2002 [cited 2015 Oct 29];119(10):366–71. Available from: http://www.elsevier.es/es-revista-medicina-clinica-2-articulo-version-espanola-una-escala-evaluacion-13037376

22. Ramos-Brieva JAA, Cordero-Villafafila A. A New Validation of the Hamilton Rating Scale for Depression. J Psychiatr Res [Internet]. 1988 [cited 2015 Oct 29];22(1):21–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3397906

23. Torrens M, Serrano D, Astals M, Pérez-Domínguez G, Martín-Santos R. Diagnosing comorbid psychiatric disorders in substance abusers: Validity of the Spanish versions of the psychiatric research interview for substance and mental disorders and the structured clinical interview for DSM-IV. Am J Psychiatry. 2004;161(7):1231–7.

24. Hasin DS. PRISM [Internet]. New York: University of Columbia; 2009 [cited 2015 Oct 18]. Available from: http://www.columbia.edu/~dsh2/prism/

25. Sonne SC, Brady KT. Bipolar Disorder and Alcoholism [Internet]. Charleston: National Institute on Alcohol Abuse and Alcoholism; 2002 [cited 2015 Oct 27]. Available from: http://pubs.niaaa.nih.gov/publications/arh26-2/103-108.htm

26. Baethge C, Baldessarini RJ, Khalsa HMK, Hennen J, Salvatore P, Tohen M. Substance abuse in first-episode bipolar I disorder: Indications for early intervention. Am J Psychiatry. 2005;162(5):1008–10.

27. Cassidy F, Ahearn EP, Carroll BJ. Substance abuse in bipolar disorder. Bipolar Disord. 2001;3(4):181–8.

28. Frye MA, Altshuler LL, Mcelroy SL, Suppes T, Keck PE, Denicoff K, et al. Gender Differences in Prevalence , Risk , and Clinical Correlates of Alcoholism Comorbidity in Bipolar Disorder. (14):883–9.

29. Dhalla S, Kopec J. The CAGE questionnaire for alcohol misuse: A review of reliability and validity studies. Clin Investig Med. 2007;30(1):33–41.

30. Parés-Badell O, Barbaglia G, Jerinic P, Gustavsson A, Salvador-Carulla L, Alonso J. Cost of disorders of the brain in Spain. PLoS One [Internet]. 2014 [cited 2015 Nov 8];9(8):e105471. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25133395

31. Estrategia en Salud Mental del Sistema Nacional de Salud. Madrid: Ministerio de Sanidad y Consumo; 2007.

32. Pulido J, Indave-Ruiz BI, Colell-Ortega E, Ruiz-García M, Bartroli M, Barrio G. Population-based studies on alcohol-related harm in Spain. Rev Esp Salud Publica [Internet]. 2014 [cited 2015 Nov 8];88(4):493–513. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25090406

33. CAGE Questionnaire [Internet]. National Institute on Alcohol Abuse and Alcoholism. 2002 [cited 2015 Nov 8]. Available from: http://pubs.niaaa.nih.gov/publications/inscage.htm

34. Holmes- Rahe Stress Inventory [Internet]. American Institute of Stress. Fort Worth; 2014 [cited 2015 Nov 8]. Available from: http://www.stress.org/holmes-rahe-stress-inventory/

APPENDICES

APPENDIX 1: DSM-5 Criteria for Bipolar I disorder

Bipolar I disorder

Diagnostic Criteria

For a diagnosis of bipolar I disorder, it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes.

	Maniac Episode
A	A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
B	During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior: 1. Inflated self-esteem or grandiosity. 2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep). 3. More talkative than usual or pressure to keep talking. 4. Flight of ideas or subjective experience that thoughts are racing. 5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed. 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity). 7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C	The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
D	The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition. **Note:** A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

Note: Criteria A-D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

	Hypomanic Episode
A	A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.
B	During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree: 1. Inflated self-esteem or grandiosity. 2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep). 3. More talkative than usual or pressure to keep talking. 4. Flight of ideas or subjective experience that thoughts are racing. 5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed. 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation. 7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C	The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.
D	The disturbance in mood and the change in functioning are observable by others.
E	The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.
F	The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment). **Note:** A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

Note: Criteria A-F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

	Major depression Episode
A	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly attributable to another medical condition. 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.) 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation). 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.) 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down). 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C	The episode is not attributable to the physiological effects of a substance or another medical condition.

Note: Criteria A-C constitute a major depressive episode. Major depressive episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.
Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully

considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.[1]

Specify:

With mixed features

- The mixed features specifier can apply to the current manic, hypomanic, or depressive episode in bipolar I disorder.

	Manic or hypomanic episode, with mixed features
A	Full criteria are met for a manic episode or hypomanic episode, and at least three of the following symptoms are present during the majority of days of the current or most recent episode of mania or hypomania: 1. Prominent dysphoria or depressed mood as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). 2. Diminished interest or pleasure in all, or almost all, activities (as indicated by either subjective account or observation made by others). 3. Psychomotor retardation nearly every day (observable by others; not merely subjective feelings of being slowed down). 4. Fatigue or loss of energy. 5. Feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick). 6. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B	Mixed symptoms are observable by others and represent a change from the person's usual behavior.
C	For individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features, due to the marked impairment and clinical severity of full mania.
D	The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment).

[1] In distinguishing grief from a major depressive episode (MDE), it is useful to consider that in grief the predominant affect is feelings of emptiness and loss, while in MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves, the so-called pangs of grief. These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of a MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of a major depressive episode. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than the self-critical or pessimistic ruminations seen in a MDE. In grief, self-esteem is generally preserved, whereas in a MDE, feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis-a-vis the deceased (e.g., not visiting frequently enough, not telling the deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such thoughts are generally focused on the deceased and possibly about "joining" the deceased, whereas in a major depressive episode such thoughts are focused on ending one's own life because of feeling worthless, undeserving of life, or unable to cope with the pain of depression.

	Depressive episode, with mixed features
A	Full criteria are met for a major depressive episode, and at least three of the following manic/hypomanic symptoms are present during the majority of days of the current or most recent episode of depression: 1. Elevated, expansive mood. 2. Inflated self-esteem or grandiosity. 3. More talkative than usual or pressure to keep talking. 4. Flight of ideas or subjective experience that thoughts are racing. 5. Increase in energy or goal-directed activity (either socially, at work or school, or sexually). 6. Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments). 7. Decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted with insomnia).
B	Mixed symptoms are observable by others and represent a change from the person's usual behavior.
C	For individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features.
D	The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment).

Note: Mixed features associated with a major depressive episode have been found to be a significant risk factor for the development of bipolar I or bipolar II disorder.
As a result, it is clinically useful to note the presence of this specifier for treatment planning and monitoring of response to treatment.

Appendix 2: DSM-5 criteria for Alcohol Use Disorder and Alcohol withdrawal

Alcohol use disorder

Diagnostic Criteria

	Alcohol use disorder
A	A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period: 1. Alcohol is often taken in larger amounts or over a longer period than was intended. 2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use. 3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects. 4. Craving, or a strong desire or urge to use alcohol. 5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home. 6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol. 7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use. 8. Recurrent alcohol use in situations in which it is physically hazardous. 9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol. 10. Tolerance, as defined by either of the following: a) A need for markedly increased amounts of alcohol to achieve intoxication or desired effect. b) A markedly diminished effect with continued use of the same amount of alcohol. 11. Withdrawal, as manifested by either of the following: a) The characteristic withdrawal syndrome for alcohol (refer to Criteria A and B of the criteria set for alcohol withdrawal) b) Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

Alcohol withdrawal

Diagnostic Criteria

	Alcohol Withdrawal
A	Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B	Two (or more) of the following, developing within several hours to a few days after the cessation of (or reduction in) alcohol use described in Criterion A: 1. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm). 2. Increased hand tremor. 3. Insomnia. 4. Nausea or vomiting. 5. Transient visual, tactile, or auditory hallucinations or illusions. 6. Psychomotor agitation. 7. Anxiety. **8.** Generalized tonic-clonic seizures**.**
C	The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D	The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Appendix 3: Hamilton Rating Scale for depression (HRS-D)

ESCALA DE HAMILTON PER VALORAR LA DEPRESSIÓ (HRS-D)

Pacient: Edat: Sexe: Història nº:

Facultatiu: data: Facultatiu: data:

Punts	Avaluació dels darrers dies, fins la setmana previa.	Data inicial	Data 1er. seg.	Data 2n. seg.	Data pre-alta	Diferència inicial-alta
0-4	**1. Estat d'ànim deprimit** (actitud malencònica, pessimista vers el futur, sentiment de tristesa, tendència al plor) 0. Absent 1. Aquests estats no són assenyalats si no s'interroga el subjecte 2. Són assenyalats verbalment espontàniament 3. Són comunicats no verbalment (p.e. expressió facial, actitud, veu, tendència a plorar) 4. El subjecte comunica aquests estats afectius mitjançant comunicacions espontànies verbals i no verbals					
0-4	**2. Culpabilitat** 0. Absent 1. Auto-retrets, sensació d'haver causat prejudici a persones 2. Idees de culpabilitat 3. La malaltia actual és un càstig. Idees delirants de culpabilitat 4. Al.lucinacions de culpabilitat					
0-4	**3. Suïcidi** 0. Absent 1. Li sembla que la vida no val la pena viure-la 2. Desitja morir-se 3. Té idees suïcides 4. Intents de suïcidi					
0-2	**4. Insomni inicial** 0. Cap dificultat en adormir-se 1. Eventuals dificultats (p.e. costar més de mitja hora) 2. Té dificultats cada nit per adormir-se					
0-2	**5. Insomni a mitad del son** 0. No en té 1. El pacient està inquiet i alterat durant la nit 2. Es desperta durant la nit					
0-2	**6. Insomni tardà** 0. No en té 1. Es despera de matinada, però es torna a adormir 2. No es pot tornar a adormir.					

0-4	**7. Treball i interessos** 0. Cap dificultat 1. Sentiments d'incapacitat, negligència, indecisió i vacil.lació en les activitats professionals o de diversió 2. Pèrdua d'interès per les activitats professionals i diversions, descrites directament per la serva apatia. Indecisió, titubeig (impresió que s'ha d'esforçar per realitzar una activitat) 3. Disminució de les activitats o de la productivitat 4. Va deixar de treballar a causa de la malaltia actual					
0-4	**8. Retardació** (alentiment del pensament, de la parla i/o conducta) 0. Normal 1. Lleuger retard durant l'entrevista 2. Evident retard durant l'entrevista 3. Entrevista dificultosa 4. Complert estupor					
0-4	**9. Agitació** 0. Cap 1. Enervament 2. Juga amb les mans, els cabells 3. Agitat, no pot estar-se quiet 4. Es retorç les mans, es mossega les ungles, es mossega els llavis					
0-4	**10. Ansietat psíquica** 0. Cap 1. Tensió i irratibilitat 2. Preocupació sobre assumptes menors 3. Actitud aprensiva 4. Temors					
0-4	**11. Ansietat somàtica** 0. Absent 1. Discreta (molèsties gastrointestinas. Indifgstió, meteorisme, boca seca, diarrera, eructosi) 2. Mitjana 3. Greu (trastorns cardiovasculars, palpitacions, cefelees) 4. Trastorns respiratoris, hiperventilació, sospirs, polaquiuria, transpiració					
0-2	**12. Símptomes somàtics digestius** 0. Cap 1. Pèrdua de la gana, sensació de pesadesa d'abdomen 2. Dificultat per menjar si no se l'obliga. Necessitat de laxants, purgants					
0-2	**13. Símptomes somàtics generals** 0. Cap 1. Pesadesa en els membres inferiors, espatlla o cap, cefalees, dolors musculars, pèrdua d'energia i fatigabilitat. 2. Apuntar 2 si qualsevol d'aquests símptomes són ben patents					
0-2	**14. Símptomes genitals** 0. Pèrdua de la líbido, alteracions menstruals 1. Absent 2. Lleugers 3. Greus					
	15. Hipocondriasi					

0-4	0. Absent 1. Atenció concentrada en el propi cos 2. Preocupació per la seva salut 3. Queixes freqüents, peticions d'ajut, etc. 4. Idees delirants hipocondriaques					
0-2	**16. Pèrdua de discerniment** 0. Reconeix que està deprimit i malalt 1. Reconeix que està malalt però ho atribueix al menjar, el clima, el cansanci, a un virus, etc. 2. Nega estar malalt					
0-2	**17. Pèrdua de pes** 0. No n'hi ha 1. Lleugera o incerta 2. Certa o important					
0-2	18. Canvis diürns (no suma a la P.Total) 0. No hi ha variació 1. Variació no important 2. Marcada variació					
0-52	**PUNTUACIÓ TOTAL**					

Valors orientatius (Vázquez C. 1995):

0 – 6 : sense depressió
7 – 17 : depressió lleu
18 – 24 : depressió moderada
25 – 52 : depressió greu

Taken from: Hospital Santa Caterina de Girona

1. Ànim deprimit
Actitud malencònica, pessimista vers el futur, sentiment de tristesa, tendència al plor.
0. Absent
1. Aquests estats no són assenyalats si no s'interroga el subjecte
2. Són assenyalats verbalment espontàniament
3. Són comunicats no verbalment (p.e. expressió facial, actitud, veu, tendència a plorar)
4. El subjecte comunica aquests estats afectius mitjançant comunicacions espontànies verbals i no verbals

2. Culpabilitat
0. Absent
1. Auto-retrets, sensació d'haver causat prejudici a persones
2. Idees de culpabilitat
3. La malaltia actual és un càstig. Idees delirants de culpabilitat
4. Al.lucinacions de culpabilitat

3. Suïcidi
5. Absent
6. Li sembla que la vida no val la pena viure-la
7. Desitja morir-se
8. Té idees suïcides
9. Intents de suïcidi

4. Insomni inicial
3. Cap dificultat en adormir-se
4. Eventuals dificultats (p.e. costar més de mitja hora)
5. Té dificultats cada nit per adormir-se

5. Insomni a mitad del son
3. No en té
4. El pacient està inquiet i alterat durant la nit
5. Es desperta durant la nit

6. Insomni tardà
0. No en té
1. Es despera de matinada, però es torna a adormir
2. No es pot tornar a adormir.

7. Treball i interès
0. Cap dificultat
1. Sentiments d'incapacitat, negligència, indecisió i vacil.lació en les activitats professionals o de diversió
2. Pèrdua d'interès per les activitats professionals i diversions, descrites directament per la serva apatia. Indecisió, titubeig (impresió que s'ha d'esforçar per realitzar una activitat)
3. Disminució de les activitats o de la productivitat
4. Va deixar de treballar a causa de la malaltia actual

8. Retardació
Lentitud del pensament, conversació i activitat
0. Normal
1. Lleuger retard durant l'entrevista
2. Evident retard durant l'entrevista
3. Entrevista dificultosa
4. Complert estupor

9. Agitació
0. Cap
1. Enervament
2. Juga amb les mans, els cabells
3. Agitat, no pot estar-se quiet
4. Es retorç les mans, es mossega les ungles, es mossega els llavis

10. Ansietat psíquica
0. Cap
1. Tensió i irratibilitat
2. Preocupació sobre assumptes menors
3. Actitud aprensiva
4. Temors

11. Ansietat somàtica
0. Absent
1. Discreta (molèsties gastrointestinas. Indifgstió, meteorisme, boca seca, diarrera, eructosi)
2. Mitjana
3. Greu (trastorns cardiovasculars, palpitacions, cefelees)
4. Trastorns respiratoris, hiperventilació, sospirs, polaquiuria, transpiració

12. Símptomes somàtics digestius
0. Cap
1. Pèrdua de la gana, sensació de pesadesa d'abdomen
2. Dificultat per menjar si no se l'obliga. Necessitat de laxants, purgants

13. Símptomes somàtics generals
0. Cap
1. Pesadesa en els membres inferiors, espatlla o cap, cefalees, dolors musculars, pèrdua d'energia i fatigabilitat.
2. Apuntar 2 si qualsevol d'aquests simptomes són ben patents

14. Símptomes genitals
0. Pèrdua de la libido, alteracions menstruals
1. Absent
2. Lleugers
3. Greus

15. Hipocondriasi
0. Absent
1. Atenció concentrada en el propi cos
2. Preocupació per la seva salut
3. Queixes freqüents, peticions d'ajut, etc.
4. Idees delirants hipocondriaques

16. Discerniment
0. Reconeix que està deprimit i malalt
1. Reconeix que està malalt però ho atribueix al menjar, el clima, el cansanci, a un virus, etc.
2. Nega estar malalt

17. Pèrdua de pes
0. No n'hi ha
1. Lleugera o incerta
2. Certa o important

18. Canvis diürns
0. No hi ha variació
1. Variació no important
2. Marcada variació

Appendix 4: Young Mania Rating Scale (YMRS)

ESCALA DE YOUNG PER VALORAR ELS ESTATS DE MANIA (YMRS)

Pacient: Edat: Sexe: Història nº:

Facultatiu: data: Facultatiu: data:

Punts	Puntuació: observació conducta a l'entrevista; informe subjectiu del pacient de les darreres 48 h.	DATA	DATA	DATA	DATA	DATA
0-4	**1. Eufòria:** 0-Absent 1-Dubtos o lleu 3-Hipertimia subjectiva clara, optimista, segur, alegre, adequat 4-Eufòria, riures inapropiats, canta					
0-4	**2. Augment de l'activitat motora, energia:** 0-Absent 1-Augmentada subjectivament 2-Animat. Augment de la gesticulació 3-Energia excessiva. Hiperactiu a vegades; inquiet (es pot contenir) 4-Excitació motora. Hiperactivitat continua (no es pot contenir)					
0-4	**3. Interès sexual:** 0-Normal, no augmentat 1-Augment lleu o possible 2-Increment definit al preguntar-li 3-Interès sexual espontani; parla de temes sexuals 4-Hipersexualitat expressada sense que se li pregunti					
0-4	**4. Son:** 0-Refereix son conservat 1-Son reduït en menys de 1 hora 2- Son reduït en més de 1 hora 3-Refereix disminució en la necessitat de dormir 4-Nega necessitat de dormir					
0-8	**5. Irritabilitat:** 0-Absent 2- Subjectivament augmentada 4-Irritable episòdicament durant l'entrevista; episodis recents d'estar molest o enfadat a la unitat d'hospitalització 6-Irritable freqüentment durant l'entrevista. Tallant, brusc 8-Hostil, manca de cooperació. Entrevista impossible					
0-8	**6. Discurs (ritme i quantitat):** 0-No augment 2-Se sent parlador 4-Augment del ritme i la quantitat, a vegades verborreic 6-Verborrea. Augment important del ritme i quantitat, difícil d'interrompre 8-Verborrea ininterrumpible, discurs continuo					

0-8	**7. Trastorn del llenguatge i del pensament:** 0-Absent 2-Circumstancial. Lleument distraible; pensaments ràpids 4-Distraible. Perd el fil; canvia de tema amb freqüència. Pensaments ràpids 6-Fuga d'idees; tangencialitat; dificultat per seguir-lo; ecolalia 8-Incoherència; comunicació impossible					
0-4	**8. Contingut del pensament:** 0-Normal 1-Plans qüestionables, nous interessos 2-Projecte/s especial/s; hiperrreligios 3-Idees de grandesa o paranoides. Idees de referència 4-Deliris. Al·lucinacions					
0-8	**9. Conducta alterada – agressiva:** 0-Absent, coopera 2-Sarcàstic, alerta, vigilant, fa soroll 4-Demandant; fa amenaces a la sala de la unitat 6-Amenaça a l'entrevistador, crida, entrevista difícil 8-Agresivo, destructivo, entrevista imposible					
0-4	**10. Aparença:** 0-Vestit i higiene adequades 1-Mínimament descuidat 2-Poc cuidat a nivell personal; desmenegat en el vestit 3-Descuidat en el vestit. A mig vestir; maquillatge cridaner 4-Totalment desmenegat; decorat, maquillatge extrany					
0-4	**11. Insight. Consciència de trastorn:** 0-Present. Admet trastorn. Creu necessitar tractament 1-Dubta del trastorn però la admet com poc possible 2-Admet un possible canvi en la conducta i nega el trastorn 4-Nega qualsevol canvi de conducta					
0-60	PUNTUACIÓ TOTAL					

Valors orientatius: (< 6 hipomania dubtosa). Resposta al tractament: reducció del **50%** de la puntuació pre-tractament. Pope HG (2000):

< 10 hipomania
10 – 19 mania lleu

Taken from: Hospital Santa Caterina de Girona

Appendix 5: CAGE Questionnaire

CAGE Questionnaire

- Have you ever felt you should cut down on your drinking?
- Have people annoyed you by criticizing your drinking?
- Have you ever felt bad or guilty about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (eye opener)?

Scoring: Item responses on the CAGE are scored 0 or 1, with a higher score an indication of alcohol problems. A total score of 2 or greater is considered clinically significant.

Taken from: National Institute on Alcohol abuse and Alcoholism (NIH) (33)

Appendix 6: Holmes and Rahe Stress Scale

The Holmes-Rahe Life Stress Inventory

The Social Readjustment Rating Scale

INSTRUCTIONS: Mark down the point value of each of these life events that has happened to you during the previous year. Total these associated points.

Life Event	Mean Value
1. Death of spouse	100
2. Divorce	73
3. Marital Separation from mate	65
4. Detention in jail or other institution	63
5. Death of a close family member	63
6. Major personal injury or illness	53
7. Marriage	50
8. Being fired at work	47
9. Marital reconciliation with mate	45
10. Retirement from work	45
11. Major change in the health or behavior of a family member	44
12. Pregnancy	40
13. Sexual Difficulties	39
14. Gaining a new family member (i.e.. birth, adoption, older adult moving in, etc)	39
15. Major business readjustment	39
16. Major change in financial state (i.e.. a lot worse or better off than usual)	38
17. Death of a close friend	37
18. Changing to a different line of work	36
19. Major change in the number of arguments w/spouse (i.e.. either a lot more or a lot less than usual regarding child rearing, personal habits, etc.)	35
20. Taking on a mortgage (for home, business, etc..)	31
21. Foreclosure on a mortgage or loan	30
22. Major change in responsibilities at work (i.e. promotion, demotion, etc.)	29
23. Son or daughter leaving home (marriage, attending college, joined mil.)	29
24. In-law troubles	29
25. Outstanding personal achievement	28
26. Spouse beginning or ceasing work outside the home	26
27. Beginning or ceasing formal schooling	26
28. Major change in living condition (new home, remodeling, deterioration of neighborhood or home etc.)	25
29. Revision of personal habits (dress manners, associations, quitting smoking)	24
30. Troubles with the boss	23
31. Major changes in working hours or conditions	20
32. Changes in residence	20
33. Changing to a new school	20
34. Major change in usual type and/or amount of recreation	19
35. Major change in church activity (i.e.. a lot more or less than usual)	19
36. Major change in social activities (clubs, movies,visiting, etc.)	18
37. Taking on a loan (car, tv,freezer,etc)	17
38. Major change in sleeping habits (a lot more or a lot less than usual)	16
39. Major change in number of family get-togethers ("")	15
40. Major change in eating habits (a lot more or less food intake, or very different meal hours or surroundings)	15
41. Vacation	13
42. Major holidays	12
43. Minor violations of the law (traffic tickets, jaywalking, disturbing the peace, etc)	11

Now, add up all the points you have to find your score.

150pts or less means a relatively low amount of life change and a low susceptibility to stress-induced health breakdown.

150 to 300 pts implies about a 50% chance of a major health breakdown in the next 2 years.

300pts or more raises the odds to about 80%, according to the Holmes-Rahe statistical prediction model.

Taken from: The American Institute of Stress (34)

Appendix 7: Information form and informed consent form

Hoja de información al paciente

Título del estudio: ***Los pacientes bipolares que consumen alcohol tendrán más recaídas? Estudio de seguimiento a 5 años.***

Estimado/a:

Agradecemos su participación en este estudio que estamos realizando desde la Red de Salud Mental en la provincia de Girona. El trastorno bipolar es una de las causas más frecuentes de discapacidad en la gente joven y disminuye la calidad de vida de los pacientes. El trastorno bipolar se asocia con frecuencia a comorbilidades como el trastorno por uso de alcohol. Es lo que se denomina "patología dual", que define la coexistencia de un trastorno mental como el bipolar y un trastorno por uso de sustancias como el alcohol. Con su participación estará contribuyendo a mejorar los conocimientos que tenemos actualmente sobre la patología dual y de esta manera entender si los pacientes bipolares que consumen alcohol van tener más recaídas que los pacientes bipolares que no consumen alcohol.

Por lo tanto, estamos muy interesados en hacer un seguimiento de nuestros participantes durante 5 años para conocer si estos pacientes van a tener más recaídas durante este tiempo.

A continuación le explicamos con detalle cuáles son los motivos por los que pedimos su participación en este estudio, para que pueda decidir con más criterio si está interesado / a o no a colaborar en el estudio. Lea detenidamente la siguiente información y tómese el tiempo que crea conveniente para hacerlo. Le recordamos que su participación es totalmente voluntaria, y que si decide no participar, esto no afectará de ninguna manera al trato de los profesionales sanitarios hacia usted.

¿Para qué necesitan hacerme un seguimiento durante 5 años?

Los estudios de seguimiento aportan mucha evidencia científica cuando lo que se busca es conocer las consecuencias de algún evento, en este caso buscamos conocer si los pacientes bipolares que consumen alcohol tienen más recaídas. Lo que necesitamos para llevar a cabo nuestro estudio es recoger todos los datos de los participantes, referentes al consumo de alcohol y su consumo al largo del estudio, a los eventos traumáticos el año anterior, al tratamiento farmacológico para el alcohol, conocer la adherencia del tratamiento farmacológico para el trastorno bipolar, las hospitalizaciones relacionadas con el trastorno bipolar y la duración de estas hospitalizaciones, si el paciente consume otras sustancias a parte del alcohol y conocer la severidad de las recaídas, en el momento en que entran en el estudio y durante los siguientes 5 años, resaltando sobre todo el consumo de alcohol. Durante el seguimiento, investigaremos las recaídas que puedan presentar los participantes durante este tiempo. Es muy importante para nuestro estudio saber de una manera fiable si nuestros participantes los pacientes consumen alcohol durante el seguimiento que haremos. Por lo tanto, de manera a garantizar la veracidad de esta información, el paciente tendrá que venir a la consulta acompañado de un familiar, que sea capaz de confirmar la información que nos da el paciente sobre su consumo de alcohol.

¿Cuál es la finalidad del estudio?

La finalidad de este estudio es conocer si los pacientes bipolares que consumen alcohol tienen más recaídas que los pacientes bipolares que no consumen alcohol. Lo que esperamos con este estudio es avanzar un poco más en el conocimiento de la "patología dual" y saber si en los pacientes bipolares que consumen alcohol van a tener más recaídas. Todos los datos que obtengamos de los participantes serán utilizados exclusivamente con fines de investigación.

¿En qué consistirá mi participación?

En este estudio de seguimiento a 5 años, los participantes tendrán visitas cada 6 meses, es decir, 2 visitas al año. En total serán 11 visitas. Las visitas se harán en el Parc Hospitalari Marti I Julià, en el Centro de Salud Mental o en el Centro de Atención a las drogodependencias, en función de cada participante. En cada visita, el paciente tiene que venir acompañado de su familia de forma a garantizar que toda la información que el paciente nos proporciona, es verdadera. De manera a garantizar que el paciente está haciendo una buena adherencia al tratamiento para el trastorno bipolar, cada 3 meses tiene que hacer una analitica para medir los niveles en el plasma del fármaco, en el Parc Hospitalari Marti I Julià, en su Centro de Salud Mental o en el Centro de Atención a las drogodependencias. Estas analíticas quedaran registradas en la historia clínica de cada participante.

En la primera visita los participantes van a ser entrevistados, para elaborar una historia clínica, se van a coger datos de antecedentes personales y de seguimiento y se hará una evaluación psiquiátrica. Para hacer esta evaluación, cada participante deberá responder una serie preguntas y serán evaluados por el equipo médico. En las consultas siguientes se van a recoger los datos de seguimiento de los participantes y cada participante será evaluado por el equipo médico.

¿Mi participación será confidencial?

Los datos personales de nuestros participantes son totalmente confidenciales. Sólo tendrán acceso a ellos los miembros del equipo investigador y personal autorizado, tal y como obliga la Ley Orgánica 15/1999 de 13 de diciembre, de Protección de Datos de Carácter Personal. Por lo tanto, todos los datos de los participantes que sean registrados en la base de datos de nuestro estudio se mantendrán estrictamente confidenciales.

¿El hecho de participar en el estudio me puede perjudicar de alguna manera?

No, ningún participante puede verse perjudicado por el hecho de formar parte de este estudio. Sólo deberán responder las preguntas que su psiquiatra les haga en cada visita.

¿Es posible cambiar mi decisión una vez he aceptado participar en el estudio?

Si, en cualquier momento los participantes pueden cambiar de opinión y decidir abandonar el estudio, y sin tener que dar ninguna explicación. Recordemos que la participación es totalmente voluntaria.

¿A quién me puedo dirigir para pedir más información?

En caso de que tenga cualquier duda o quiera más información, pregunte a su entrevistador o contacte con la dirección de correo electrónico que él le proporcionará.

Full d'informació al pacient

Títol de l'estudi: *Els pacients bipolars que consumeixen alcohol tindran més recaigudes? Estudi de seguiment a 5 anys.*

Benvolgut / a:

Agraïm la seva participació en aquest estudi que estem realitzant des de la Xarxa de Salut Mental a la província de Girona. El trastorn bipolar és una de les causes més freqüents de discapacitat en la gent jove i disminueix la qualitat de vida dels pacients. El trastorn bipolar s'associa amb freqüència a comorbiditats com el trastorn per ús d'alcohol. És el que s'anomena "patologia dual", que defineix la coexistència d'un trastorn mental com el bipolar i un trastorn per ús de substàncies com l'alcohol. Amb la seva participació estarà contribuint a millorar els coneixements que tenim actualment sobre la patologia dual i d'aquesta manera entendre si els pacients bipolars que consumeixen alcohol van tenen més recaigudes que els pacients bipolars que no consumeixen alcohol.

Per tant, estem molt interessats a fer un seguiment dels nostres participants durant 5 anys per conèixer si aquests pacients van a tenir més recaigudes durant aquest temps.

A continuació li expliquem amb detall quins són els motius pels quals demanem la seva participació en aquest estudi, perquè pugui decidir amb més criteri si està interessat / o no a col·laborar en l'estudi. Llegiu detingudament la següent informació i prengui el temps que cregui convenient per fer-ho. Li recordem que la seva participació és totalment voluntària, i que si decideix no participar, això no afectarà de cap manera al tracte dels professionals sanitaris d'aquí en endavant.

¿Per què necessiten fer-me un seguiment durant 5 anys?

Els estudis de seguiment aporten molta evidència científica quan el que es busca és conèixer les conseqüències d'algun esdeveniment, en aquest cas busquem conèixer si els pacients bipolars que consumeixen alcohol tenen més recaigudes. El que necessitem per dur a terme el nostre estudi és recollir totes les dades dels participants, referents al consum d'alcohol i el seu consum a l'llarg de l'estudi, als esdeveniments traumàtics l'any anterior, al tractament farmacològic per a l'alcohol, conèixer l'adherència del tractament farmacològic per el trastorn bipolar, les hospitalitzacions relacionades amb el trastorn bipolar i la durada d'aquestes hospitalitzacions, si el pacient consumeix altres substàncies a part de l'alcohol i conèixer la severitat de les recaigudes, en el moment en què entren en l'estudi i durant els següents 5 anys, ressaltant sobretot el consum d'alcohol. Durant el seguiment, investigarem les recaigudes que puguin presentar els participants durant aquest temps. És molt important per al nostre estudi saber d'una manera fiable si els nostres participants els pacients consumeixen alcohol durant el seguiment que farem. Per tant, de manera a garantir la veracitat d'aquesta informació, el pacient haurà de venir a la consulta acompanyat d'un familiar, que sigui capaç de confirmar la informació que ens dóna el pacient sobre el seu consum d'alcohol.

Quina és la finalitat de l'estudi?

La finalitat d'aquest estudi és conèixer si els pacients bipolars que consumeixen alcohol tenen més recaigudes que els pacients bipolars que no consumeixen alcohol. El que esperem amb aquest estudi és avançar una mica més en el coneixement de la "patologia dual" i saber si en els pacients bipolars que consumeixen alcohol van a tenir més recaigudes. Totes les dades que obtinguem dels participants seran utilitzades exclusivament amb fins d'investigació.

En què consistirà la meva participació?

En aquest estudi de seguiment a 5 anys, els participants tindran visites cada 6 mesos, és a dir, 2 visites a l'any. En total seran 11 visites. Les visites es faran al Parc Hospitalari Martí i Julià, al Centre de Salut Mental o al Centre d'Atenció a les drogodependències, en funció de cada participant. En cada visita, el pacient ha de venir acompanyat de la seva família per tal de garantir que tota la informació que el pacient ens proporciona, és veritable. De manera a garantir que el pacient està fent una bona adherència al tractament per al trastorn bipolar, cada 3 mesos ha de fer una analitica per mesurar els nivells en el plasma del fàrmac, al Parc Hospitalari Martí i Julià, al seu Centre de Salut mental o al Centre d'Atenció a les drogodependències. Aquestes analítiques quedaran registrades en la història clínica de cada participant.

A la primera visita els participants serán entrevistats, per elaborar una història clínica, es van a agafar dades d'antecedents personals i de seguiment i es farà una avaluació psiquiàtrica. Per fer aquesta avaluació, cada participant haurà de respondre una sèrie preguntes i seran avaluats per l'equip mèdic. En les consultes següents es van a recollir les dades de seguiment dels participants i cada participant serà avaluat per l'equip mèdic.

¿La meva participació serà confidencial?

Les dades personals dels nostres participants són totalment confidencials. Només tindran accés a ells els membres de l'equip investigador i personal autoritzat, tal com obliga la Llei Orgànica 15/1999 de 13 de desembre, de protecció de dades de caràcter personal. Per tant, totes les dades dels participants que siguin registrats a la base de dades del nostre estudi es mantindran estrictament confidencials.

¿El fet de participar en l'estudi em pot perjudicar d'alguna manera?

No, cap participant pot veure perjudicat pel fet de formar part d'aquest estudi. Només hauran de respondre les preguntes que el seu psiquiatre els faci en cada visita.

És possible canviar la meva decisió una vegada he acceptat participar en l'estudi?

Si, en qualsevol moment els participants poden canviar d'opinió i decidir abandonar l'estudi, i sense haver de donar cap explicació. Recordem que la participació és totalment voluntària.

A qui em puc adreçar per demanar més informació?

En cas que tingui qualsevol dubte o vulgui més informació, pregunti al seu entrevistador o contacti amb l'adreça de correu electrònic que ell li proporcionarà.

HOJA DE CONSENTIMIENTO INFORMADO

Título del estudio: ***Los pacientes bipolares que consumen alcohol tendrán más recaídas? Estudio de seguimiento a 5 años***

Yo (Nombre y apellidos): _____, confirmo que:

- He leído detenidamente y he entendido toda la hoja de información que me han entregado
- He recibido suficiente información sobre el estudio
- El entrevistador me ha explicado de manera clara todo el procedimiento
- Todas mis dudas han sido resueltas de manera satisfactoria
- Entiendo que todos mis datos serán tratados de forma confidencial
- Entiendo cuál será mi papel como participante del estudio
- Entiendo que mi participación es voluntaria, y que en cualquier momento del estudio puedo decidir dejar de participar y, además, sin tener que dar ninguna explicación y sin que eso repercuta en mi atención sanitaria futura.

Por lo tanto, acepto participar en el estudio *Los pacientes bipolares que consumen alcohol tendrán más recaídas? Estudio de seguimiento a 5 años.*

_____	_____	_____
(Nombre)	(Firma)	(Fecha)

_____

(Firma del investigador)

FULL DE CONSENTIMENT INFORMAT

Títol de l'estudi: *Els pacients bipolars que consumeixen alcohol tindran més recaigudes? Estudi de seguiment a 5 anys.*

Jo (Nom i cognoms):
_____ confirmo que:

- He llegit detingudament i he entès tot el full d'informació que m'han entregat
- He rebut suficient informació sobre l'estudi
- L'entrevistador m'ha explicat de manera entenedora tot el procediment
- Tots els meus dubtes han estat resolts de manera satisfactòria
- Entenc que totes les meves dades seran tractades de manera estrictament confidencial
- Entenc quin serà el meu paper com a participant de l'estudi
- Entenc que la meva participació és voluntària, i que en qualsevol moment de l'estudi puc decidir deixar de participar i, a més, sense haver de donar cap explicació i sense que això repercuteixi en la meva atenció sanitària futura.

Per tant, accepto participar en l'estudi: *Els pacients bipolars que consumeixen alcohol tindran més recaigudes? Estudi de seguiment a 5 anys.*

_____ _____ _____

(Nom) (Signatura) (Data)

_____

(Signatura de l'investigador)

Appendix 8: Case Report Form

Case Report Form

Nº Historia Clinica: **Fecha: _ /_ /_**

Visita nº:

Edad __

Sexo

F ☐ M ☐

Edad de diagnóstico de la enfermedad bipolar: ___ *(rellenar sólo en visita nº1)*

Previo problema de consumo de alcohol: *(rellenar sólo en visita nº1)*

Sí ☐ No ☐

Educación *(rellenar sólo en visita nº1)*

☐ menos que escuela secundaria ☐ escuela secundaria ☐ licenciatura

☐ máster o doctorado

Estado civil *(rellenar sólo en visita nº1)*

☐ casado/a ☐ pareja ☐ soltero/a ☐ separado/a ☐ divorciado/a

☐ viudo/a

Trabajo *(rellenar sólo en visita nº1)*

☐ empleado/a ☐ desempleado/a ☐ estudiante ☐ jubilado/a

Datos de seguimiento

Consumo de alcohol (X):

	Visitas										
Puntuación Cage Questionnaire	1	2	3	4	5	6	7	8	9	10	11
<2 (no hay consumo de alcohol)											
≥2 (hay consumo de alcohol)											

Consumo de alcohol al largo del estudio (X):

	Visitas									
Consumo de alcohol al largo del estudio	2	3	4	5	6	7	8	9	10	11
El consumo de alcohol al largo del estudio ha cambiado										
El consumo de alcohol al largo del estudio no ha cambiado										

Recaídas (X):

	Visitas										
Recaídas	1	2	3	4	5	6	7	8	9	10	11
El paciente tiene criterios DSM-5 para depresión											
El paciente tiene criterios DSM-5 para manía											
El paciente tiene criterios DSM-5 para episodios mixtos											
El paciente no ha tenido recaídas (no tiene criterios del DSM-5 para depresión o manía o episodios mixtos)											

Severidad de las recaídas (no rellenar, si no han habido recaídas en los últimos 6 meses) (X):

	Visitas										
Recaídas	1	2	3	4	5	6	7	8	9	10	11
Depresión (HRS-D)											
Depresión leve (10-19)											
Depresión grave (>19)											
Manía (YMRS)											
Manía leve (18-24)											
Manía grave (>25)											
Episodios mixtos (HRS-D + YMRS)											
Depresión leve (10-19)											
Depresión grave (>19)											
Manía leve (18-24)											
Manía grave (>25)											

Puntuación Holmes and Rahe (X):

	Visitas					
Puntuación Holmes and Rahe	1	3	5	7	9	11
<150 (el riesgo de tener la enfermedad es leve)						
150-299 (el riesgo de tener la enfermedad es moderado)						
>300 (el riesgo de tener la enfermedad es elevado)						

Adherencia al tratamiento farmacológico del trastorno bipolar (X):

	Visitas										
Adherencia al tratamiento farmacológico del trastorno bipolar	1	2	3	4	5	6	7	8	9	10	11
Buena adherencia al tratamiento											
Mala adherencia al tratamiento											

Tratamiento farmacológico para el trastorno de uso de alcohol (X):

	Visitas										
Tratamiento farmacológico para el trastorno de uso de alcohol	1	2	3	4	5	6	7	8	9	10	11
Sí											
No											

Hospitalizaciones relacionadas con el trastorno bipolar en los últimos 6 meses (X):

	Visitas										
Hospitalizaciones relacionadas con el trastorno bipolar en los últimos 6 meses	1	2	3	4	5	6	7	8	9	10	11
Sí											
No											

Duración de las hospitalizaciones relacionadas con el trastorno bipolar en los últimos 6 meses (rellenar en caso de haber habido hospitalizaciones):

	Visitas										
Duración de las hospitalizaciones relacionadas con el trastorno bipolar en los últimos 6 meses	1	2	3	4	5	6	7	8	9	10	11
Nº de días que ha estado hospitalizado											

Consumo de otras sustancias (X):

	Visitas										
Consumo de otras sustancias	1	2	3	4	5	6	7	8	9	10	11
Cocaína											
Cafeína											
Sedantes											
Heroína											
Alucinógenos											
Hipnóticas											
Tabaco											
Inhalantes											
Ansiolíticos											
Cannabis											
Opioides											
Estimulantes											
Otras sustancias o desconocidas											
No consume otras sustancias											

Observaciones

Firmado por,

_____