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EFFECTS OF MENSTRUAL CYCLE PHASE IN GLUCOCORTICOID-INDUCED NEUROPSYCHIATRIC DISORDERS

A PROSPECTIVE COHORT STUDY

FINAL DEGREE PROJECT

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1. ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
BBB	Blood brain barrier
BDNF	Brain-derived neurotrophic factor
CBG	Corticosteroid binding globulin
CEIC	*Comitè d'Ètica d'Investigació Clínica*
CH50	50% haemolytic complement
CNS	Central nervous system
CRH	Corticotropin releasing hormone
CSF	Cerebrospinal fluid
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
ER-α	Oestrogen receptor alpha
ER-β	Oestrogen receptor beta
FSH	Follicle stimulating hormone
GABA-A	Gamma-aminobutyric acid A
GH	Growing hormone
GnRH	Gonadotropin releasing hormone
GR	Glucocorticoid receptor
HPA axis	Hypothalamic – pituitary – adrenal axis
HPG axis	Hypothalamic – pituitary – gonadal axis
IL-1	Interleukin 1
IκB	Nuclear factor kappa B inhibitor
LH	Luteinizing hormone
MHC	Major histocompatibility complex
MINI	Mini International Neuropsychiatric Interview
MMSE	Mini Mental State Examination

MR	Mineralocorticoid receptor
NFκB	Nuclear factor kappa B
NSAIDs	Nonsteroidal anti-inflammatory drugs
PHQ-9	Patient Health Questionnaire-9
PVN	Paraventricular nucleus
RANKL	Receptor activator for nuclear factor κ B ligand
SLE	Systemic lupus erythematosus
SSRIs	Selective serotonin reuptake inhibitors
THIN	The Health Improvement Network
TNF-α	Tumoral necrosis factor α
TSH	Thyroid stimulating hormone

2. ABSTRACT

BACKGROUND. Glucocorticoids are widely used. Unfortunately, they are not exempt of adverse effects, including glucocorticoid-induced neuropsychiatric disorders. These do not have any preventive strategy, as there is still unknown information about its aetiopathogenesis and risk factors. An unclear one is female sex. Existent literature tables some hypotheses, such as the interaction between hypothalamus-pituitary-adrenal axis and hypothalamus-pituitary-gonadal axis. This happens between responses of cortisol to psychosocial stress and menstrual cycle phases, so this originates the hypothesis of a possible contribution of menstrual cycle to these induced disorders.

OBJECTIVES. The main objective of this study is to determine if there is a variation in the incidence of glucocorticoid-induced neuropsychiatric disorders across the phases of the menstrual cycle, in women with a regular cycle and no use of hormonal contraception, who are undergoing corticotherapy at high dosages, depending on the phase when they start the treatment. Secondary objectives aim to evaluate the type of disorder, other risk factors, and the necessity of pharmacological management.

DESIGN. This is an unicentric prospective cohort study to be done by the Psychiatric Interconsultation Service of *Hospital Santa Caterina* and *Hospital Josep Trueta*.

PARTICIPANTS. Women aged 18-45 with a regular cycle and no use of hormonal contraception, who are undergoing corticotherapy at 40 mg/day or more of prednisone or its equivalent, with no mental disorder in the past 6 months or current.

METHODS. 204 participants will be enrolled using a consecutive sampling method with a time of recruitment of 2 years. Women will be divided into two groups according to the phase of the cycle when they start the treatment (follicular or luteal) using LH tests and menses self-report. Data about other risk factors will be collected. They will be followed during a maximum of 6 months to assess if they develop an induced disorder, using MINI Plus, PHQ-9 and MMSE to help in the diagnosis. Information about a pharmacologic management will also be collected.

KEYWORDS. Glucocorticoid-induced neuropsychiatric disorders, glucocorticoids, substance/medication-induced neuropsychiatric disorders, menstrual cycle, hypothalamus-pituitary-adrenal axis, hypothalamus-pituitary-gonadal axis.

3. PREFACE

This project started earlier than I first imagined. I was a medicine student, without many ideas on how to focus my own career in a future after finishing my degree, when I started my fourth grade, and I could say that then was when I found my "medical self".

That year I first discovered the fascinating world of Psychiatry and Domènec, Pep and the other professors of this subject transmitted me their enthusiasm for Psychiatry. However, this did not end there, as then I started Endocrinology, and the doors of another fascinating word opened to me. It was on that moment that I discovered the subtle and complex processes that interrelated the hormones and the mind. That leaved me astonished about the mysteries of medicine, and that was the moment when I knew that I was on the right way in my career.

As could not be in another way, when on fifth grade we were informed about the start of the final degree project, I knew that I wanted to deepen in that interrelated processes between Psychiatry and Endocrinology. Then I started to investigate on them, and I discovered the final topic of this project. Glucocorticoids and their characteristics were the perfect relationship that I was searching for.

Substance/medication-induced neuropsychiatric disorders suppose an intricate cascade of events, effect of biological dysregulations. The fact that something with a good intention such as a medication prescription, could conduct to these repercussions surprised me, and even alarmed me, because of the ease with which physicians prescribe those medications (such as glucocorticoids, that are a recurrent treatment during all the medical career subjects).

However, how to explore that relationship? Menstrual cycle. Women were disregarded in the past medical literature, and nowadays, although progressively we are giving that a solution, still further research is needed. Accordingly, a fact that sometimes is neglected is the following: women are cyclic. This acquires a highlighted importance when talking about processes with a hormonal interaction, such as glucocorticoids intake.

Do you understand my fascination, now? Let us talk about it.

4. INTRODUCTION

4.1 SUBSTANCE/MEDICATION-INDUCED NEUROPSYCHIATRIC DISORDERS

As described in DSM-5-TR (1), "the substance/medication-induced mental disorders are potentially severe, usually temporary, but sometimes persisting CNS (Central Nervous System) syndromes that develop in the context of the effects of substances of abuse, medications and some toxins".

In addition, neuropsychiatric adverse effects have been found to constitute 30% of adverse drug reactions seen in general practice (2).

In general, to consider a substance/medication-induced neuropsychiatric disorder and not an independent mental disorder, there must be evidence that the symptoms observed are not likely to be better explained by the independent one, which would be more likely to be in case of symptoms present before the severe intoxication or withdrawal or medication administration, or continued more than one month after cessation of acute withdrawal, severe intoxication, or use of the medications. In the same way, the substance/medication-induced neuropsychiatric disorders are an important part of the differential diagnoses for the independent neuropsychiatric disorders (1,2).

Its differential diagnosis with substance use disorders is based on that, in these last ones, there is a group of cognitive, behavioural and psychological symptoms that contribute to the continued use of a substance despite significant substance-related problems (1).

Between all the range of medications that can produce an

Table 1. Examples of drugs or drug families associated with substance/medication induced neuropsychiatric disorders. Adapted from (2).

- Glucocorticoids
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- ACE inhibitors
- Anabolic steroids
- Beta-blockers
- Calcium antagonists
- Antidepressants
- Sedative-hypnotics
- Antiepileptic drugs
- Antihistaminics
- Antihypertensives
- Antineoplastic drugs
- Antiviral agents
- Antimicrobials
- Cholesterol-lowering drugs
- Digitalis
- Levodopa
- Antimalarials
- Opioid analgesics

induced neuropsychiatric disorder, some that must not be overlooked but sometimes are, are glucocorticoids (1–3).

4.2 GLUCOCORTICOIDS

Glucocorticoids seen as human hormones are synthetised in the adrenal cortex of adrenal glands, concretely in the *zona fasciculata* (4,5). These hormones have extensive actions in human body, from their intervention in human metabolism to their regulatory paper in the immune system (5).

These actions are regulated by the HPA axis (hypothalamic – pituitary – adrenal axis). In human body, this circuit results in the synthesis of hydrocortisone, also known as cortisol, which is liberated in a pulsatile fashion into the bloodstream, by following a circadian rhythm that changes its concentrations during the day: it is highest early in the morning, gradually diminishes during the day, and reaches its lowest values in the night (5,6).

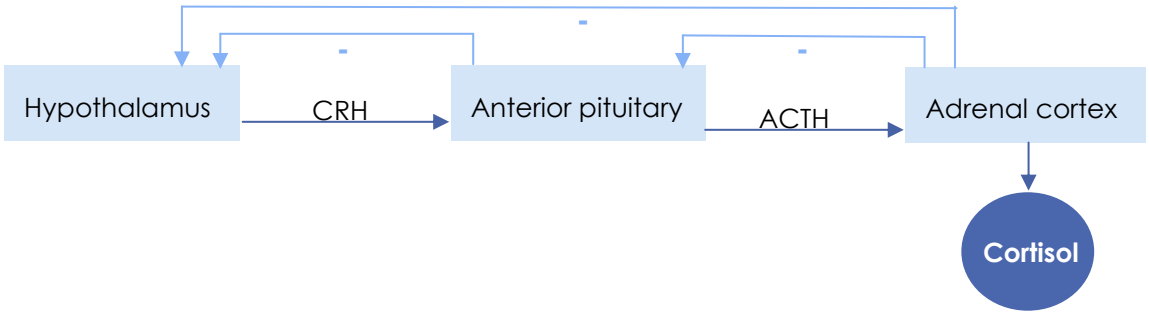

Figure 1. HPA axis.

Although we differentiate glucocorticoids from mineralocorticoids (mainly aldosterone in humans, which is synthetised in the *zona glomerulosa* by the action of the renin-angiotensin-aldosterone system and has effects in water and electrolyte balance), all glucocorticoids have a mineralocorticoid action, which tends to be inversely related with the anti-inflammatory power (the more anti-inflammatory effect, the less sodium and water retention) (4,5).

Due to all the important functions glucocorticoids do, they have an important paper in a wide number of illnesses that makes them an important factor in which we can have a bearing on. From this idea, it appears the aim to create synthetic analogous of cortisol

(as we want to separate the glucocorticoid effect from the mineralocorticoid one, which usually appears to be an adverse effect), which are widely used nowadays (5). In fact, as Akid *et al* says (7), "corticosteroids are among the most widely used drugs in the world since their discovery in the 1940s."

Table 2. Comparison of the main corticosteroid agents used for systemic therapy (using hydrocortisone as a standard). Extracted from (5).

Compound	Relative affinity for GR	Approximate relative potency in clinical use		Duration of action after oral dose[a]	Comments
		Anti-inflammatory	Sodium retaining		
Hydrocortisone (cortisol)	1	1	1	Short	Drug of choice for replacement therapy.
Cortisone	0 (Prodrug)	0.8	0 8	Short	Inactive until converted to hydrocortisone; not used as anti inflammatory because of mineralocorticoid effects.
Deflazacort	0 (Prodrug)	3	Minimal	Short	Converted by plasma esterases into active metabolite. Similar utility to prednisolone.
Prednisolone	2.2	4	0.8	Intermediate	Drug of choice for systemic anti-inflammatory and immunosuppressive effects.
Prednisone	0 (Prodrug)	4	0.8	Intermediate	Inactive until converted to prednisolone.
Methylprednisolone	11.9	5	Minimal	Intermediate	Anti-inflammatory and immunosuppressive.
Triamcinolone	1.9	5	None	Intermediate	Relatively more toxic than others.
Dexamethasone	7.1	27	Minimal	Long	Anti-inflammatory and immunosuppressive, used especially where water retention is undesirable (e.g. cerebral oedema); drug of choice for suppression of ACTH production.
Betamethasone	5.4	27	Negligible	Long	Anti-inflammatory and immunosuppressive, used especially when water retention is undesirable.
Fludrocortisone	3.5	15	150	Short	Drug of choice for mineralocorticoid effects.
Aldosterone	0.38	None	500	N/A	Endogenous mineralocorticoid.

[a]Duration of action (half-lives in hours): short, 8–12; intermediate, 12–36; long, 36 72 Some drugs are inactive until converted to active compounds in vivo and therefore have negligible affinity for the glucocorticoid receptor.
GR, glucocorticoid receptor.
(Data for relative affinity obtained from Baxter & Rousseau, 1979.)

4.2.1 MECHANISM OF ACTION

Glucocorticoids have intranuclear receptors. The union of the hormone with the receptor forms a complex, which then is united with another receptor forming a dimer. This one is transported through the cytoplasm by several chaperones, which also influence the glucocorticoid receptors sensitivity, and penetrates the nucleus of the cell and binds to DNA (mediated by the chaperones, too), causing the expression of messenger RNA that will codify for a protein that will bring to a determinate effect (4,5,8). Therefore, they interfere in gene transcription. However, it has also been studied that some effect can be extracted from the interaction of the glucocorticoid with the

receptor even without the formation of the dimer, so in the cytoplasm of the cell, by triggering mechanisms of transduction of signals (5).

4.2.2 PHARMACOKINETICS

Glucocorticoids can be administered orally, systemically, intraarticularly and topically. The 90% of them are transported along the bloodstream by the corticosteroid binding globulin (CBG) or the albumin and can access to cells by simple diffusion. Their metabolism is hepatic and then the metabolites bind to glucuronic acid or sulphate and have a renal excretion.

Cortisone and prednisone need a conversion to hydrocortisone and prednisolone, respectively, before they become biologically active (4,5).

4.2.3 PHARMACODYNAMICS

4.2.3.1 EFFECTS

Glucocorticoids are widely used because of their immunosuppressive, anti-inflammatory and anti-allergic effects. They act in a dose-dependent fashion, which may interfere in the therapeutic result we have, as the anti-inflammatory and anti-allergic effects are related with low dosages, whereas the immunosuppressive effects are characteristic of high dosages (9).

Their metabolic action leads mainly to the increase of blood glucose concentrations, which is crucial in stress situations. This effect is accomplished by opposing the action of insulin and increasing glycolysis and gluconeogenesis. However, they lead to a catabolic status in our body in order to have enough energy to confront the stressor, so we will have other accompanying processes such as the stimulation of proteolysis and lipolysis, and also the increase in osteoclast function and the decrease in osteoblast function (via RANKL, which is less stimulated because of decrease of the synthesis of proinflammatory cytokines such as IL-1 and TNF-α), and the decrease of calcium absorption and increase of renal calcium excretion (5,9).

Their action in immune cells consists of (5,9):

- Decrease of prostanoids, cytokines and interleukins production.

- Decrease in the number of circulating monocytes, eosinophils and basophils (although the number of neutrophils increases, so they only reduce the number of mononuclear cells).
- Decrease in the expression of MHC class II molecules and Fc receptors.
- Decrease of circulating T and B lymphocytes (mainly T).
- Decrease of IgG production (at high dosages).

Glucocorticoids affect vascular system by reducing vasodilatation and fluid exudation, and decreasing components of the complement system; and also diminishes fibroblasts proliferation and fibronectin production (leading to an alteration of cicatrisation) (5).

They also lead to a negative feedback in the HPA axis, with reduction of endogenous glucocorticoids liberation, and have a negative effect on growing hormone (GH), thyroid stimulating hormone (TSH) and luteinizing hormone (LH) (5,9).

4.2.3.2 ADVERSE EFFECTS

As glucocorticoids act on lots of organs and systems, it becomes a challenge not to produce a wide number of adverse effects, as it is difficult to separate one process from another. There are adverse effects affecting multiple organs and processes, added to an increased susceptibility to infections when using high dosages over long periods of time. This led to the synthesis of new glucocorticoids in the 1950-1960s, such as prednisolone and methylprednisolone, in order to obtain stronger anti-inflammatory and immunosuppressive effects, but less mineralocorticoid effects (5,9,10).

As exposed on Strehl *et al* (9), a process called "transactivation", consisting of synthesis of anti-inflammatory proteins such as lipocortin 1 or inhibitor of NFκB (IκB), and also regulator proteins involved in metabolism processes, is thought to be the responsible of many of the adverse effects of glucocorticoids. Also in this article, it is explained that "the most important variable in the likelihood of therapeutically desired and adverse effects of glucocorticoids is dosage, modified by the rate of absorption, concentration in target tissues, and affinity of glucocorticoids for glucocorticoid receptors (GR)". However, adverse effects can occur at any dosage, and they can widely vary depending on the route of administration. They are also more frequent in a long-term administration, but can also appear in a short-term use (9,10).

Glucocorticoid therapy side effects may be endocrine, neuropsychiatric, gastrointestinal, musculoskeletal, cardiovascular, dermatologic, ocular or immunologic, and they occur in up to 90% of the patients that take glucocorticoids for more than 60 days (7,10).

Neuropsychiatric adverse effects are the ones exposed in **section 4.3.3**. Other glucocorticoid adverse effects can be found, classified by the affected system, in **Annex 1.**

It is highly important to consider the effects of glucocorticoid discontinuation, as a sudden removal of the drug in a patient that has follow the treatment during a large period (often considered as more than 10 days of continuous treatment) and so has a suppression of the HPA axis, causes acute adrenal insufficiency. Withdrawal can also cause an exacerbation of the disease. Therefore, the dose must be tapered slowly according to individual tolerance (4,5).

4.2.4 INDICATIONS

Glucocorticoids in general are used in replacement therapy, and in asthma, allergic reactions, rheumatoid arthritis and other inflammatory disorders, and also have an important paper in oncology. The therapeutic uses can be summarised in the following ones (4,5):

- **Replacement therapy for Addison disease (adrenocortical insufficiency):** in Addison disease we have a lack of response to ACTH (adenocorticotropic hormone) because of an adrenal cortex dysfunction, and so hydrocortisone is given to patients to correct the deficiency, by following an administration that pretends to mimic circadian rhythm of cortisol.
- **Replacement therapy for secondary or tertiary adrenocortical insufficiency**: they are caused by a defect in CRH (corticotropin releasing hormone) production by the hypothalamus or in ACTH production by the hypophysis, so in this case is also needed the use of hydrocortisone in the same way than the anterior case.
- **Replacement therapy for congenital adrenal hyperplasia**: it is a disease in which there is a defect in a specific enzyme (a different one depending on the kind),

resulting in an alteration in the synthesis of one or more of the adrenal hormones, normally with an overproduction of adrenal androgens. Replacement therapy is needed to supress release of CRH and ACTH and thus decreasing the production of adrenal androgens (and also covering the possible lack of other hormones).

- **Dexamethasone suppression test for the diagnosis of Cushing syndrome**: in Cushing syndrome we have an hypercortisolism due to different causes (for example tumours, or even an iatrogenic Cushing syndrome due to treatment with high dosages of glucocorticoids). Dexamethasone is a synthetic glucocorticoid that in normal people supresses cortisol release, but not in patients with Cushing syndrome.
- **Relief of inflammatory symptoms**: for example, in rheumatoid arthritis, connective tissue diseases (systemic lupus erythematosus, polymyositis…), skin conditions, eyes conditions, ears conditions, asthma or bowl disease. Also, in metastatic or primary brain tumours to reduce cerebral oedema, or in other neoplastic diseases.
- **Treatment of allergies**: in allergic rhinitis or in other allergic reactions.
- **Acceleration of lung maturation**: foetal cortisol regulates lung maturation, so betamethasone or dexamethasone are used in premature deliveries to accelerate lung maturation.

4.2.5 CONTRAINDICATIONS

Some of the glucocorticosteroids main contraindications are (11):

- Hypersensitivity to any component of the formulation
- Uncontrolled hyperglycaemia or diabetes mellitus
- Uncontrolled hypertension
- Glaucoma
- Osteoporosis
- Systemic fungal infection
- Varicella infection or herpes simplex keratitis
- Joint infection

- And, when using immunosuppressive dosages: current administration of live or live-attenuated vaccines

In addition, some of the possible adverse effects, if currently happening because of other reasons, should be considered as relative contraindications, such as: not controlled viral or bacterial infections, peptic ulcer or congestive heart failure.

4.2.6 EQUIVALENT DOSES OF SYSTEMIC GLUCOCORTICOIDS

Table 3. Equivalent doses of systemic glucocorticoids. Adapted from (12,13)

GLUCOCORTICOID	EQUIVALENT DOSES (mg)
Short acting (8 to 12 hours)	
Hydrocortisone (cortisol)	20
Cortisone acetate	25
Intermediate acting (12 to 36 hours)	
Prednisone	5
Prednisolone	5
Methylprednisolone	4
Triamcinolone	4
Deflazacort	7,5
Long acting (36 to 72 hours)	
Dexamethasone	0,75
Betamethasone	0,6

4.3 GLUCOCORTICOID-INDUCED NEUROPSYCHIATRIC DISORDERS

4.3.1 CONCEPT AND EPIDEMIOLOGY

Shortly after the beginning of use of glucocorticoids across a wide range of medical conditions following their discovery, specifically in February 1952, Lincoln Clark first described the clinical correlation between glucocorticoids and neuropsychiatric

disorders (14,15). These clinical presentations later would be collected under the name of *steroid psychosis*. However, this term, which has persisted in the literature over the decades, refers not only to psychosis but also to any of the neuropsychiatric effects of steroids. As a result, it has contributed to create confusion surrounding the neuropsychiatric complications of glucocorticoid therapy (16). Therefore, nowadays there is an effort in the current literature to avoid the use of this term and to start using *glucocorticoid-induced neuropsychiatric disorders*.

Glucocorticoid use has increased over the past three decades, even despite advances in targeted biologic therapy for many conditions, with 10% of medical inpatients and 1% to 3% of the general population maintained on long-term corticotherapy (16,17).

The incidence of these neuropsychiatric disturbances ranges from 3% to 57%, and they are mainly stablished in the first two weeks of treatment and depend on the used dosage (7,11,15,16,18). The symptoms can even start within hours of starting treatment (16,17). Studies show a median time to onset of 11.5 days. 39% of cases have onset during the first week and 62% within two weeks. In addition, it may take days to weeks before the symptoms start to subside after stopping or reducing the glucocorticoid (17,19).

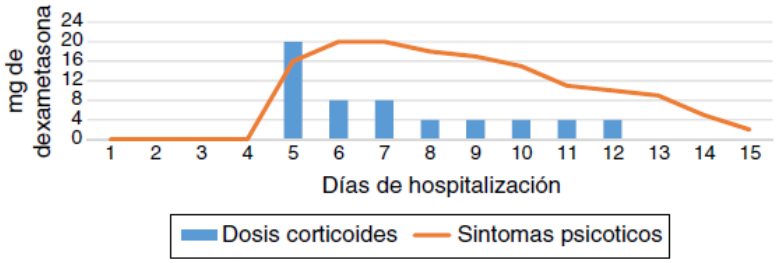

Figure 2. Relationship between glucocorticoid dose and psychotic symptoms in a clinical case. The patient was a 51-year-old woman who underwent surgery for myelopathy secondary to compression from an intradural extramedullary mass. She received 16 mg of dexamethasone during the procedure and 4 mg every 12 hours in the immediate post-operative period. On the first day of the post-operative period, she developed an acute psychotic episode, which was ultimately resolved by discontinuing the glucocorticoid and administering antipsycotic medication. Extracted from (20).

It is estimated that around a 20% of patients receiving glucocorticoid therapy in high dosages, defined as 40 mg/day or more of prednisone or its equivalent, will develop a neuropsychiatric disturbance. However, the dose does not predict the apparition, the kind, the duration or the severity of the clinical picture (15,21). There does not seem to exist a safe low dose of glucocorticoids (22).

The incidence ranges from 6% for severe reactions, 28% for moderate reactions, and can reach up to 72% when including mild reactions (15,21).

Hypomania accounts for nearly 50% of psychiatric disorders induced by glucocorticoids. In the concrete case of cancer patients, in whose therapy corticoids are a common treatment, the risk of developing hypomania increases by 15% compared to patients receiving similar treatment without an oncological condition (15,16).

The arguably most significant epidemiological study in the field to date was published in 2012 by Fardet *et al* (23). This study from the United Kingdom used the primary care database from THIN (The Health Improvement Network) to assess the incidence rates of depression, mania, delirium, confusion, disorientation, panic disorder and suicidal behaviours in adult patients receiving prescriptions for oral glucocorticoids from 1990 to 2008, comparing them to those in patients who did not receive such prescriptions (an age- and gender-matched group with the same underlying medical condition). Fardet *et al* defined a glucocorticoid-induced outcome as "one that was recorded after glucocorticoid initiation and with a preceding interval of at least 6 months with no similar entry".

It found that 8,5% of patients received an oral glucocorticoid prescription, including 2,3% that received long-term glucocorticoid treatment (≥ 3 months). The overall incidence of the studied outcomes was 15,7/100 person-years of glucocorticoid exposure for all glucocorticoid courses, with an incidence of 22,2/100 person-years at risk for first courses, 14,0 for second courses and 11,7 for third and later courses. For each entity, hazard ratios were adjusted for age, sex, past history of neuropsychiatric disorders, and the underlying medical disease. Daily dose of glucocorticoids was also taken into account as a potential confounder.

The results shown a risk of suicide or suicide attempt increased five- to sevenfold in people treated with corticoids, and markedly higher risks of the other severe neuropsychiatric conditions examined: a twofold higher risk of developing depression, and a four- to fivefold higher risk of developing mania, delirium, confusion or disorientation. The most marked increase of risk was for delirium, confusion or disorientation, and mania when compared to depression and panic disorder. However,

depression was the most common outcome (with a prevalence three times higher compared to patients not exposed to glucocorticoids). The adjusted hazard ratios obtained in the study are exposed in **table 4**, extracted from a review made by Judd *et al* (24).

Table 4. Risk of five severe neuropsychiatric outcomes associated with first course of oral glucocorticoid prescription, compared with unexposed adult population matched for age, gender, practitioner, and underlying medical conditions. Extracted from (24).

Neuropsychiatric Outcome	Adjusted Hazard Ratio	95% CI
Suicide or suicide attempt	6.89	4.52, 10.50
Delirium, confusion, or disorientation	5.14	4.54, 5.82
Mania (nonpsychotic)	4.35	3.67, 5.16
Depression (nonpsychotic)	1.83	1.72, 1.94
Panic disorder	1.45	1.15, 1.85
>5 neuropsychiatric outcomes	2.26	2.15, 2.37

[a] Data From Fardet et al. (6), analysis of records for adult patients in the U.K. Health Improvement Network (THIN) medical database for the period 1989–2008. The overall estimates of incidence rates of five severe neuropsychiatric outcomes of oral glucocorticoid therapy are low because the authors did not analyze psychotic bipolar disorder or depression, generalized anxiety disorder, or other severe neuropsychiatric outcomes.

This study by Fardet *et al* (23) also shows relevant data about risk factors, which will be discussed lately in **section 4.3.2.1**.

Another posterior cohort study from Fardet *et al* (25), also using THIN database, analysed the neuropsychiatric outcomes following discontinuation of long-term glucocorticoid therapy and found that the highest risk was for both depression (adjusted hazard ratio of 1,92, 95% CI 1,07 – 3,46) and delirium/confusion (adjusted hazard ratio of 4,96, 95% CI 2,60 – 9,49).

4.3.2 AETIOPATHOGENESIS

The pathophysiology of glucocorticoid-induced neuropsychiatric disorders remains to be not clearly understood, with limited data on the topic, but it seems to follow that of other diseases like Cushing's or Addison's, on which there is a disturbance in cortisol pathway (concretely, there is a suppression of its secretion on adrenal glands), leading to abnormalities in the HPA axis and, by this, having the potential to result in mood disorders. Furthermore, nowadays it is well known that inflammation plays an important role in the etiopathogenesis of major psychiatric disorders (26,27).

Furthermore, synthetic steroids activate glucocorticoid receptors (GR) preferentially to mineralocorticoid receptors (MR), creating an imbalance between glucocorticoid stimulation over mineralocorticoid stimulation that leads to emotional disturbances and cognitive impairment, which is mainly due to its paper in stress response, as MR are

important for appraisal processes and the onset of stress reaction, while GR terminate the stress response and promote recovery, memory and adaptation (24,28,29). This has led to the hypothesis that reduced brain MR activity in addition to strongly stimulated GR may underlie neuropsychiatric adverse effects of glucocorticoid therapy, and it is supported by the evidence of decreased MR expression in several psychiatric disorders (30). Moreover, studies have found that a genetic gain-of-function variant of MR may have protective effects. Concretely, MR haplotype 2 has been found to enhance optimism and protecting against depression in females, mainly before menopause (31).

Apart from this, there is an increased resistance to cortisol and glucocorticoids in individuals taking synthetic glucocorticoids, resulting in inhibition of BDNF (brain-derived neurotrophic factor). Low levels of BDNF in brain regions such as hippocampus and neocortex are thought to play a role in development of mood disturbances such as depression and anxiety (17,24,29). In addition to this mechanism, studies in animal models have shown that prolonged high dosages of glucocorticoids impair brain function in other ways, such as decreasing branching of dendrites and sprouting axons in some regions, thus impairing recovery from neuronal damage, by attenuating synaptic strength (which is essential for memory formation), or by decreasing glucose availability in some brain regions, causing a decrease in postnatal neurogenesis (16,24,32).

Both hippocampus and prefrontal cortex have a large number of MR and GR, and so disfunction on their circuits leads to deficits in working memory (dependent on prefrontal cortex and involved in temporary storage of the information necessary to do a cognitive task) and declarative memory (dependent on hippocampus and involved in recall of verbal information, facts and events).

These deficits can be also attributed to the reduction of hippocampal volume and activity (mainly in left hippocampus) (17,33,34), reduced glucose metabolism or glutamate accumulation in the area (17,24,27). Declarative memory impairment, as shown in the study by de Quervain *et al* (35), can also be associated with reduced blood flow in the right medial temporal lobe during corticotherapy. Accordingly, in a study by Brown *et al* (36), glucocorticoid exposure was associated with smaller hippocampal

volume and lower levels of N-acetylaspartate in temporal lobe (a marker of neuronal viability). Another study from the same authors (37) later shown the presence of atrophy of the right amygdala (an important structure for regulation of mood and anxiety) when receiving a long-term treatment with prednisone.

4.3.2.1 RISK FACTORS

4.3.2.1.1 FEMALE SEX

Female sex is a well-known risk factor. Women are more prone to developing neuropsychiatric disorders when taking glucocorticoids, with a 2:1 ratio (22). The exact reasons behind this phenomenon are not entirely clear. One plausible explanation is that a significant majority of autoimmune diseases treated with corticoids are more prevalent in women (22). Additionally, these diseases themselves may contribute to the development of neuropsychiatric disorders. This makes it challenging to determine whether the root cause is the autoimmune disease or its treatment. For instance, this is frequently observed in conditions like systemic lupus erythematosus (SLE) and rheumatoid arthritis. However, this cannot be the only reason, as some studies have indicated that even after excluding diseases that occur more often in women, the female predominance in neuropsychiatric complications of this treatment persists (16). Moreover, many of the potential neuropsychiatric outcomes are inherently more common in women, regardless of glucocorticoid usage.

These differences could be explained by the interactions between HPA axis and the HPG (hypothalamic – pituitary – gonadal) axis (6,8,38). Gonadal hormones are known to interact with GR expression and action, through effects on proteins in the chaperone and co-chaperone complex (8), as will be discussed lately in **section 4.4.2**. In addition, sex steroids have been shown to have a potential role in epidemiological differences in the propensity for affective disorders, with these differences first emerging in early puberty. Women tend to develop more episodes of depression and anxiety since puberty, which then decrease after menopause, whereas men, when exposed to chronic stress, appear to adopt adaptations that protect them against those outcomes (6,8,39).

Males, based on animal studies, show less inflammatory activation after psychosocial stress or injuries, and present a sex-specific pattern of the glucocorticoid sensitivity of

proinflammatory cytokines production, leading to increased susceptibility to immunosuppression (and so infections) and metabolic disease. On the other hand, the specific pattern in females leads to higher susceptibility to autoimmune and inflammatory processes (8,38,40,41). The female sex steroid oestrogen stimulates glucocorticoid secretion, whereas the male sex steroid testosterone has an inhibitory impact. Responses of cortisol to psychosocial stress are similar between men and women in the luteal phase of the menstrual cycle, in which oestrogen levels are reduced, but differ to the ones of women in follicular phase or women using oestrogen-containing contraceptive medication (38).

Furthermore, there are sex differences in the effects of stress on memory. An excess in glucocorticoid values can decrease dendritic spine development (8,42), whereas oestrogens enhance dendritic spine density (8,43). As a result, in follicular phase, when oestrogens are higher, stress and glucocorticoids can have a negative impact in memory (8,43).

4.3.2.1.2 OTHER RISK FACTORS

As we have mentioned before, the administered **dose** is the most important risk factor for the development of glucocorticoid-induced psychiatric disorders (16,17). The cut-off point has been normally stablished at 40 mg/day of prednisone or its equivalent along existent literature, but, as we said, there is not a safe dosage, and this value must be a guidance to know where to start to take caution and to be aware of the possible onset of neuropsychiatric symptoms. Moreover, the **duration of the treatment** of around two weeks or more must be considered an important risk factor as well, such as the **duration of action**, as long-acting glucocorticoids (e.g., dexamethasone or betamethasone) significantly increase the risk for withdrawal-induced depression and delirium, confusion or disorientation, when compared with short- or intermediate-acting glucocorticoids (e.g., prednisone, prednisolone, methylprednisolone) (24,25).

Some other risk factors that have been discussed on literature include the following:

- **Pharmacological interactions**: drugs that inhibit steroid metabolism, such as oestrogen-containing oral contraceptives, can increase blood levels of glucocorticoids, leading to increased adverse effects. It is also relevant the

interaction with other drugs that inhibit cytochrome P450 system (CYP3A4), such as clarithromycin, ketoconazole, protease inhibitors, etc., as they increase glucocorticoid levels (16,17,44).

- **Blood brain barrier (BBB) damage**: increased permeability of BBB, as the one that can be found in CNS SLE or in some kinds of chemotherapy, may allow hydrophobic steroid molecules to more easily penetrate CNS, thus leading to increased neuropsychiatric disturbances (16,27,45). BBB damage is evaluated with CSF (cerebrospinal fluid)/serum albumin ratio (19).
- **Hypoalbuminemia**: as glucocorticoids are normally inactive when they are bound to albumin (as well as to CBG) in the bloodstream, and glucocorticoids are mainly bonded to a carrier protein due to their lipophilic nature, low levels of serum albumin are related to higher levels of free and active glucocorticoids. Therefore, there is an increase in glucocorticoid effect and adverse effects may be potentiated (17,19,21). A study by Appenzeller *et al* (46) described hypoalbuminemia as the only variable associated with psychotic episodes related with glucocorticoid treatment in patients with SLE diagnosis, together with a severe activity of the disease.
- **Low complement values**: it has been described as an independent risk factor for glucocorticoid-induced neuropsychiatric disorders and it is usually found in SLE patients that develop neuropsychiatric disturbances during their treatment with corticosteroids (16,20,45). Low CH50 (50% haemolytic complement), as a measure of low complement values, has been found to be significatively related to glucocorticoid-induced neuropsychiatric disorders (45).
- **Underlying disease**: suffering from a disease that is frequently associated with neuropsychiatric manifestations, such as SLE (22), may increase the risk of glucocorticoid-induced neuropsychiatric disorders. SLE patients are also at higher risk of developing these outcomes because of the possibility of BBB damage and low complement values (20,45). On the other hand, the study by Fardet *et al* (23) found that people with asthma, polymyalgia rheumatica or giant cell arteritis may be at lower risk of developing neuropsychiatric disturbances.

Previous history of neuropsychiatric disorders, whether being **induced by glucocorticoid treatment** or **not**, has been widely discussed as a possible risk factor, but no clear relationship has been identified, as data seems contradictory in the few studies on which it has been studied (27). In the studies about the topic, the information about prior neuropsychiatric illness often is not reported, or is even excluded to demonstrate a clear relationship between glucocorticoids and psychiatric effects (16).

The study by Fardet *et al* (23) found that risk of depression, mania, panic disorder or suicide attempt during glucocorticoid treatment increased for patients with previous history of this conditions. Other studies support these findings (21,47). For example, the study by Morrow et al (48), studied the frequency of depressive and hypomanic or manic symptoms in patients with multiple sclerosis treated with high doses of corticoids for acute relapses, and found that personal history of depression or substance abuse in the past increased the risk of hypomanic or manic symptoms during the treatment, but there was no found any factor predicting an increase in depressive symptoms.

By contrast, other ones show that neither previous glucocorticoid-induced neuropsychiatric disturbances nor previous treatments free of such disturbances predict future responses to treatment, and that a history of psychiatric illness does not predict occurrence (49).

Hepatic or renal disfunction have not been studied as risk factors, but they should be taken into account, as exogenous glucocorticoids are cleared from the body via hepatic and renal mechanisms (16). A hepatic or renal disease could increase glucocorticoid bioavailability, resulting on a similar effect to the one of increasing the dosage.

Age has not been reported as a risk factor for glucocorticoid-induced neuropsychiatric disorders (16). However, the frequency of polypharmacy and so the possibility of pharmacological interactions makes the elderly a susceptible group of age. Furthermore, the group of age has been found to influence on the particular neuropsychiatric outcome. For example, patients from 18 to 50 have the highest risk of suicidal behaviour, and those from 18 to 30 have the highest risk of panic disorder. Also the risk of depression, mania, and delirium, confusion or disorientation increases with

age, with the last three ones being the ones with the highest risk in patients aged 80 years old or older (23–25).

4.3.3 CLINICAL PRESENTATION

In general, the most common psychiatric outcomes of glucocorticoid usage are affective disorders, mainly mania or hypomania, but also anxiety and depression. Other possible glucocorticoid-induced symptoms include psychosis, dementia, panic disorder, delirium (also with confusion and disorientation), suicidal ideation and behaviour, aggressive behaviour, insomnia, agitation, depersonalisation, catatonia, euphoria, distractibility and deficits in attention and psychomotor speed (7,17,19,23,24,34,50,51).

The clinical presentation of glucocorticoid-induced neuropsychiatric disturbances may vary depending on the length of the treatment, with patients initially experiencing mania or hypomania, and long-term therapy being more frequently associated with depression. However, cognitive deficits appear to be common during both short- and long-term treatment, mainly affecting declarative memory (16,19,20,24,34,49).

In 1952, Rome and Barceland (52) described a classification into 4 grades of psychiatric responses in patients receiving glucocorticoids or ACTH, that has been widely used and can be seen in **table 5**.

Table 5. Rome and Barceland's (52) grades of psychiatric responses to glucocorticoid or ACTH use. Adapted from (16).

Grade I	General feeling of well-being and stimulation, with improved concentration, energy and clarity of thought.
Grade II	Elevation of mood accompanied by restlessness, insomnia, increased motor activity, and accelerated mental activity (bordering on flight of ideas).
Grade III	Severe anxiety, ruminations, and obsessions. Patients exhibit mood swings, lethargy, indifference, crying spells, hopelessness and helplessness, excitement, restlessness, and flight of ideas.
Grade IV	Hallucinations, delusions, and extreme variations in mood.

4.3.4 DIAGNOSIS

When talking about the diagnosis of glucocorticoid-induced neuropsychiatric disorders, we should consider the diagnostic criteria included in the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR)* (1) and, therefore, we should take into account the diagnostic criteria for the substance/medication-induced mental disorders, which are exposed in **Table 6**:

Table 6. DSM-5-TR diagnostic criteria for substance/medication-induced mental disorders. Adapted from (1).

A. A clinically significant presentation of the symptoms characteristic of disorders in the relevant diagnostic class predominates in the clinical picture.
B. There is evidence from the history, physical examination, or laboratory findings of the following:
1. The symptoms in Criterion A developed during or soon after substance intoxication, substance withdrawal, or exposure to or withdrawal from a medication; and
2. The involved substance/medication is capable of producing the symptoms in Criterion A.
C. The disturbance is not better explained by an independent mental disorder (i.e., one that is not substance- or medication-induced). Such evidence of an independent mental disorder could include the following:
1. The disturbance preceded the onset of severe intoxication or withdrawal or exposure to the medication; or
2. The disturbance persisted for a substantial period of time (e.g., at least 1 month) after the cessation of acute withdrawal or severe intoxication or taking the medication. This criterion does not apply to substance-induced neurocognitive disorders or hallucinogen persisting perception disorder, which persist beyond the cessation of acute intoxication or withdrawal.
D. The disturbance does not occur exclusively during the course of a delirium.
E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

As said in Criterion A, the presentation of the disorder is similar to the one of the relevant diagnostic class, and so in each diagnostic class we have a list of criteria more specific for the substance/medication-induced mental disorder. These criteria can be found in psychotic disorders, bipolar and related disorders, depressive disorders, anxiety disorders, obsessive-compulsive disorders, sleep-wake disorders, sexual disfunctions and neurocognitive disorders, and can be found in **Annex 2**, together with delirium, as it can be also induced by glucocorticoids. In the concrete case of glucocorticoid-induced neuropsychiatric disorders, due to the possible clinical presentations, we will not consider sexual disfunctions and obsessive-compulsive disorders.

4.3.5 DIFFERENTIAL DIAGNOSIS

DSM-5-TR (1) contemplates some possible differential diagnoses for substance/medication-induced mental disorders, and the following ones must be considered when there is a glucocorticoid-induced neuropsychiatric disorder suspicion:

- **Substance intoxication or substance withdrawal.**
- **Independent disorder**: a disorder not caused by a substance or medication. In the specific case of neurocognitive disorders, some entities that we could consider are traumatic brain injury, or infections accompanied by substance use disorder (e.g., HIV, HCV or syphilis).
- **Disorder due to another medical condition**: this could be the case of neuropsychiatric SLE. Although SLE is linked to a greater risk of glucocorticoid-induced neuropsychiatric disorders, neuropsychiatric SLE must be considered a potential differential diagnosis. As reported in Bhangle *et al* (51), imaging and EEG (electroencephalogram) abnormalities, the coexistence of non-CNS manifestations of SLE, and the presence of serious disturbances in memory and concentration are more suggestive of neuropsychiatric SLE than glucocorticoid-induced neuropsychiatric disorders. Also positive antiphospholipid antibodies are more frequently observed in patients with neuropsychiatric SLE (46).

  In addition, other differential diagnoses to consider are other autoimmune diseases with psychiatric symptoms, such as autoimmune encephalitis (21).
- **Other specified or unspecified disorders of each entity.**

4.3.6 TREATMENT

Firstly, the main step in the treatment of glucocorticoid-induced neuropsychiatric disorders, if possible, is to discontinue them or attempt to decrease the dosage to less than 40 mg/day of prednisone or its equivalent. With this, a vast majority of patients achieve clinical recovery (16,17,19–21,29,49,53). Glucocorticoid tapering is of special importance for patients who have received long-term treatment, as they need to be closely monitored for signs of new or increased depression, delirium or confusion. If these appear, we should check for adrenocortical insufficiency, which can be resolved by re-administering or increasing the dosage of the glucocorticoid (17,19).

Nowadays, there are no approved medications or other treatment options for managing these manifestations, and so all other treatment options are off-label and mainly based on evidence of case reports, case series and few small trials (7,16,17,19,54). However, these options are often required because of the medical necessity of the glucocorticoid, which impedes its discontinuation, or because of the severity of the psychiatric symptoms (19–21,50,53).

The main therapeutic options for some of the more common entities, apart from dosage tapering, include the following:

- **Mania or hypomania** (17–21,29,51,55):
    - Mood stabilizers: valproate, carbamazepine, lithium, lamotrigine
    - Antipsychotics (typical or atypical): quetiapine, olanzapine, aripiprazole, risperidone, haloperidol. With or without an added benzodiazepine
- **Depression** (7,16–20,22,24,29,49,55):
    - SSRIs (selective serotonin reuptake inhibitors): sertraline, paroxetine
    - Atypical antipsychotics (specially risperidone or olanzapine)
    - Lithium (mood stabilizer): alone or in combination with SSRIs
    - ECT (electroconvulsive therapy): it must be considered in patients with persistent or unresponsive depression, or in case of psychotic depression
- **Agitation** (7,17,19):
    - Benzodiazepines
    - Haloperidol (typical antipsychotic)

    - Atypical antipsychotics (specially risperidone or olanzapine)
- **Psychosis** (7,18,22,24,29,50,51):
    - Haloperidol (typical antipsychotic)
    - Atypical antipsychotics (specially risperidone or olanzapine)
    - Lithium (mood stabilizer)
    - SSRIs: sertraline, paroxetine
    - ECT: it must be considered in patients with persistent or unresponsive psychosis
- **Cognitive and/or memory impairment** (18,20):
    - Lamotrigine (mood stabilizer)
- **Delirium** (19,24):
    - Benzodiazepines
    - Haloperidol (typical antipsychotic)
    - Atypical antipsychotics (specially risperidone or olanzapine)

4.3.7 PREVENTION

The risks of glucocorticoid-induced neuropsychiatric disorders should be discussed with patients and their families previous to treatment initiation, so an early diagnosis and appropriate intervention could be implemented (17,19,21). Moreover, it is important to review patient's current medications in order to ensure glucocorticoid indication and to check potential drug interactions, and also to review if the patient presents certain illnesses associated with the development of psychiatric symptoms (17,19,22).

Furthermore, there have been done some studies regarding a possible pharmacological prophylaxis.

The DEXA-CORT clinical trial from Koning *et al* (56) is currently being conducted to study the prevention of dexamethasone-induced neuropsychiatric disorders after high dosages of dexamethasone use for reducing cerebral oedema due to elective brain tumour resection, by using 10 mg of hydrocortisone two times per day during the perioperative treatment, with the aim of stabilising the GR-MR imbalance caused by dexamethasone with physiological doses of cortisol (hydrocortisone use at low dosages, which refills unoccupied brain MR). This study is mainly based on a previous clinical trial

from Warris *et al* (57), about hydrocortisone usage in paediatric patients with acute lymphoblastic leukaemia following a dexamethasone treatment. In this previous study, hydrocortisone use significantly decreased dexamethasone-induced behavioural difficulties, emotional disorders, and sleep problems, specifically in patients who experienced the most severe neuropsychiatric adverse effects (57,58).

In addition, there are some other studies about pharmacological prevention with significative results, although they were all conducted in small samples, and so further investigations should be done. There are studies showing a significative reduction of psychiatric outcomes with the use of lithium (59), lamotrigine (60–62) (specifically to improve performance on declarative memory), memantine (63) (also specifically to improve performance on declarative memory), and phenytoin (54) (specifically to reduce the incidence of hypomania). A study with levetiracetam (64) showed no difference in mood or cognition.

4.3.8 PROGNOSIS

In general terms, prognosis of glucocorticoid-induced neuropsychiatric disorders is favourable. More than 50% of patients show total remission of symptoms after two weeks from treatment suspension, and 90% after six weeks (15). Symptoms can last anywhere from a few days up to some weeks (28). Patients who can discontinue the glucocorticoid experience a quicker resolution of symptoms.

The duration of the symptoms seems to be related with the clinical presentation: delirium uses to resolve within days and psychosis within a week; depression or manic symptoms may last up to 6 weeks after discontinuation of corticotherapy (15,17,20,28,49).

Glucocorticoid-induced dementia is reversible, but in a slower way than other symptoms of cognitive deficits, following drug discontinuation, and may leave residual cognitive effects. Improvement may be apparent 1 month after discontinuation, despite deficits in learning and memory may persist for 6 months or more (19,20).

4.4 MENSTRUAL CYCLE AND ITS RELATIONSHIP WITH CORTISOL

As exposed in **section 4.3.2.1**, female sex is an important risk factor for glucocorticoid-induced neuropsychiatric disorders, and some of its influences vary according to menstrual cycle phases.

Menstrual cycle consists of rhythmic variations of female hormones secretion depending on the HPG axis, and its corresponding physical alterations in ovaries and other sexual organs, from puberty to menopause. Every cycle takes 28 days on average. However, it can last from 20 days to 45 days among different individuals (65).

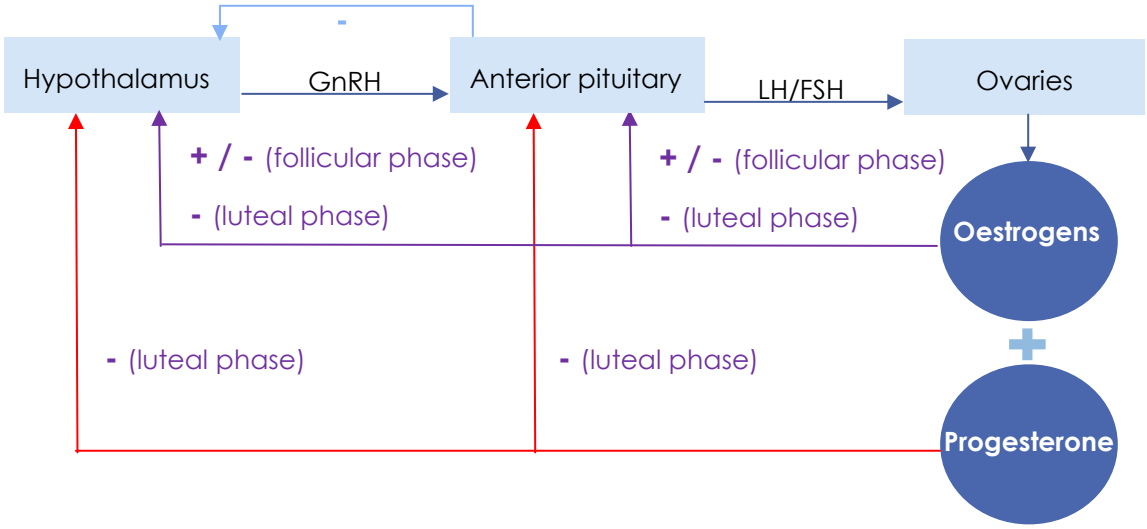

Figure 3. HPG axis.

4.4.1 MENSTRUAL CYCLE PHASES

1. **Follicular phase**: it begins in the first day of menstruation (also known as menses) util ovulation, so approximately from day one to day 14, based on the average duration of 28 days. It is remarkable to say that the variability in the length of the menstrual cycle is due to variations in the length of follicular phase (66,67). At the beginning of this phase, it starts the development of primary follicles, due to the high levels of FSH (follicle stimulating hormone) related with an increase of GnRH (gonadotropin releasing hormone) pulsatile secretion (68). This hormone also increases the number of LH (luteinizing hormone) receptors in granulosa and theca cells to facilitate the production of ovarian oestrogens. Sexual hormones in this phase are low due to the regression of the corpus luteum from previous cycle (69).

With phase progression, cells acquire the capacity to synthetise oestrogens, which progressively rise, also with inhibin, and both diminish FSH, allowing the relationship FSH/LH to be inferior to 1 (69). The follicles with less FSH receptors suffer a gradual process of atresia and the one more receptive to FSH will continue to develop until becoming the dominant follicle (65). This one increments the sensitivity to LH, the androgen production and the aromatase function (68,69). The main produced androgen is androstenedione, which will be aromatised to estrone and then converted to oestradiol (68).

At the end of this phase, the maximum peak of oestradiol secretion induces LH and FSH rise to result in the ovulatory peak, with a greater increment of LH (65,67,69).

2. **Ovulation**: it occurs approximately 16 hours after LH surge, which correlates with day 14 of a regular cycle. As a result of previous high levels of FSH and LH, the follicle breaks and releases the oocyte (65,66,68,69).
3. **Luteal phase**: it goes from day 15 to 28 of a regular cycle. In the three days following the ovulation, due to LH action and the follicular rests, the corpus luteum is formed (66,69). There is a rapid increase in progesterone levels, and oestrogens, after a postovulatory decrease, reach a second peak (lower than the first one). The values of progesterone are greater than the oestrogens' ones. LH and FSH are in their lowest values in the cycle because of negative feedback of both oestrogens and progesterone (65,69), and also of inhibin secreted by the corpus luteum (65).

   At the end of this phase, if there is no fertilised oocyte implanted in the endometrium, the corpus luteum progressively degrades, leading to a decrease of progesterone and oestrogens, until oestrogen levels reach practically zero. With low plasmatic levels, the negative feedback stops and FSH levels rise. The low oestrogen levels also promote the initiation of menstruation (65,66,69).

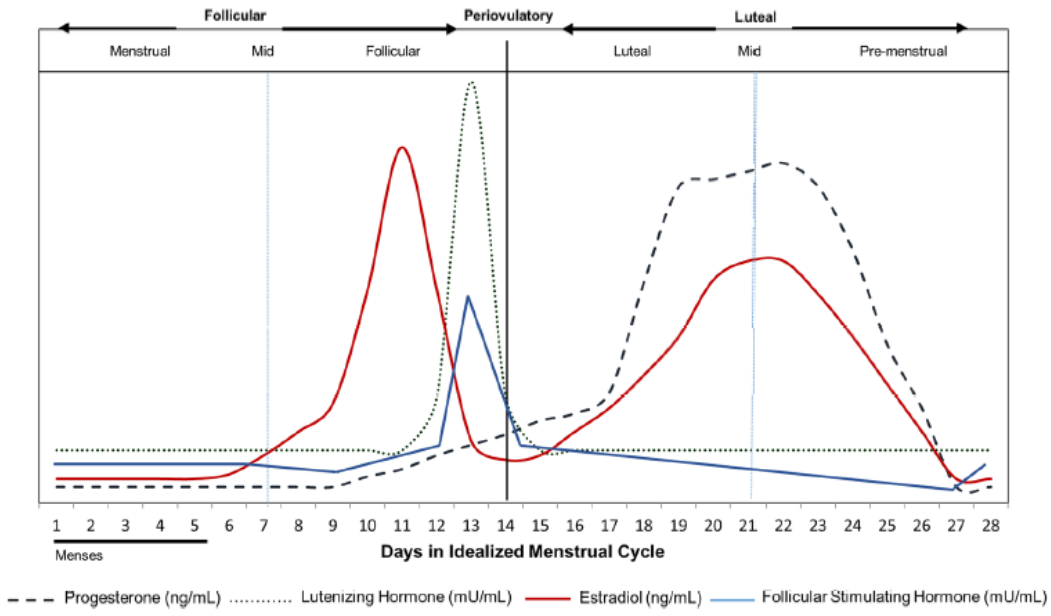

Figure 4. Hormone levels according to menstrual cycle phase. Extracted from (70).

4.4.2 HPA AXIS AND HPG AXIS INTERACTION: THE PAPER OF CORTISOL

Studies have shown circulating cortisol levels change throughout the menstrual cycle, depending on the phase, with the highest levels during early and mid follicular phase. This is due to its requirement to mediate adaptative physiological processes in response to environmental stimuli, when both oestradiol and progesterone are low (71).

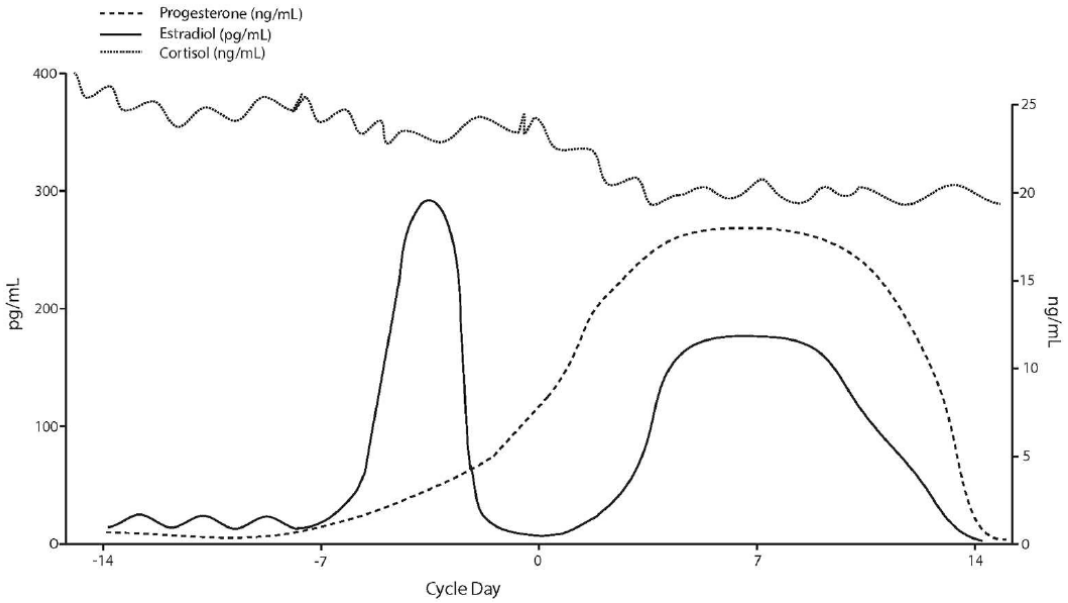

Figure 5. Hypothetical cortisol levels across the menstrual cycle. Extracted from (71).

There are many known mechanisms by which HPA axis and HPG axis interact:

In the HPA axis physiology, it is the paraventricular nucleus (PVN) of the hypothalamus the one that integrates circadian and environmental inputs to integrate them in neurons that express this information through CRH. PVN neurons have been founded to express high levels of oestrogen receptor beta (ER-β) and low levels of oestrogen receptor alpha (ER-α). Oestradiol, through the interaction with these receptors, can selectively increase or decrease HPA axis function. Stimulation of ER-β produces a decrease in cortisol levels, whereas stimulation of ER-α impairs glucocorticoid-mediated negative feedback of the HPA axis, thus leading to an increase in cortisol levels (8,71). Because of this, on luteal phase, on which there are higher levels of oestradiol for a greater period of time than in follicular phase, oestradiol will tend to decrease cortisol levels through a greater ER-β interaction.

Moreover, during the luteal phase, progesterone metabolite allopregnanolone binds to an allosteric binding site of gamma-aminobutyric acid A (GABA-A) receptors in PVN, potentiating the negative feedback on the HPA axis (8,71). Like this, as in luteal phase allopregnanolone levels are high, cortisol levels are expected to decrease from their values on follicular phase (6,71).

In addition, another possible mechanism is through CBG: changes in circulating CBG modify total cortisol concentrations, and oestradiol exerts a regulation in CBG concentrations. Women express greater concentrations of CBG than men, and these increment during pregnancy or oestrogen-containing oral contraception use (6,72). However, it remains unclear if changes in oestradiol levels across the menstrual cycle can alter CBG (71).

Finally, gonadal hormones interact with GR expression and action through effects on proteins in the chaperone and co-chaperone complex, and can induce changes in GR sensitivity, for example through transactivation (8,38), which in fact was mentioned in **section 4.2.3.2** as a potential mechanism of glucocorticoid adverse effects. However, this has not been studied across the menstrual cycle.

5. JUSTIFICATION

Health professionals could widely recognise that practically there is no other treatment apart from glucocorticoids capable of holding the position of the most used treatment across such a wide number of medical specialties.

As it was said in the introduction, apart from its versatility across specialties, glucocorticoid use has augmented during the last three decades, with long-term corticotherapy accounting for 10% in medical inpatients and 1 to 3 % in the general population (16,17).

Unfortunately, the capability of acting in lots of organs and systems also supposes a factor against them, as it leads to a great possibility of adverse effects. These have been demonstrated to occur in up to 90% of the patients that take glucocorticoids for more than 60 days (9,10).

Some of these adverse effects consist of induced neuropsychiatric disorders, with an incidence ranging from 3% to 57% for all glucocorticoid usages, and around a 20% in patients receiving high dosages, defined as 40 mg/day or more of prednisone or its equivalent (15–17,21). They are mainly stablished in the first two weeks of treatment (15,16,18,26,73).

Whereas the somatic reactions to glucocorticoids have been well studied and documented, the neuropsychiatric effects have been less attended, because of their complexity and unpredictability (15,26). There is a lack of randomized controlled trials, varying definitions of the behavioural changes and no clear strategies for identifying patients in need of prophylaxis, which leads to a limited understanding of glucocorticoid-induced neuropsychiatric disorders (18,73). An important part of the available data today comes from individual case or case series reports and their reviews (24).

Among other neuropsychiatric outcomes, glucocorticoids show a risk of suicide or suicide attempt increased five- to sevenfold in people in treatment (23), which even alone can be considered a matter of worry in our society (in Spain, last statistics from 2022 show an average of 11,2 people per day died by suicide, supposing a total of 4.097 people (74,75)). Glucocorticoid usage is a potential modifiable risk factor, and this

highlights the importance of prevention of neuropsychiatric disturbances when using them, and so the necessity of further research for the comprehension of its pathophysiology. Moreover, other markedly facts are a twofold higher risk of developing depression and a four- to fivefold higher risk of developing mania, delirium, confusion or disorientation (23).

With the aim of prevention, first of all it is important the understanding of the existing risk factors, which were described in the introduction. Between these, one that remains partially unclear is female sex (16,22), with a 2:1 ratio (22). Existent literature tables some plausible explanations: a significant majority of autoimmune diseases treated with glucocorticoids (which sometimes can lead to neuropsychiatric disorders by themselves) are more prevalent in women (16,22), many of the potential neuropsychiatric outcomes are inherently more common in women (regardless of glucocorticoid usage), or even this could be a pathological consequence of the external intervention in a purely physiological human process such as the interaction between HPA axis and HPG axis (8,38).

Furthermore, this hormonal interaction shows us an important fact: responses of cortisol to psychosocial stress are similar between men and women in the luteal phase of the menstrual cycle, in which oestrogen levels are reduced, but differ to the ones of women in follicular phase (38). This raises an important question: could this be one of the mechanisms increasing the risk of glucocorticoid-induced neuropsychiatric disorders in women, as we are applying a synthetic analogous of cortisol?

If we knew the response to this, we could make some adjustments when prescribing high dosages of glucocorticoids, such as delaying the onset of the treatment to a concrete phase of the menstrual cycle on which we knew that the posterior incidence of neuropsychiatric disorders would be smaller. Like this, we could be one step closer to a proper prevention of this neuropsychiatric disturbances.

6. HYPOTHESES

6.1 MAIN HYPOTHESIS

The incidence of glucocorticoid-induced neuropsychiatric disorders is expected to vary across the different phases of the menstrual cycle, in women aged 18-45 with a regular cycle and no use of hormonal contraception, who are undergoing corticotherapy at high dosages (40 mg/day or more of prednisone or its equivalent), depending on the phase when they start the treatment. We hypothesise that the incidence will be higher when starting the treatment during the follicular phase.

6.2 SECONDARY HYPOTHESES

- The type of glucocorticoid-induced neuropsychiatric disorder will vary depending on the phase of the menstrual cycle on which the women start the treatment.
- Women developing a glucocorticoid-induced neuropsychiatric disorder diagnosis will exhibit in all phases of menstrual cycle a higher prevalence of currently known risk factors associated with such disorders.
- Women developing a glucocorticoid-induced neuropsychiatric disorder diagnosis, regardless of the phase of menstrual cycle on which they start the treatment, will have a similar necessity of pharmacologic treatment for its management.

7. OBJECTIVES

7.1 MAIN OBJECTIVE

The aim of this study is to determine whether there is a variation in the incidence of glucocorticoid-induced neuropsychiatric disorders across the different phases of the menstrual cycle, in women aged 18-45 with a regular cycle and no use of hormonal contraception, who are undergoing corticotherapy at high dosages (40 mg/day or more of prednisone or its equivalent), depending on the phase when they start the treatment.

7.2 SECONDARY OBJECTIVES

- To evaluate the different types of glucocorticoid-induced neuropsychiatric disorders based on the phase of the menstrual cycle on which women are when they start the treatment.
- To assess whether women developing a glucocorticoid-induced neuropsychiatric disorder in each menstrual cycle phase exhibit a higher prevalence of currently known risk factors associated with such disorders.
- To determine whether women developing a glucocorticoid-induced neuropsychiatric disorder in each menstrual cycle phase have a greater necessity of pharmacologic treatment for glucocorticoid-induced neuropsychiatric disorder management.

8. METHODOLOGY

8.1 STUDY DESIGN

This study is designed as an unicentric observational prospective cohort study to be carried out by the Psychiatric Interconsultation Service of *Hospital Santa Caterina* of Salt (Girona) and *Hospital Josep Trueta* of Girona.

8.2 STUDY SETTINGS

The selection of patients and the follow-up tests will be conducted in both *Hospital Santa Caterina* and *Hospital Josep Trueta*. Despite involving two hospitals in the development of the study, we categorise it as unicentric, since all the patients belong to the reference area of *Hospital Josep Trueta*.

It is important to note that *Hospital Josep Trueta* lacks its own Psychiatric Unit; thus, the Psychiatric Unit of reference for the province of Girona is situated at *Hospital Santa Caterina*. Consequently, the Psychiatric Interconsultation Service of both hospitals is functionally integrated, operating as a unified service across the two hospitals.

8.3 STUDY POPULATION

The target population of this study will be women aged 18-45 with a regular cycle and no use of hormonal contraception, who are undergoing corticotherapy at high dosages (40 mg/day or more of prednisone or its equivalent). This women should not fulfil DSM-5-TR criteria of any mental disorder, with a time from remission allowed of minimum 6 months, and must start the corticotherapy at the beginning of the follow-up period.

The study population will be divided in two groups:

- Exposed cohort: women starting corticotherapy at high dosages in the **follicular phase** of menstrual cycle.
- Non-exposed cohort: women starting corticotherapy at high dosages in the **luteal phase** of the menstrual cycle.

8.3.1 INCLUSION CRITERIA

- Women aged 18 – 45 years.
- Presence of a regular menstrual cycle (length of 25 – 35 days).
- Use of non-hormonal contraception, with a period of minimum 1 month of not using hormonal contraception, if previously used.
- Possibility of starting glucocorticoid treatment the day after (1st visit of the follow-up process).
- Spanish or Catalan oral and written comprehension.

8.3.2 EXCLUSION CRITERIA

- Use of hormonal contraception, or a period of less than 1 month since last use.
- Current pregnancy, current breastfeeding, or up to 12 weeks after giving birth (puerperium process).
- Current fulfilling of DSM-5-TR criteria of any mental disorder, or a time from remission of the mental disorder of less than 6 months.
- Consumption of toxic substances.
- Patient's inability to complete the study tests on her own (physical or mental cause).

8.3.3 WITHDRAWAL CRITERIA

- Patient's decision to drop out of the study for personal reasons.
- Low compliance of the glucocorticoid treatment.
- Patient's pregnancy during the follow-up process.
- Patient's demise during the follow-up process.
- Incorrect use of LH tests or evidence of a non-ovulatory cycle.
- Patient's absence on the scheduled follow-up visits*.

*This one will not be considered a withdrawal criterion if the reason is a hospitalisation in the Psychiatric Unit of *Hospital Santa Caterina*, or in any other Psychiatric Unit on Catalonia if this can be seen in the *Història Clínica Compartida a Catalunya*, as these situations will be considered a possible study outcome.

8.4 SAMPLE

8.4.1 SAMPLE SIZE

GRANMO sample size calculator was used to estimate the required sample size of the study. Accepting an alpha risk (α) of 5% and a statistical power (1-β) of 80% in a two-tailed test, **102 exposed subjects** and **102 non-exposed subjects** (**204 in total**) are necessary to recognize as statistically significant a Relative Risk greater than or equal to 2. An incidence rate in the non-exposed group has been estimated to be 0.2. A drop-out rate of 10% has been anticipated.

As this is the first study to date studying the relationship between menstrual cycle and glucocorticoid-induced neuropsychiatric disorders, there is no data about the incidence rate in luteal phase. Therefore, to calculate the sample we have considered that the rate in luteal phase would be lower than in follicular phase, but also greater than the rate in men and, in balance, this could lead to an incidence in luteal phase similar to the one in general population, which is the one currently known.

8.4.2 SAMPLE SELECTION

We will use a **non-probabilistic consecutive sampling** method in this study.

All patients who meet the inclusion criteria and none of the exclusion criteria* will be informed by the physician that prescribes the glucocorticoid treatment about the study objectives, and if they are interested, they will be given the opportunity to voluntarily participate. They will receive the information document (**Annex 7**) and the informed consent document (**Annex 8**). The signature of the informed consent is mandatory to participate in the study.

*In order to determine if the patient meets the inclusion criterion “current fulfilling of DSM-5-TR criteria of any mental disorder, or a time from remission of the mental disorder of less than 6 months” the physician that prescribes the glucocorticoid treatment will have to determine it through medical history. Then, the next day (1st visit), looking forward a greater accuracy, the psychiatrist will perform the following tests (which are explained in **section 8.5**):

- **Mini International Neuropsychiatric Interview (MINI)** (see Annex 3)
- **Patient Health Questionnaire-9 (PHQ-9)** (see Annex 5)
- **Mini Mental State Examination (MMSE)** (see Annex 6)

These will allow a proper screening of current mental disorders and, if any, the patient will be excluded from the study.

8.4.3 ESTIMATED TIME FOR SAMPLE RECUITMENT

As we have already calculated, 204 subjects are required to carry out the study.

Due to the fact that glucocorticoids are a widely used treatment, even at high dosages, according to non-official data proportioned from the Pharmacology Unit of *Hospital Santa Caterina*, an estimated time of 1 year would be enough to recruit all the participants for the study.

However, as not all the patients meeting all the inclusion criteria and none of the exclusion criteria will accept to participate in the study, and not all the patients with a high-dosage glucocorticoid prescription will meet all the inclusion criteria and none of the exclusion criteria, we will dedicate a period of **two years** to achieve the required sample size.

8.5 STUDY VARIABLES AND MEASURING INSTRUMENTS

8.5.1 INDEPENDENT VARIABLE

Menstrual cycle phase

Menstrual cycle phase is a qualitative nominal dichotomous variable that will be categorised as “follicular phase” or “luteal phase”.

In order to accomplish the greatest accuracy in data collection, we will use an author adaptation to the classification method recommended by Schmalenberger *et al* (76), as it produces more meaningful results regarding the association between specific hormonal levels and outcomes. This method has been recently used in some studies in the psychiatric field (77,78). The modifications by the author are made in order to avoid

not coded days in the original method (which would lead to exclusion from the statistical analysis of patients which cycle day does not fall into a predefined phase), as they are stablished to well-define the relationship of the outcomes with specific hormonal changes of a 5 phases division (perimenstrual, midfollicular, periovulatory, early luteal and midluteal) and avoiding possible confusions between these phases. These changes will be done taking into account that at the end we will summarize the cycle only into two phases (follicular and luteal), which onset and end are already well defined using this method.

With this method, the menstrual cycle phase is codified using a combination of last menses onset self-report (using forward count from menses) and urine LH-surge detection (ovulatory testing). This method, with the author adaptations, codes phases following some definitory facts:

1. LH-surge detection is the gold standard, but it only allows to calculate accurately the ovulation day. If ovulation has already happened, it will not detect it.
2. Last menses onset self-report is useful to detect the first days of the menstrual cycle, corresponding to follicular phase. However, due to interindividual and intraindividual variability on phases length (even in regular individuals), it is difficult to determine when the ovulation is going to occur.
3. Day of menses onset is considered day 1 (there is no day 0).
4. Even individuals with short cycles (<21 days) are not expected to ovulate before day 8, so days 1 to 7 will be always considered part of the follicular phase (76).

In consequence, the menstrual cycle will be coded as follows: in the first visit, patient will be asked about the last day of menses onset. If this first visit occurs between days 1 to 7 before this day, the patient will be given some urine LH-surge detection tests, in order to do one test every day after the visit until it yields a positive result (thus determining ovulatory peak) or until a new menstruation takes place. If there is a positive result in one test, the patient's first visit day will be considered part of the follicular phase. If there is not a positive result and the next menstruation starts, the menstrual cycle will be considered non-ovulatory and the patient will be excluded from the study. If the first visit occurs at day 8 from the last day of menses onset or after, the

patient will also be given some urine LH-surge detection tests, in order to do one test every day after the visit until it yields a positive result (thus determining ovulatory peak) or until a new menstruation takes place. If there is a positive result in one test, patient's first visit day will be considered part of the follicular phase. If there is not a positive result and the next menstruation starts, patient's first visit day will be considered part of the luteal phase.

For a better understanding of cycle phase coding, see **figure 6**.

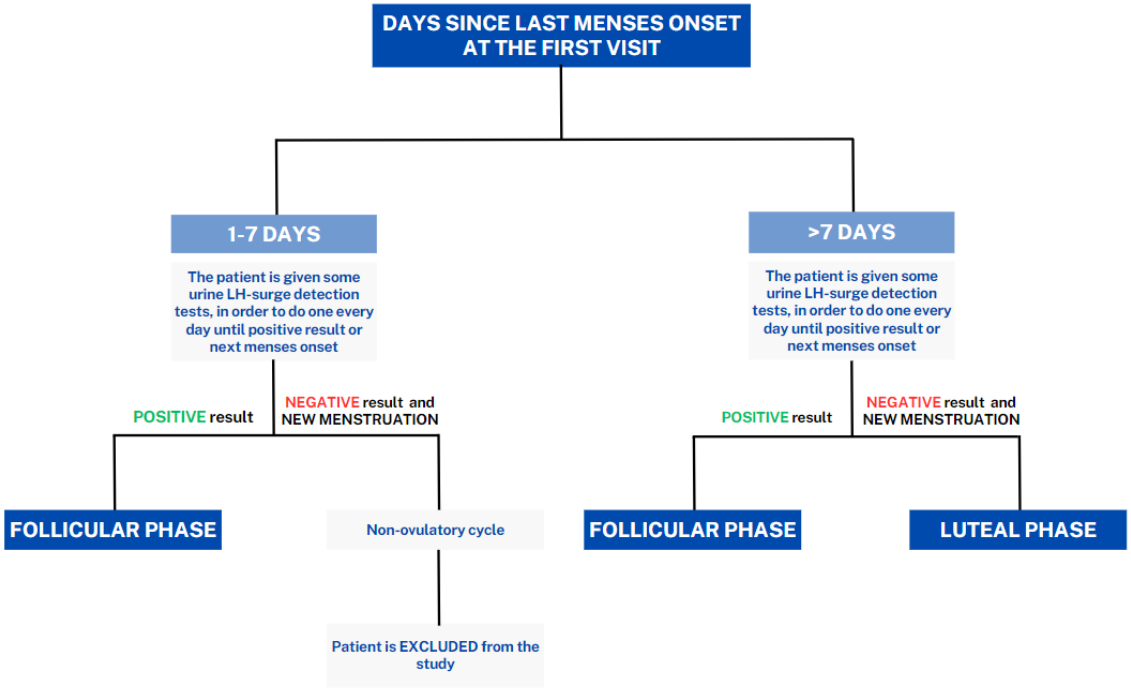

Figure 6. Menstrual cycle phase coding based on Schmalenberger *et al* (76) method with the author's adaptations to the current study.

8.5.2 DEPENDENT VARIABLES

Glucocorticoid-induced neuropsychiatric disorder diagnosis

Glucocorticoid-induced neuropsychiatric disorder diagnosis is a qualitative nominal dichotomous variable that will be categorised as "glucocorticoid-induced neuropsychiatric disorder diagnosis" or "absence of glucocorticoid-induced neuropsychiatric disorder".

The diagnosis of glucocorticoid-induced neuropsychiatric disorder will be made by a psychiatrist following the DSM-5-TR diagnostic criteria for the substance/medication-

induced mental disorders exposed in **section 4.3.4**, regarding glucocorticoid use. This variable will be analysed through patients' follow-up.

If the patient assists to each follow-up visit, the psychiatrist will be the responsible for the diagnosis either at the visit moment or in the period since last follow-up visit, through anamnesis and medical history.

If the patient does not assist to a follow-up visit, the psychiatrist will be responsible of searching whether the reason is a hospitalisation in the Psychiatric Unit of *Hospital Santa Caterina*, or in any other Psychiatric Unit on Catalonia if this can be seen in the *Història Clínica Compartida a Catalunya*, as these situations, if already diagnosed, will be categorised as "glucocorticoid-induced neuropsychiatric diagnosis".

Type of glucocorticoid-induced neuropsychiatric disorder

Type of glucocorticoid-induced neuropsychiatric disorder is a qualitative nominal polytomous variable, that will be categorised as:

- Glucocorticoid-induced psychotic disorder
- Glucocorticoid-induced bipolar and related disorder
- Glucocorticoid-induced depressive disorder
- Glucocorticoid-induced anxiety disorder
- Glucocorticoid-induced sleep disorder
- Glucocorticoid-induced delirium
- Glucocorticoid-induced major or mild neurocognitive disorder

This variable will be collected by a psychiatrist in follow-up visits, using anamnesis and data from the patient's medical history, always using DSM-5-TR criteria (see **Annex 2**). Furthermore, in order to unify psychiatrists' criteria and to help in the diagnose of this dependent variable, at each visit (except from the first one) the psychiatrist will use some measuring instruments consisting on diagnostic scales and structured interviews:

- **Mini International Neuropsychiatric Interview Plus (MINI Plus)** (79)
  MINI is a short structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders, that has already been validated in Spanish and for DSM-5 criteria (80).

This interview allows to diagnose some psychiatric disorders in a specific time frame for each disorder, mainly using "yes" or "no" questions. The MINI Plus version allows the diagnosis of substance-induced disorders, so it will be used regarding glucocorticoid use. Apart from suicidality, only the questions about these diagnoses will be done to the patients (see in **Annex 4**). We will evaluate the following disorders:

- Substance-induced depressive disorder (current or past)
- Suicidality (last month)
- Substance-induced manic episode (current or past)
- Substance-induced hypomanic episode (current or past)
- Substance-induced anxiety disorder with panic attacks (current)
- Substance-induced obsessive-compulsive disorder (current)
- Substance-induced psychotic disorder (current or lifetime)
- Substance-induced generalised anxiety disorder (current)

In order to perform the interview, the psychiatrist will have to follow some general instructions, which are the same as in MINI International Neuropsychiatric Interview (MINI) and can be seen in **Annex 3**.

At the beginning of every diagnostic category (identified as "module" with a letter) there is a text box with "filter" questions corresponding to principal diagnostic criteria of the disorder. At the end of each module, there is one or more boxes where the psychiatrist will have to indicate if the patient meets the diagnostic criteria.

- **Patient Health Questionnaire-9 (PHQ-9)** (81)

  PHQ-9 is a 9-question instrument that is administered to the patient in order to self-complete it, to detect the presence and severity of depression (see **Annex 5**). It was originally created to make a diagnosis according to the DSM-IV criteria. However, it has already been validated in Spanish and for DSM-5 criteria (80).

  Major depressive disorder is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least more than half the days in the past 2 weeks, and one of the symptoms is depressed mood or anhedonia. Other depressive disorders are diagnosed if 2, 3 or 4 depressive symptoms have been present at least more than half the days in the past 2 weeks, and one of the symptoms is

depressed mood or anhedonia. To note, one of the 9 criteria ("thoughts that you would be better off dead or of hurting yourself in some way") counts if present at all, regardless of the duration.

Severity of the depressive disorder is assessed with a score that can range from 0 to 27, since each of the 9 items can be scored 0 (not at all), 1 (several days), 2 (more than half the days) or 3 (nearly every day). This score represents severity of depression as follows (82):

- 1 to 4: none
- 5 to 9: mild
- 10 to 14: moderate
- 15 to 19: moderately severe
- 20 to 27: severe

- **Mini Mental State Examination (MMSE)** (83)

  MMSE is a brief test that allows the establishment of cognitive impairment, such as in dementia or delirium, and the evaluation of its evolution, which takes 5-10 minutes to be done (see **Annex 6**). It has already been validated in Spanish (84). Its realisation gives a score with a maximum of 30 points, evaluating the following cognitive areas: orientation, registration (by repeating some words), attention and calculation, recall, language and ability to follow simple commands. The score can be interpreted as follows:

  - 27 to 30: no cognitive impairment
  - 25 to 26: possible mild cognitive impairment
  - 10 to 24: mild to moderate cognitive impairment
  - 6 to 9: moderate to severe cognitive impairment
  - 0 to 5: severe cognitive impairment

In order to facilitate the multivariate statistical analysis, the variable "Type of glucocorticoid-induced neuropsychiatric disorder" will be separated into different dependent variables corresponding to the categories of the original variable. The objective is to have 7 different secondary dependent variables (one for each category), with "yes" or "no" values, thus converting a qualitative nominal polytomous variable into 7 different qualitative nominal dichotomous variables.

Pharmacologic treatment necessity for glucocorticoid-induced neuropsychiatric disorder management

Pharmacologic treatment necessity for glucocorticoid induced neuropsychiatric disorder management is a qualitative nominal dichotomous variable, that will be categorised as "pharmacologic treatment necessity" or "no pharmacologic treatment necessity".

This variable will be collected from anamnesis and medical history during the follow-up visits.

8.4.3 COVARIATES

- **Age**: qualitative ordinal polytomous variable, expressed in age ranges:
    - 18 to 25 years
    - 26 to 35 years
    - 36 to 45 years

  The age of the patient will be consulted from the identification data of the patient shown in the medical history.
- **Underlying disease**: qualitative nominal polytomous variable. Any disease that supposes the cause of patient's glucocorticoid treatment onset will be collected (e.g. Addison disease, SLE, rheumatoid arthritis, etc.).

  This variable will be collected from anamnesis and medical history.
- **Glucocorticoid dosage**: qualitative ordinal polytomous variable, expressed in prednisone equivalent milligrams:
    - ≥40 mg/day and <60 mg/day
    - ≥60 mg/day and <80 mg/day
    - ≥80 mg/day

  This variable will be collected from medical history.
- **Duration of glucocorticoid treatment**: quantitative continuous variable, expressed in number of days that the patient has been undergoing the corticotherapy. This variable will be collected from anamnesis and medical history. In every follow-up visit the patient will be asked about if she maintains the treatment. If not, she will be asked about the duration.

- **Type of systemic glucocorticoid**: qualitative nominal polytomous variable. Categorised in:
    - Short acting: hydrocortisone or cortisone acetate.
    - Intermediate acting: prednisone, prednisolone, methylprednisolone, triamcinolone or deflazacort.
    - Long acting: dexamethasone or betamethasone.

  This variable will be collected from medical history.
- **Previous history of glucocorticoid-induced neuropsychiatric disorder:** qualitative nominal dichotomous variable, categorised in:
    - Presence of previous history of glucocorticoid-induced neuropsychiatric disorder
    - Absence of previous history of glucocorticoid-induced neuropsychiatric disorder

  This variable will be collected from anamnesis and medical history.
- **Previous history of non-glucocorticoid-induced neuropsychiatric disorder**: qualitative nominal dichotomous variable, categorised in:
    - Presence of previous history of non-glucocorticoid-induced neuropsychiatric disorder.
    - Absence of previous history of non-glucocorticoid-induced neuropsychiatric disorder.

  This variable will be collected from anamnesis and medical history.
- **Use of medication that inhibits cytochrome P450 system (CYP3A4)**: qualitative nominal dichotomous variable, categorised in:
    - Use of medication that inhibits cytochrome P450 system (CYP3A4): e.g. clarithromycin, ketoconazole, protease inhibitors, etc.
    - No use of medication that inhibits cytochrome P450 system (CYP3A4).

  This variable will be collected from medical history.
- **Hypoalbuminemia**: qualitative nominal dichotomous variable, categorised in:
    - Presence of hypoalbuminemia: ≤3,5 g/dL
    - Absence of hypoalbuminemia: >3,6 g/dL

  This variable will be collected using a blood test (albuminemia).

- **Low complement values**: qualitative nominal dichotomous variable, categorised in:
    - Presence of low complement values: CH50 ≤30 U/mL
    - Absence of low complement values: CH50 >30 U/mL

  This variable will be collected using a blood test (CH50).
- **Hepatic disfunction**: qualitative nominal dichotomous variable, categorised in:
    - Presence of hepatic disfunction
    - Absence of hepatic disfunction

  This variable will be collected from medical history.
- **Renal disfunction**: qualitative nominal dichotomous variable, categorised in:
    - Presence of hepatic disfunction
    - Absence of hepatic disfunction

  This variable will be collected from medical history.

The covariates “age”, “underlying disease”, “glucocorticoid dosage”, “type of systemic glucocorticoid”, “previous history of glucocorticoid-induced neuropsychiatric disorder”, “previous history of non-glucocorticoid-induced neuropsychiatric disorder”, “use of medication that inhibits cytochrome P450 system (CYP3A4)”, “hypoalbuminemia”, “low complement values”, “hepatic disfunction” and “renal disfunction” will be evaluated only at the 1st visit.

The covariate “duration of glucocorticoid treatment” will be evaluated through all the follow-up period and not in the 1st visit.

It is important to note that all the covariates, as all of them are known as possible risk factors for glucocorticoid-induced neuropsychiatric disorder, will be treated as dependent variables in the specific case of the secondary objective of assessing whether women developing a glucocorticoid-induced neuropsychiatric disorder in each menstrual cycle phase exhibit a higher prevalence of currently known risk factors associated with such disorders.

Table 7. Description of the variables included in the study. *This variable in the multivariant analysis will be separated into 7 secondary dependent variables (1 for each category) that will be qualitative nominal dichotomous variables with "yes" or "no" values.

	VARIABLE	TYPE	MEASURING INSTRUMENT	CATEGORIES
INDEPENDENT VARIABLE	**Menstrual cycle phase**	Qualitative nominal dichotomous	Urine LH-surge detection and last menses onset self-report	Follicular phase / Luteal phase
DEPENDENT VARIABLES	**Glucocorticoid-induced neuropsychiatric disorder diagnosis**	Qualitative nominal dichotomous	Anamnesis and medical history	Glucocorticoid-induced neuropsychiatric disorder diagnosis / Absence of glucocorticoid-induced neuropsychiatric disorder
	Type of glucocorticoid-induced neuropsychiatric disorder*	Qualitative nominal polytomous	Anamnesis, medical history, MINI Plus, PHQ-9 and MMSE	Psychotic disorder / Bipolar and related disorder / Depressive disorder / Anxiety disorder / Sleep disorder / Delirium / Major or mild neurocognitive disorder
	Pharmacologic treatment necessity for glucocorticoid-induced neuropsychiatric disorder management	Qualitative nominal dichotomous	Anamnesis and medical history	Pharmacologic treatment necessity / No pharmacologic treatment necessity
COVARIATES	**Age**	Qualitative ordinal polytomous	Medical history	18 to 25 years / 26 to 35 years / 36 to 45 years
	Underlying disease	Qualitative nominal polytomous	Anamnesis and medical history	Addison disease / SLE / Rheumatoid arthritis / …
	Glucocorticoid dosage	Qualitative nominal polytomous	Medical history	≥40 mg/day and <60 mg/day / ≥60 mg/day and <80 mg/day / ≥80 mg/day
	Duration of glucocorticoid treatment	Quantitative continuous	Anamnesis and medical history	Number of days
	Type of systemic glucocorticoid	Qualitative nominal polytomous	Medical history	Short acting / Intermediate acting / Long acting
	Previous history of glucocorticoid-induced neuropsychiatric disorder	Qualitative nominal dichotomous	Anamnesis and medical history	Presence of previous history of glucocorticoid-induced neuropsychiatric disorder / Absence of previous history of glucocorticoid-induced neuropsychiatric disorder
	Previous history of non-glucocorticoid-	Qualitative nominal dichotomous	Anamnesis and medical history	Presence of previous history of non-glucocorticoid-induced neuropsychiatric

	induced neuropsychiatric disorder			disorder / Absence of previous history of non-glucocorticoid-induced neuropsychiatric disorder
	Use of medication that inhibits cytochrome P450 system (CYP3A4)	Qualitative nominal dichotomous	Medical history	Use of medication that inhibits cytochrome P450 system (CYP3A4) / No use of medication that inhibits cytochrome P450 system (CYP3A4)
	Hypoalbuminemia	Qualitative nominal dichotomous	Blood test (albuminemia)	Presence of hypoalbuminemia / Absence of hypoalbuminemia
	Low complement values	Qualitative nominal dichotomous	Blood test (CH50)	Presence of low complement values / Absence of low complement values
	Hepatic disfunction	Qualitative nominal dichotomous	Medical history	Presence of hepatic disfunction / Absence of hepatic disfunction
	Renal disfunction	Qualitative nominal dichotomous	Medical history	Presence of renal disfunction / Absence of renal disfunction

8.4.4 OTHER MEASURING INSTRUMENTS

- **MINI International Neuropsychiatric Interview (MINI)** (79)

  MINI is a short structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders, that has been already validated in Spanish and for DSM-5 criteria (80) (see on **Annex 3**). The administration time is of approximately 15 minutes. This interview allows to diagnose 22 of the most common disorders in a specific time frame for each disorder, mainly using “yes” or “no” questions:

  - Major depressive disorder (past 2 weeks or relapsing)
  - Major depressive disorder with melancholic symptoms (past 2 weeks)
  - Dysthymic disorder (past 2 years)
  - Suicidality (past month)
  - Manic episode (current or past)
  - Hypomanic episode (current or past)
  - Panic disorder (past month or lifetime)
  - Agoraphobia (current)
  - Social phobia (past month)
  - Obsessive-compulsive disorder (past month)
  - Posttraumatic stress disorder (past month)

- Alcohol dependence (past 12 months)
- Alcohol abuse (past 12 months)
- Drug dependence (nonalcohol) (past 12 months)
- Drug abuse (nonalcohol) (past 12 months)
- Psychotic disorder (current or lifetime)
- Affective disorder with psychotic symptoms (current)
- Anorexia nervosa (past 3 months)
- Anorexia nervosa type compulsive/purgative (current)
- Bulimia nervosa (past 3 months)
- Generalised anxiety disorder (past 6 months)
- Antisocial personality disorder (lifetime)

This structured interview will be used only in the 1st visit, with the aim of ruling out exclusion criteria.

8.6 DATA COLLECTION

Once the patient has been included in the study accordingly to the exposed in **section 8.4.2**, in the **first visit** (the day when the patient must start the glucocorticoid treatment), apart from conducting the diagnostic scales and interviews required to assess exclusion criteria by a psychiatrist, the patient will be asked about the required variables through anamnesis. In the same day, a blood test will be performed to determine possible hypoalbuminemia or low complement values.

All the data will be collected by the pertinent co-investigator and then will be computerised. In order to anonymise the information in the study database, a numerical code will be assigned to each patient.

During this first visit, the patient will be given some urine LH-surge detection tests and will be instructed about how to use them. The patient will have to do one of them every day until one of them gives a positive result or until a new menstruation starts. If there is a positive result, the patient will have to contact with the investigators (through a telephone call to a previous given number) and to take a photograph of the positive

result and send it to the investigators (through email to a previous given address). With this we will be able to categorise menstrual cycle phase though our coding method.

The **follow-up process** will consist in a possibility of four more visits at 1 month (2nd visit), 2 months (3rd visit), 3 months (4th visit) and 6 months (5th visit).

In all this visits, the possible glucocorticoid-induced disorder diagnosis will be done by a psychiatrist, according to anamnesis, medical history, and the realisation of the required diagnostic scales and interviews. In addition, the patient will be asked about the required variables through anamnesis.

At the 2nd visit, the patient will be asked about the urine LH-surge detection tests in order to ensure if a correct use has been done. If not, the results will not be reliable and the patient must be excluded from the study.

The interval of 1 month between follow-up visits is established because the MINI Plus defines a diagnosis as "current" mainly if it has happened in an interval of one month before the visit or is happening in the same visit, so with this we will avoid a possible information bias. The 5th visit is established to follow-up patients with long-term corticotherapy, or to make a differential diagnosis between a glucocorticoid-induced disorder and a primary disorder (that not due to the substance use, but on which glucocorticoid exposure has got a trigger role), as patients with a primary disorder diagnosis would be finally considered as non-diagnosed of glucocorticoid-induced neuropsychiatric disorder. It would be possible if the clinical presentation does not disappear with proper treatment, or it takes too much time to disappear.

If the patient does not assist to a follow-up visit, the psychiatrist will be responsible of searching whether the reason is a hospitalisation in the Psychiatric Unit of *Hospital Santa Caterina*, or in any other Psychiatric Unit on Catalonia if this can be seen in the *Història Clínica Compartida a Catalunya*, as these situations, if already diagnosed, will be categorised as "glucocorticoid-induced neuropsychiatric diagnosis". The visit then will be rescheduled in order to ensure the unification of psychiatrists' criteria in the study.

Consecutive visits will depend on whether in any of the follow-up visits there is a diagnosis of a glucocorticoid-induced neuropsychiatric disorder. If there is a diagnosis

and it has already been treated successfully before the visit, there will be only one more follow-up visit (until a maximum of 5 visits) in order to evaluate a period of one month since last day of exposure to glucocorticoids (to exclude a primary disorder). If there is a diagnosis at the same time of the visit, or before but the symptomatology still persists, the next visit will be scheduled.

All data collected during the follow-up process will also be anonymised and included in the study database.

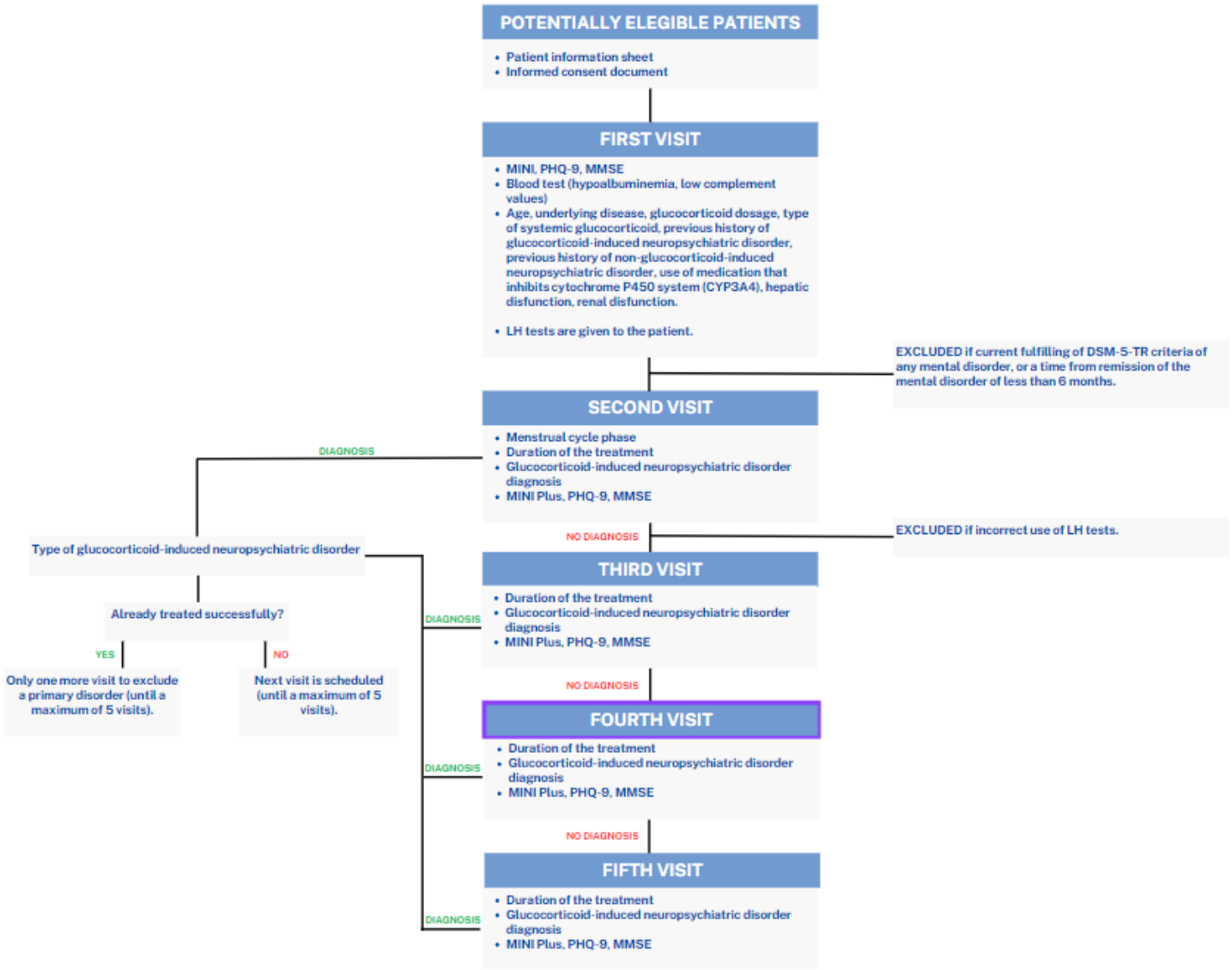

Figure 7. Data collection flowchart. Other withdrawal criteria will be considered across all the process.

9. STATISTICAL ANALYSIS

The statistical analysis will be carried out by the statistician and it will be done using the Statistical Package for Social Sciences (SPSS) software version 29.0.1.

We will establish a $p < 0,05$ value as statistically significant, defining a 95% confidence interval for all analyses.

9.1 DESCRIPTIVE ANALYSIS

Firstly, a descriptive analysis of the variables will be performed. As dependent variables ("glucocorticoid-induced neuropsychiatric disorder diagnosis", "type of glucocorticoid-induced neuropsychiatric disorder" pharmacologic treatment necessity for glucocorticoid induced neuropsychiatric disorder management", first two primary and last one secondary objectives, respectively) and all the covariables in our study except from "duration of glucocorticoid treatment" are qualitative, they will be summarized by proportions or percentages. "Duration of glucocorticoid treatment" is a quantitative variable and will be summarized by mean +/- standard deviation (SD), and median and interquartile range.

We will carry out a bivariate descriptive stratify of all dependent variables, by the groups defined by our independent variable ("menstrual cycle", which will be classified into "follicular phase" or "luteal phase").

All these analyses will be further stratified by the covariables. Therefore, as covariates are known as possible risk factors, assessing the stratification by covariates of the dependent variable "glucocorticoid-induced neuropsychiatric disorder diagnosis" we will be able to evaluate the secondary objective of assessing whether women developing a glucocorticoid-induced neuropsychiatric disorder in each menstrual cycle phase exhibit a higher prevalence of currently known risk factors associated with such disorders. "Duration of glucocorticoid treatment" will be categorised in quartiles.

9.2 BIVARIATE INFERENCE

The difference in "glucocorticoid-induced neuropsychiatric disorder diagnosis" between both groups, exposed (follicular phase) and non-exposed (luteal phase), will be tested using the Chi-square or the Fisher's exact test (in case that in any cell the expected number of cases was lower than 5).

In the same way, the difference in "type of glucocorticoid-induced neuropsychiatric disorder" between both groups, exposed (follicular phase) and non-exposed (luteal phase), will also be tested using the Chi-square or the Fisher's exact test (in case that in any cell the expected number of cases was lower than 5).

All the analyses will be stratified by the covariates.

The difference of proportions needed to accomplish the secondary objective of assessing whether women developing a glucocorticoid-induced neuropsychiatric disorder in each menstrual cycle phase exhibit a higher prevalence of currently known risk factors associated with such disorders, will also be tested using the Chi-square or the Fisher's exact test (in case that in any cell the expected number of cases was lower than 5) for qualitative variables, and Student's t test for quantitative variables.

9.2 MULTIVARIATE ANALYSIS

Finally, a multivariate analysis will be performed, in order to analyse the relationship between the independent and the dependent variables, by controlling for the covariates, to avoid potential confounders and obtain interpretable results. It will be carried out using logistic regression models.

To note, the polytomous dependent variable "type of glucocorticoid-induced neuropsychiatric disorder" will be separated into 7 dichotomous secondary dependent variables (one for each category), in order to perform the multivariate analysis avoiding non-standard models. As this requires applying lots of models, we will have the multiple comparisons problem, thus increasing the probability of type I errors (false positives). To correct it, we will apply the Bonferroni correction.

10. ETHICAL AND LEGAL CONSIDERATIONS

The present study will be evaluated by the *CEIC Girona* (Clinical Research Ethical Committee from *Institut d'Asistència Sanitària de Girona* and *Hospital Josep Trueta*) for its approval. In case of any objections, modifications will be done to achieve their conditions. Only after receiving their approval, the study will begin.

Patients will enter the study only after they have been properly informed and they have signed the informed consent document, already evaluated by the CEIC.

All the investigators of the study will declare that they have no conflicts of interest, and no financial expense will be provided to encourage participation.

The study will be carried out following the ethical requirements set up by the "*Declaration of Helsinki of ethical principles for medical research involving human subjects"* of the World Medical Association (revised in October 2013). It will also respect the "*Belmont Report: ethical principles and guidelines for the protection of human subjects of research*" (written in 1979) and the bioethical principles of Beauchamp and Childress as follows:

- **Autonomy**: all the participants of the study will receive an information document (**Annex 7**) which explains all the study information and will be able to ask any questions they have. In case they voluntarily agree to participate, they must sign the informed consent document (**Annex 8**). They will have the right of withdrawal from the study whenever they want and without any perjudice. In Spain, this is regulated by the law "*Ley Orgánica 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica*". And, in Catalonia, it is also regulated by the law "*Llei 16/2010, del 3 de juny, de modificació de la Llei 21/2000, del 29 de desembre, sobre els drets d'informació concernent la salut i l'autonomia del pacient, i la documentación clínica*".

  The autonomy of the patient will also be preserved by the patient's confidentiality and data protection, as all the personal data of the patients will be codified in a database with a code number for every patient, avoiding the

possibility of patients' recognition. Only researchers will have access to this information, with the purpose of performing the study, and no third parties will be allowed to access to the patient's data. Patients' confidentiality will be protected by the following laws: "*Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativa a la protección de las personas físicas en lo que respecta al tratamiento de los datos personales y a la libre circulación de estos datos y por el que se deroga la Directiva 95/46/CE (Reglamento general de protección de datos)*", "*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales*" and "*Real Decreto 1720/2007, de 21 de diciembre, por el que se aprueba el Reglamento de Desarrollo de la Ley Orgánica 15/1999, de 13 de diciembre, de protección de datos de carácter personal*".

- **Beneficence**: this study aims to discover if there is a relationship between menstrual cycle phase when starting the glucocorticoid treatment at high dosages and the development of glucocorticoid-induced neuropsychiatric disorders. In consequence, this information could help to the development of preventive strategies in the future to avoid glucocorticoid-induced neuropsychiatric disorders and its consequences in patient's heath.
- **Non-maleficence**: given the observational nature of the study, no harm will be done to the patient.
- **Justice**: all the patients who meet the inclusion criteria and none of the exclusion criteria, and who have signed the informed consent document, will be considered equally for the participation in the study, without any kind of positive or negative discrimination, as these criteria are established in order to ensure the proper evaluation of the study objectives.

In addition, as this is an observational study with drugs, the study will be conducted under the regulation of the following laws:

- *"Real decreto 957/2020, de 3 de noviembre, por el que se regulan los estudios observacionales con medicamentos de uso humano".*

- *"Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la ley de garantías y uso racional de los medicamentos y productos sanitarios".*
- *"Ley 14/2007, de 3 de julio, de Investigación biomédica".*

11. WORK PLAN AND CHRONOGRAM

11.1 RESEARCH TEAM

Personnel involved in the study include:

- **Principal investigator**: the person who will direct the execution of the project and ensure the correct application of the protocol, as well as the proper formation of the psychiatrists who will perform the interviews in each visit. Furthermore, he/she will be the responsible for developing the study design, writing the protocol, presenting it to the CEIC for its approval, supervising sample recruitment process, and proceeding with the interpretation and the presentation of the final results.
- **Study coordinators**: in each hospital (*Hospital Santa Caterina* and *Hospital Josep Trueta*) there will be a person assigned to perform the supervision of the study in his/her centre, and to facilitate coordination with the principal investigator.
- **Co-investigators**: the psychiatrists from the Psychiatric Interconsultation Service of *Hospital Santa Caterina* and *Hospital Josep Trueta* who will collect the data from the anamnesis, the medical history and the scales and interviews performed at each visit, and will introduce it to the study database.
- **Data manager**: the person who will create the database of the study, and will attend the data processing, the quality control of the data and the anonymisation process.
- **Statistician**: the person who will be responsible for carrying out the statistical analysis of the study.
- **Collaborators**: all the health professionals necessary to carry out this study, such as the physicians of any specialty that prescribe a glucocorticoid treatment and preliminarily determine if patients meet the inclusion criteria and none of the exclusion criteria, nurses, nursing assistants, physicians specialised in clinical analysis, laboratory technicians, clinical pharmacologists, etc.

11.2 STUDY STAGES

This study will be carried in 6 stages distributed within a total period of **3 years and 9 months**, starting in November 2023 and finishing in June 2027. It will be organised as follows:

STAGE 0: STUDY DESIGN (*November 2023 – January 2024*)

- **Protocol development** (*November 2023 – January 2024*): establishment of the study objectives and hypotheses, definition of the variables and design of the methodology. To develop the present protocol, exhaustive bibliographic research has been performed. This process has been led by the principal investigator.
- **Personnel recruitment** (*January 2024*): in this period study coordinators and co-investigators will be selected.

STAGE 1: ETHICAL EVALUATION AND STUDY APPROVAL (*January 2024 – March 2024*)

The protocol will be submitted to *CEIC Girona* (Clinical Research Ethical Committee from *Institut d'Asistència Sanitària de Girona* and *Hospital Josep Trueta*) for its approval. If necessary, adjustments to the protocol will be made. The duration of this stage may vary depending on how long it will take to achieve the approval. This process will be led by the principal investigator and the study coordinators.

STAGE 2: INITIAL COORDINATION (*March 2024 – April 2024*)

- **First meeting of the research team** (*March 2024*): the principal investigator, the study coordinator of each centre and the co-investigators of each centre will meet to discuss their roles and their organisation, and to address any issues they could have.
- **Database creation** (*March 2024 – April 2024*): a data manager will be hired by the principal investigator, to develop an online codified database.
- **Coordination with other units from both hospitals** (*March 2024 – April 2024*): several meetings will be scheduled between the main investigator, the study

coordinator of each hospital and the heads of all units that can prescribe glucocorticoid treatments to the study population from both hospitals. The protocol will be presented and explained to each head of unit in order to achieve its collaboration in the selection of patients that could enter into the study.

- **Training workshops** (*April 2024*): all the co-investigators will meet to attend a formation on how to perform the interviews with the study patients and how to use the measurement instruments of the study. The aim of this formation is to homogenise the process and to unify psychiatrists' criteria. This process will be led by the principal investigator and the co-investigators.

STAGE 3: SAMPLE RECRUITMENT, DATA COLLECTION AND FOLLOW-UP (*May 2024 – October 2026*)

- **Sample recruitment** (*May 2024 – May 2026*): a consecutive non-probabilistic sampling method will be used in each centre to achieve the sample size. The physicians from the collaborating units that prescribe corticoids to the study population will perform the preliminary selection of patients meeting the inclusion criteria and none of the exclusion criteria, and will give to them the patient information sheet (**Annex 7**) and the informed consent document (**Annex 8**). Then the definitive selection of patients will be done in the 1st visit by the coinvestigators if the patient has signed the informed consent.
- **Data collection and follow-up** (*May 2024 – October 2026*): each patient will be followed-up a maximum of 6 months, starting in the date when the patient is added to the study. In each follow-up visit, the data will be collected into the study database.

This process will be led by the whole team, except from the statistician. During this stage, at least once a year the principal investigator, the study coordinator of each centre and the co-investigators of each centre will meet to evaluate if the protocol is being carried out correctly.

STAGE 4: STATISTICAL ANALYSIS AND INTERPRETATION OF THE RESULTS (*November 2026 – February 2027*)

- **Statistical analysis** (*November 2026 – January 2027*): once the data has been collected a qualified statistician will be hired to perform the statistical analysis.
- **Interpretation of the results** (*February 2027*): the principal investigator, the study coordinators and the co-investigators will meet to discuss the results of the study and define the final conclusions.

STAGE 5: PUBLICATION AND DISSEMINATION OF THE RESULTS (*March 2027 – July 2027*)

In this stage, the principal investigator and the study coordinators will write the research article according to the results, in order to publish it in a scientific journal. The results will be also presented in national and international congresses.

11.3 CHRONOGRAM

Table 8. Chronogram.

	2023		2024												2025	2026			2027			
	Nov	Des	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Des	Jan-Des	Jan-May	Jun-Oct	Nov-Des	Jan	Feb	Mar-Apr	Jun-Jul
STAGE 0: STUDY DESIGN																						
Protocol development																						
Personnel recruitment																						
STAGE 1: ETHICAL EVALUATION AND STUDY APPROVAL																						
Ethical evaluation and study approval																						
STAGE 2: INITIAL COORDINATION																						
First meeting of the research team																						
Database creation																						
Coordination with other units from both hospitals																						
Training workshops																						
STAGE 3: SAMPLE RECRUITMENT, DATA COLLECTION AND FOLLOW-UP																						
Sample recruitment																						
Data collection and follow-up																						
STAGE 4: STATISTICAL ANALYSIS AND INTERPRETATION OF THE RESULTS																						
Statistical analysis																						
Interpretation of the results																						
STAGE 5: PUBLICATION AND DISSEMINATION OF THE RESULTS																						
Publication and dissemination of the results																						

12. BUDGET

12.1 PERSONNEL EXPENSES

Since the main research team (principal investigator, study coordinators and co-investigators) is composed by physicians who are employed by the hospitals included in the study, and the collaborators already work in the respective hospitals, their implication in the study will not imply an additional cost, as they will perform their duties as part of their work activity.

The only extra costs in terms of personnel will be hiring an independent statistician and a data manager.

The **data manager** approximated salary will be 35,00€/hour and we estimate approximately 200 hours of work, so it will have a total cost of 7.000,00€.

The **statistician** approximated salary will be 35,00€/hour and we estimate approximately 80 hours of work, so it will have a total cost of 2.800,00€.

12.2 EXECUTION EXPENSES

To perform this study, there are extra expenses derived from the need for additional material, such as:

- **MINI copyright license agreement**: both MINI and MINI Plus require a payment of 13,68€ (15$) per each administration. If all the patients underwent the totality of follow up visits, this would suppose a total of 1.020 administrations. The estimated total cost will be 13.953,60€.
- **MMSE forms**: this test has now been copyrighted and it is necessary to purchase every form. They are sold in packages of 25 forms, with a price of 38,72€ per package. Assuming a total of 1.020 possible administrations, we would need a total of 41 packages. The estimated total cost will be 1.587,52€.
- **Printing costs**: a cost of 0,05€/page will be considered. The estimated total cost will be 979,20€.
    - MINI printing: 204 administrations x 22 pages x 0,05 € = 224,40€

  - MINI Plus printing: 816 administrations x 16 pages x 0,05 € = 652,80€
  - PHQ-9 printing: 1020 administrations x 1 page x 0,05€ = 51,00€
  - Informed consent and patient information sheet printing: 204 administrations x 5 pages x 0,05€ = 51,00€
- **Urine LH-surge detection tests**: if we consider the improbable situation that all the patients start the study follow-up in the first day of their cycle and had a cycle of 35 days (the maximum to enter in the study) with the possibility of no detecting any positive result until next menstruation onset, we will need a total of 7.140 tests. With a cost of 0,30 €/test, the estimated total cost will be 2.142,00€.
- **CH50 determination**: the approximated cost of each determination is 7,04 €. With a total of 204 determinations, the total cost will be 3.060,00 €.
- **Albuminemia determination**: the approximated cost of each determination is 2,07€. With a total of 204 determinations, the total cost will be 285,60€.

As we consider this study unicentric due to the characteristics of the Psychiatric Unit in Girona, there will be no travel expenses related with the realisation of the meetings between the main research team.

12.3 RESULTS DISSEMINATION EXPENSES

- **Publication expenses**: we estimate that 2.000,00€ will be expended for the publication of the study results in a journal article.
- **Attendance to national and international congresses**: in order to disseminate the results of our study, we assume an estimated cost of 3.000,00€ for the attendance of two investigators to two congresses (one national and one international), considering the inscription costs and the expenses derived from the trip (assuming 1.000,00€ for the national congress and 2.000,00€ for the international congress).

Table 9. Estimated budget for the study.

	COST PER UNIT	NUMBER OF UNITS	SUBTOTAL
PERSONNEL EXPENSES			
Data manager	35,00€/hour	200 hours	7.000,00€
Statistician	35,00€/hour	80 hours	2.800,00€
EXECUTION EXPENSES			
MINI copyright license agreement	13,68€/administration	1.020 administrations	13.953,60€
MMSE forms	38,72€/25 forms package	41 packages	1.587,52€
MINI printing	0,05€/page	204 administrations x 22 pages	224,40€
MINI Plus printing	0,05€/page	816 administrations x 16 pages	652,80€
PHQ-9 printing	0,05€/page	1020 administrations x 1 page	51,00€
Informed consent and patient information sheet printing	0,05€/page	204 administrations x 5 pages	51,00€
Urine LH-surge detection tests	0,30€/test	35 tests x 204 participants	2.142,00€
CH50 determination	7,04€/determination	204 determinations	1.436,16€
Albuminemia determination	2,07€/determination	204 determinations	422,28€
RESULTS DISSEMINATION EXPENSES			
Publication expenses	2.000,00€/publication	1 publication	2.000,00€
Inscription and trip cost for the national congress	1.000,00€/congress	1 congress	1.000,00€
Inscription and trip cost for the international congress	2.000,00€/congress	1 congress	2.000,00€
TOTAL			**35.320,76€**

13. STUDY STRENGTHS AND LIMITATIONS

13.1 STUDY LIMITATIONS

- This study is a unicentric one, as all patients depend on the same Psychiatric Unit in the province of Girona.
- In participants' recruitment we use a non-probabilistic consecutive method, which could leave to a greater risk of a selection bias than other methods, due to the possibility of selecting a non-representative sample. This is tried to be minimised with the inclusion and exclusion criteria.
- This study only includes patients with corticotherapy at high dosages prescribed in the hospital, thus also leading to the possibility of a selection bias, as primary care patients could also be prescribed with this treatment but they are not considered in the study. This would need further research in a future.
- With regards to inclusion and exclusion criteria, we are only contemplating patients with a regular menstrual cycle in order to ensure that if we find a relationship between the variables, this is due to the cycle phase itself and no to specifics hormonal dysregulations of the patient. Moreover, we only include patients up to 45 years old because the likelihood of non-ovulatory cycles increases with age, especially as women approach to menopause onset.
- Patients with a current mental disorder or past but with a time from remission of less than 6 months are excluded from the study in order to avoid a confusion bias.
- As this is an observational study, we expect confusion bias to occur. In order to reduce this possibility, both bivariate and multivariate analysis will be carried out with all the potential confounding factors.
- A this is a prospective study, there is a risk of patients' loss during the follow-up process. However, to reduce it we have calculated the sample size with a drop-out rate of 10%.
- This study requires the coordination with all the units from both hospitals that could prescribe a glucocorticoid treatment at high dosages in their habitual practice, in order to obtain patients to participate in.

- There may be interprofessional variability when a diagnosis is done, even with the use of DSM-5-TR criteria. However, the use of validated measuring instruments and the training to perform the interviews in the follow-up visits aims to reduce this variability.

13.2 STUDY STRENGTHS

- This is the first study in the subject, as the relationship between glucocorticoid-induced neuropsychiatric disorders and menstrual cycle phase has never been explored before. Additionally, it would contribute to a better understanding of its etiopathogenesis, as the role of female sex as a risk factor is not yet fully understood. The results of this study could provide a valuable knowledge for the prevention of these disorders.
- This is a longitudinal study, which provides robustness to the results, compared to cross-sectional studies.
- This is a prospective study, which allows to prevent a memory bias.
- In order to determine the cycle phase of each individual, this study follows current evidence-based recommendations, with menstruation onset self-report and urine LH-surge determinations, to avoid imprecise methods that could lead to an information bias.
- The proposed follow-up method provides the possibility of avoiding the confusion between a glucocorticoid-induced neuropsychiatric disorder diagnosis and a primary disorder that could have been triggered by glucocorticoid usage.
- The interval of 1 month between follow-up visits (except from between the 4th and the 5th visit) allows to diagnose with a validated measurement instrument (the MINI Plus) a disorder that could have been successfully treated before the visit, thus avoiding a possible information bias.

14. FEASIBILITY

We believe this study to be feasible, as resources and methodology have been optimized to achieve the highest possible feasibility.

This is a unicentric study, as there is a common Psychiatric Unit in Girona, but actually with two hospitals, which allows for a higher quantity of potential participants. With our sample size of 204 patients, we estimate than the entire sample could be recruited within 1 year. However, to enhance the study's feasibility, we will dedicate 2 years to sample recruitment. This is because not all the patients with a prescription for high-dosage glucocorticoids will meet the inclusion criteria and none of the exclusion criteria. Moreover, not all those patients that meet the inclusion criteria and none of exclusion criteria will provide their informed consent.

In order to perform the sample recruitment, ensuring the collaboration of all the units from both hospitals that could prescribe a glucocorticoid treatment at high dosages in their habitual practice could be difficult. Nevertheless, there will be meetings with heads of those units to achieve it, and a period of two months will be assigned to this purpose.

All the professionals that will compose the research team are already working on those hospitals, so no additional hiring of health professionals will be required, only needing to hire a data manager and a statistician. Furthermore, these health professionals already have a great training and experience for the tasks to be developed throughout the study, but they will also attend training workshops to unify their criteria.

With regards to the budget, although it could be considered quietly high, we must take into account that this is a prospective cohort study with the use of biological samples, and other measuring tools (tests and structured interviews) that, although they are widely used in general practice, are copyrighted, and we must cover the expense.

In summary, we consider this study to be feasible, and that the potential benefits outweigh any possible inconveniences associated with its execution.

15. PROJECT IMPACT AND FUTURE PERSPECTIVES

Glucocorticoid-induced neuropsychiatric disorders appear in a 20% of patients receiving dosages of 40 mg/day or more of prednisone or its equivalent (15–17,21), and these drugs are some of the most used ones in daily practice. Consequently, due to the severe repercussions that these diagnoses can have in patients' life, prevention gains a relevant paper.

However, to develop an appropriate prophylactic strategy, first we must comprehend the processes involved on its physiopathology, such as the ones promoting a higher risk among women.

This project aims to discover whether menstruation cycle, due to its modifications on HPG axis, has an effect in glucocorticoid-induced neuropsychiatric disorders appearance, as glucocorticoids modify HPA axis, and we already know the existence of an interaction between HPG and HPA axis.

Therefore, proving this study main hypothesis of a higher risk when starting the treatment during follicular phase, we could design some prophylactic strategies, such as postponing the corticotherapy onset until the luteal phase if possible, or following the patient more closely if we must start the treatment during the follicular phase. Moreover, discovering which type of glucocorticoid-induced neuropsychiatric disorder women are more prone to develop depending on the phase when they start the treatment, could give us clues to its proper diagnosis and could highlight the importance of its prevention.

In addition, this is the first study to date that studies this possible relationship, thus possibly proportioning a valuable knowledge that could serve as a guide for future research. For example, future studies could focus on whether there is a specific event in follicular phase that promotes the higher risk among women, or could focus on proving different prophylactic strategies, as the ones proposed by us.

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17. ANNEXES

ANNEX 1. MAIN ADVERSE EFECTS OF GLUCOCORTICOIDS APART FROM NEUROPSYCHIATRIC ONES

Table 10. Main side-effects of glucocorticoids. Modified from (10).

SYSTEM AFFECTED	SIDE EFFECTS
Musculoskeletal	Osteoporosis Avascular necrosis of bone Myopathy
Endocrine and Metabolic	Hyperglycaemia Hypokalaemia Diabetes Mellitus Dyslipidaemia Weight gain Cushingoid features Growth suppression Adrenal suppression
Gastrointestinal	Gastritis Peptic ulcer Gastrointestinal bleeding Visceral perforation Hepatic steatosis Pancreatitis
Cardiovascular	Hypertension Coronary heart disease Ischemic heart disease Heart failure
Dermatologic	Dermatoprosis Skin atrophy Ecchymosis Purpura Erosions Striae Delayed wound healing Easy bruising Acne Hirsutism Hair loss
Ophthalmologic	Cataract Glaucoma Ptosis Mydriasis Opportunistic ocular infections Central serous chorioretinopathy
Immunologic	Suppression of cell-mediated immunity Predisposition to infections

ANNEX 2. DSM-5-TR SPECIFIC DIAGNOSTIC CRITERIA FOR ALL THE SUBSTANCE/MEDICATION-INDUCED MENTAL DISORDER ENTITIES

Adapted from (1).

SUBSTANCE/MEDICATION-INDUCED PSYCHOTIC DISORDER

A. Presence of one or both of the following symptoms:

1. Delusions.
2. Hallucinations.

B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to or withdrawal from a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by a psychotic disorder that is not substance/medication-induced. Such evidence of an independent psychotic disorder could include the following:

- The symptoms preceded the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence of an independent non-substance/medication-induced psychotic disorder (e.g., a history of recurrent non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: tis diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms in Criterion A predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Specify:
• **With onset during intoxication**: if criteria are met for intoxication with the substance and the symptoms develop during intoxication.
• **With onset during withdrawal**: if criteria are met for the withdrawal from the substance and the symptoms develop during, or shortly after, withdrawal.
• **With onset after medication use**: if symptoms developed at initiation of medication, with a change in use of medication, or during withdrawal of medication.
Specify current severity:
• Severity is rated by a quantitative assessment of the primary symptoms od psychosis, including delusions, hallucinations, abnormal psychomotor behaviour, and negative symptoms. Each of these symptoms may be rated for its current severity (most severe in the last 7 days) on a 5-point scale ranging from 0 (not present) to 4 (present and severe). • **Note**: diagnosis of substance/medication-induced psychotic disorder can be made without this severity specifier.

SUBSTANCE/MEDICATION-INDUCED BIPOLAR AND RELATED DISORDER

A. A prominent and persistent disturbance in mood that predominates in the clinical picture and is characterised by abnormally elevated, expansive, or irritable mood and abnormally increased activity or energy.
B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):
1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to or withdrawal from a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by a bipolar or related disorder that is not substance/medication-induced. Such evidence of an independent bipolar or related disorder could include the following:

- The symptoms precede the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced bipolar and related disorder (e.g., a history of recurrent non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress of impairment in social, occupational, or other important areas of functioning.

Note: this diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms in Criterion A predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Specify:

- **With onset during intoxication**: if criteria are met for intoxication with the substance and the symptoms develop during intoxication.
- **With onset during withdrawal**: if criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, withdrawal.
- **With onset after medication use**: if symptoms developed at initiation of medication, with a change in use of medication, or during withdrawal of medication.

SUBSTANCE/MEDICATION-INDUCED DEPRESSIVE DISORDER

A. A prominent and persistent disturbance in mood that predominates in the clinical picture and is characterised by depressed mood or markedly diminished interest or pleasure in all, or almost all, activities.

B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to or withdrawal from a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by a depressive disorder that is not substance/medication-induced. Such evidence of an independent depressive disorder could include the following:

- The symptoms preceded the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced depressive disorder (e.g., a history of recurrent non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: the diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when symptoms in Criterion A predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Specify:

- **With onset during intoxication**: if criteria are met for intoxication with the substance and the symptoms develop during intoxication.
- **With onset during withdrawal**: if criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, withdrawal.
- **With onset after medication use**: if symptoms developed at initiation of medication, with a change in use of medication, or during withdrawal of medication.

SUBSTANCE/MEDICATION-INDUCED ANXIETY DISORDER

A. Panic attacks or anxiety is predominant in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to or withdrawal from a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by an anxiety disorder that is not substance/medication-induced. Such evidence of an independent anxiety disorder could include the following:

- The symptoms precede the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced anxiety disorder (e.g., a history of recurrent non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: the diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when symptoms in Criterion A predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Specify:

- **With onset during intoxication**: if criteria are met for intoxication with the substance and the symptoms develop during intoxication.
- **With onset during withdrawal**: if criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, withdrawal.

- **With onset after medication use**: if symptoms developed at initiation of medication, with a change in use of medication, or during withdrawal of medication.

SUBSTANCE/MEDICATION-INDUCED OBSESSIVE-COMPULSIVE AND RELATED DISORDER

A. Obsessions, compulsions, skin picking, hair pulling, other body-focused repetitive behaviours, or other symptoms characteristic of the obsessive-compulsive and related disorders predominate in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to or withdrawal from a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by an obsessive-compulsive and related disorder that is not substance/medication-induced. Such evidence of an independent obsessive-compulsive and related disorder could include the following:

- The symptoms precede the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced obsessive-compulsive and related disorder (e.g., a history of recurrent non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: the diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when symptoms in Criterion A predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Specify:

- **With onset during intoxication**: if criteria are met for intoxication with the substance and the symptoms develop during intoxication.
- **With onset during withdrawal**: if criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, withdrawal.
- **With onset after medication use**: if symptoms developed at initiation of medication, with a change in use of medication, or during withdrawal of medication.

SUBSTANCE/MEDICATION-INDUCED SLEEP DISORDER

A. A prominent and severe disturbance in sleep.

B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to or withdrawal from a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by a sleep disorder that is not substance/medication-induced. Such evidence of an independent sleep disorder could include the following:

- The symptoms precede the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced sleep disorder (e.g., a history of recurrent non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: the diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when symptoms in Criterion A predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Specify whether:

- **Insomnia type**: characterised by difficulty falling asleep or maintaining sleep, frequent nocturnal awakenings, or nonrestorative sleep.
- **Daytime sleepiness type**: characterised by predominant complaint of excessive sleepiness/fatigue during waking hours or, less commonly, a long sleep period.
- **Parasomnia type**: characterised by abnormal behavioural events during sleep.
- **Mixed type**: characterised by a substance/medication-induced sleep problem characterised by multiple types of sleep symptoms, but no symptom clearly predominates.

Specify:

- **With onset during intoxication**: if criteria are met for intoxication with the substance and the symptoms develop during intoxication.
- **With onset during withdrawal**: if criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, withdrawal.
- **With onset after medication use**: if symptoms developed at initiation of medication, with a change in use of medication, or during withdrawal of medication.

SUBSTANCE/MEDICATION-INDUCED SEXUAL DYSFUNCTION

A. A clinically significant disturbance in sexual function is predominant in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to or withdrawal from a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by a sexual dysfunction that is not substance/medication-induced. Such evidence of an independent sexual dysfunction could include the following:

- The symptoms precede the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced sexual dysfunction (e.g., a history of recurrent non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: the diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when symptoms in Criterion A predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Specify:

- **With onset during intoxication**: if criteria are met for intoxication with the substance and the symptoms develop during intoxication.
- **With onset during withdrawal**: if criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, withdrawal.
- **With onset after medication use**: if symptoms developed at initiation of medication, with a change in use of medication, or during withdrawal of medication.

Specify current severity:

- **Mild:** occurs on 25%-50% of occasions of sexual activity.

- **Moderate**: occurs on 50%-75% of occasions of sexual activity.
- **Severe**: occurs on 75% or more of occasions of sexual activity.

DELIRIUM

Delirium is often seen as a differential diagnosis of all the other substance-induced mental disorders. However, we should take into account that delirium itself may have the specifier "medication-induced delirium", as exposed below:

A. A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) accompanied by reduced awareness of the environment.

B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.

C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).

D. The disturbances in Criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.

E. There us evidence from the history, physical examination, or laboratory findings, that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Specify if:

- **Acute**: lasting a few hours or days.
- **Persistent**: lasting weeks or months.

Specify if:

- **Hyperactive**: the individual has a hyperactive level of psychomotor activity that may be accompanied by mood lability, agitation, and/or refusal to cooperate with medical care.
- **Hypoactive**: the individual has a hypoactive level of psychomotor activity that may be accompanied by sluggishness and lethargy that approaches stupor.

- **Mixed level of activity**: the individual has a normal level of psychomotor activity even though attention and awareness are disturbed. Also includes individuals whose activity level rapidly fluctuates.

Specify whether:

- **Substance intoxication delirium**: this diagnosis should be made instead of substance intoxication when the symptoms in Criteria A and C predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.
- **Substance withdrawal delirium**: this diagnosis should be made instead of substance withdrawal when symptoms in Criteria A and C predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.
- **Medication-induced delirium**: this diagnosis applies when the symptoms in Criteria A and C arise as a side effect of a medication taken as prescribed.
- **Delirium due to another medical condition**: there is evidence from the history, physical examination, or laboratory findings that the disturbance is attributable to the physiological consequences of another medical condition.
- **Delirium due to multiple etiologies**: there is evidence from the history, physical examination, or laboratory findings that the delirium has more than one etiology (e.g., more than one etiological medical condition; another medical condition plus substance intoxication or medication side effect).

SUBSTANCE/MEDICATION-INDUCED MAJOR OR MILD NEUROCOGNITIVE DISORDER

A. The criteria are met for major or mild neurocognitive disorder.

B. The neurocognitive impairments do not occur exclusively during the course of a delirium and persist beyond the usual duration of intoxication and acute withdrawal.

C. The involved substance or medication and duration and extent of use are capable of producing the neurocognitive impairment.

D. The temporal course of the neurocognitive deficits is consistent with the timing of substance or medication use and abstinence (e.g., the deficits remain stable or improve after a period of abstinence).
E. The neurocognitive disorder is not attributable to another medical condition or is not better explained by another mental disorder.

ANNEX 3. MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (MINI)

Nombre del paciente: _____ Número de protocolo: _____
Fecha de nacimiento: _____ Hora en que inició la entrevista: _____
Nombre del entrevistador: _____ Hora en que terminó la entrevista: _____
Fecha de la entrevista: _____ Duración total: _____

	Módulos	*Periodo explorado*	*Cumple los criterios*	*DSM-IV*	*CIE-10*
A	EPISODIO DEPRESIVO MAYOR (EDM)	Actual (2 semanas)	☐	299.20-296.26 episodio único	F32.x
		Recidivante	☐	296.30-296.36 recidivante	F33.x
	EDM CON SÍNTOMAS MELANCÓLICOS (opcional)	Actual (2 semanas)	☐	296.20-296.26 episodio único 296.30-296.36 recidivante	F32.x F33.x
B	TRASTORNO DISTÍMICO	Actual (últimos 2 años)	☐		
C	RIESGO DE SUICIDIO	Actual (último mes)	☐	300.4	F34.1
		Riesgo: ☐ leve ☐ moderado ☐ alto	☐		
D	EPISODIO MANÍACO	Actual	☐	296.00-296.06	F30.x-F31.9
		Pasado	☐		
	EPISODIO HIPOMANÍACO	Actual	☐	296.80-296.89	F31.8-F31.9/F34.0
		Pasado	☐	300.01/300.21	F40.01-F41.0
E	TRASTORNO DE ANGUSTIA	Actual (último mes)	☐		
		De por vida	☐	300.22	F40.00
F	AGORAFOBIA	Actual	☐		
G	FOBIA SOCIAL (*Trastorno de ansiedad social*)	Actual (último mes)	☐	300.23	F40.1
H	TRASTORNO OBSESIVO-COMPULSIVO	Actual (último mes)	☐	300.3	F42.8
I	ESTADO POR ESTRÉS POSTRAUMÁTICO (opcional)	Actual (último mes)	☐	309.81	F43.1
J	DEPENDENCIA DE ALCOHOL	Últimos 12 meses	☐	303.9	F10.2x
	ABUSO DE ALCOHOL	Últimos 12 meses	☐	305.00	F10.1
K	DEPENDENCIA DE SUSTANCIAS (no alcohol)	Últimos 12 meses	☐	304.00-.90/305.20-.90	F11.1-F19.1
	ABUSO DE SUSTANCIAS (no alcohol)	Últimos 12 meses	☐	304.00-.90/305.20-.90	F11.1-F19.1
L	TRASTORNOS PSICÓTICOS	De por vida	☐	295.10-295.90/297.1	F20.xx-F29
		Actual	☐	297.3/293.81/293.82 293.89/298.8/298.9	
	TRASTORNO DEL ESTADO DEL ÁNIMO CON SÍNTOMAS PSICÓTICOS	Actual	☐	296.24	F32.3/F33.3
M	ANOREXIA NERVIOSA	Actual (últimos 3 meses)	☐	307.1	F50.0
N	BULIMIA NERVIOSA	Actual (últimos 3 meses)	☐	307.51	F50.2
	ANOREXIA NERVIOSA TIPO COMPULSIVA/PURGATIVA	Actual	☐	307.1	F50.0
O	TRASTORNO DE ANSIEDAD GENERALIZADA	Actual (últimos 6 meses)	☐	300.02	F41.1
P	TRASTORNO ANTISOCIAL DE LA PERSONALIDAD (opcional)	De por vida	☐	301.7	F60.2

MINI 5.0.0 (1 de enero de 2000)

Instrucciones generales

La MINI es una entrevista diagnóstica estructurada de breve duración que explora los principales trastornos psiquiátricos del Eje I del DSM-IV y la CIE-10. Estudios de validez y de confiabilidad se han realizado comparando la MINI con el SCID-P para el DSM-III-R y el CIDI (una entrevista estructurada desarrollada por la Organización Mundial de la Salud para entrevistadores no clínicos para la CIE-10). Los resultados de estos estudios demuestran que la MINI tiene una puntuación de validez y confiabilidad aceptablemente alta, pero puede ser administrada en un período de tiempo mucho más breve (promedio de 18,7 ± 11,6 minutos, media 15 minutos) que los instrumentos mencionados. Puede ser utilizada por clínicos tras una breve sesión de entrenamiento. Entrevistadores no clínicos deben recibir un entrenamiento más intenso.

ENTREVISTA:
Con el fin de hacer la entrevista lo más breve posible, informe al paciente que va a realizar una entrevista clínica que es más estructurada de lo usual, en la cual se le van a hacer unas preguntas precisas sobre sus problemas psicológicos y las cuales requieren unas respuestas de sí o no.

PRESENTACIÓN:
La MINI está dividida en módulos identificados por letras, cada uno corresponde a una categoría diagnóstica.
- Al comienzo de cada módulo (con excepción del módulo de los trastornos psicóticos), se presentan en un **recuadro gris**, una o varias preguntas «**filtro**» correspondientes a los criterios diagnósticos principales del trastorno.
- Al final de cada módulo, una o varias casillas diagnósticas permiten al clínico indicar si se cumplen los criterios diagnósticos.

CONVENIOS:
Las oraciones escritas en «letra normal» deben leerse «palabra por palabra» al paciente con el objetivo de regularizar la evaluación de los criterios diagnósticos.

Las oraciones escritas en «MAYÚSCULAS» no deben de leerse al paciente. Éstas son las instrucciones para asistir al entrevistador a calificar los algoritmos diagnósticos.

Las oraciones escritas en «**negrita**» indican el período de tiempo que se explora. El entrevistador debe leerlas tantas veces como sea necesario. Sólo aquellos síntomas que ocurrieron durante el período de tiempo explorado deben ser considerados al codificar las respuestas.

Respuestas con una flecha encima (➡) indican que no se cumple uno de los criterios necesarios para el diagnóstico. En este caso el entrevistador debe pasar directamente al final del módulo, rodear con un círculo «**NO**» en todas las casillas diagnósticas y continuar con el siguiente módulo.

Cuando los términos están separados por una barra (/) el entrevistador debe leer sólo aquellos síntomas que presenta el paciente (p. ej., la pregunta H6).

Frases entre paréntesis () son ejemplos clínicos de los síntomas evaluados. Pueden leerse para aclarar la pregunta.

INSTRUCCIONES DE ANOTACIÓN:
Todas las preguntas deben ser codificadas. La anotación se hace a la derecha de la pregunta enmarcando SÍ o NO.

El clínico debe asegurarse de que cada dimensión de la pregunta ha sido tomada en cuenta por el paciente (p. ej., período de tiempo, frecuencia, severidad, alternativas y/o).

Los síntomas que son mejor explicados por una causa médica o por el uso de alcohol o drogas no deben codificarse sí en la MINI. La MINI Plus tiene preguntas que explora estos problemas.

Para preguntas, sugerencias, sesiones de entrenamiento o información acerca de los últimos cambios en la MINI se puede comunicar con:

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MINI 5.0.0 (1 de enero de 2000)

A. Episodio depresivo mayor

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, RODEAR CON UN CÍRCULO **NO** EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

A1		¿En las últimas 2 semanas, se ha sentido deprimido o decaído la mayor parte del día, casi todos los días?	NO	SÍ	1
A2		¿En las últimas 2 semanas, ha perdido el interés en la mayoría de las cosas o ha disfrutado menos de las cosas que usualmente le agradaban?	NO	SÍ	2
		¿CODIFICÓ **SÍ** EN **A1** O EN **A2**?	➡ NO	SÍ	
A3		**En las últimas 2 semanas, cuando se sentía deprimido o sin interés en las cosas:**			
	a	¿Disminuyó o aumentó su apetito casi todos los días? ¿Perdió o ganó peso sin intentarlo (p. ej., variaciones en el último mes de ± 5 % de su peso corporal o ± 8 libras o ± 3,5 kg, para una persona de 160 libras/70 kg)? CODIFICAR **SÍ**, SI CONTESTÓ **SÍ** EN ALGUNA	NO	SÍ	3
	b	¿Tenía dificultad para dormir casi todas las noches (dificultad para quedarse dormido, se despertaba a media noche, se despertaba temprano en la mañana o dormía excesivamente)?	NO	SÍ	4
	c	¿Casi todos los días, hablaba o se movía usted más lento de lo usual, o estaba inquieto o tenía dificultades para permanecer tranquilo?	NO	SÍ	5
	d	¿Casi todos los días, se sentía la mayor parte del tiempo fatigado o sin energía?	NO	SÍ	6
	e	¿Casi todos los días, se sentía culpable o inútil?	NO	SÍ	7
	f	¿Casi todos los días, tenía dificultad para concentrarse o tomar decisiones?	NO	SÍ	8
	g	¿En varias ocasiones, deseó hacerse daño, se sintió suicida, o deseó estar muerto?	NO	SÍ	9
		¿CODIFICÓ **SÍ** EN **5** O MÁS RESPUESTAS (**A1-A3**)?	**NO**	**SÍ**	
					EPISODIO DEPRESIVO MAYOR ACTUAL

SI EL PACIENTE CODIFICA POSITIVO PARA UN EPISODIO DEPRESIVO MAYOR ACTUAL, CONTINÚE CON A4, DE LO CONTRARIO CONTINÚE CON EL MÓDULO B:

A4	a	¿En el transcurso de su vida, tuvo otros períodos de dos o más semanas, en los que se sintió deprimido o sin interés en la mayoría de las cosas y que tuvo la mayoría de los problemas de los que acabamos de hablar?	➡ NO	SÍ	10
	b	¿Ha tenido alguna vez un período de por lo menos dos meses, sin depresión o sin la falta de interés en la mayoría de las cosas y ocurrió este período entre dos episodios depresivos?	**NO**	**SÍ**	11
					EPISODIO DEPRESIVO MAYOR RECIDIVANTE

MINI 5.0.0 (1 de enero de 2000)

Episodio depresivo mayor con síntomas melancólicos (opcional)

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, RODEAR CON UN CÍRCULO **NO** Y CONTINUAR CON EL SIGUIENTE MÓDULO)

SI EL PACIENTE CODIFICA POSITIVO PARA UN EPISODIO DEPRESIVO MAYOR ACTUAL (**A3 = SÍ**), EXPLORAR LO SIGUIENTE:

A5	a	¿CODIFICÓ **SÍ** EN **A2**?	NO	SÍ	
	b	¿Durante el periodo más grave del episodio depresivo actual, perdió la capacidad de reaccionar a las cosas que previamente le daban placer o le animaban? **Si NO:** ¿Cuando algo bueno le sucede, no logra hacerle sentirse mejor aunque sea temporalmente?	NO	SÍ	12
		¿CODIFICÓ **SÍ** EN **A5a** O **A5b**?	➡ NO	SÍ	
A6		**Durante las últimas 2 semanas, cuando se sintió deprimido o sin interés en la mayoría de las cosas:**			
	a	¿Se sentía deprimido de una manera diferente al tipo de sentimiento que ha experimentado cuando alguien cercano a usted se ha muerto?	NO	SÍ	13
	b	¿Casi todos los días, por lo regular se sentía peor en las mañanas?	NO	SÍ	14
	c	¿Casi todos los días, se despertaba por lo menos dos horas antes de su hora habitual, y tenía dificultades para volver a dormirse?	NO	SÍ	15
	d	¿CODIFICÓ **SÍ** EN **A3c** (ENLENTECIMIENTO O AGITACIÓN PSICOMOTORA)?	NO	SÍ	
	e	¿CODIFICÓ **SÍ** EN **A3a** (ANOREXIA O PÉRDIDA DE PESO)?	NO	SÍ	
	f	¿Se sentía excesivamente culpable o era su sentimiento de culpa desproporcionado con la realidad de la situación?	NO	SÍ	16
		¿CODIFICÓ **SÍ** EN **3** O MÁS RESPUESTAS DE **A6**?	**NO**	**SÍ**	

EPISODIO DEPRESIVO MAYOR CON SÍNTOMAS MELANCÓLICOS ACTUAL

MINI 5.0.0 (1 de enero de 2000)

B. Trastorno distímico

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, RODEAR CON UN CÍRCULO **NO** Y CONTINUAR CON EL SIGUIENTE MÓDULO)

SI LOS SÍNTOMAS DEL PACIENTE ACTUALMENTE CUMPLEN CON LOS CRITERIOS DE UN EPISODIO DEPRESIVO MAYOR, NO EXPLORE ESTE MÓDULO

B1		¿En los últimos 2 años, se ha sentido triste, desanimado o deprimido la mayor parte del tiempo?	➡ NO	SÍ	17
B2		¿Durante este tiempo, ha habido algún período de 2 meses o más, en el que se haya sentido bien?	NO	➡ SÍ	18
B3		**Durante este período en el que se sintió deprimido la mayor parte del tiempo:**			
	a	¿Cambió su apetito notablemente?	NO	SÍ	19
	b	¿Tuvo dificultad para dormir o durmió en exceso?	NO	SÍ	20
	c	¿Se sintió cansado o sin energía?	NO	SÍ	21
	d	¿Perdió la confianza en sí mismo?	NO	SÍ	22
	e	¿Tuvo dificultades para concentrarse o para tomar decisiones?	NO	SÍ	23
	f	¿Tuvo sentimientos de desesperanza?	NO	SÍ	24
		¿CODIFICÓ **SÍ** EN **2** O MÁS RESPUESTAS DE **B3**?	➡ NO	SÍ	
B4		¿Estos síntomas de depresión, le causaron gran angustia o han interferido con su función en el trabajo, socialmente o de otra manera importante?	➡ NO	SÍ	25

¿CODIFICÓ **SÍ** EN **B4**?	NO	SÍ
	TRASTORNO DISTÍMICO ACTUAL	

MINI 5.0.0 (1 de enero de 2000)

C. Riesgo de suicidio

	Durante este último mes:			**Puntos:**
C1	¿Ha pensado que estaría mejor muerto, o ha deseado estar muerto?	NO	SÍ	1
C2	¿Ha querido hacerse daño?	NO	SÍ	2
C3	¿Ha pensado en el suicidio?	NO	SÍ	6
C4	¿Ha planeado cómo suicidarse?	NO	SÍ	10
C5	¿Ha intentado suicidarse?	NO	SÍ	10
	A lo largo de su vida:			
C6	¿Alguna vez ha intentado suicidarse?	NO	SÍ	4

¿CODIFICÓ **SÍ** EN POR LO MENOS **1** RESPUESTA?

NO	**SÍ**
RIESGO DE SUICIDIO	
1-5 puntos	Leve ☐
6-9 puntos	Moderado ☐
≥ 10 puntos	Alto ☐

SI **SÍ**, SUME EL NÚMERO TOTAL DE PUNTOS DE LAS RESPUESTAS (C1-C6) RODEAR CON UN CÍRCULO «SÍ» Y ESPECIFICAR EL NIVEL DE RIESGO DE SUICIDIO

MINI 5.0.0 (1 de enero de 2000)

D. Episodio (hipo)maníaco

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, RODEAR CON UN CÍRCULO **NO** EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

D1	a	¿Alguna vez ha tenido un período de tiempo en el que se ha sentido exaltado, eufórico, o tan lleno de energía, o seguro de sí mismo, que esto le ha ocasionado problemas u otras personas han pensado que usted no estaba en su estado habitual? (No considere períodos en el que estaba intoxicado con drogas o alcohol.) SI EL PACIENTE PARECE CONFUNDIDO O NO ENTIENDE A LO QUE SE REFIERE CON «EXALTADO» O «EUFÓRICO», CLARIFÍQUESELO DE LA SIGUIENTE MANERA: Lo que queremos decir con «exaltado o «eufórico» es un estado de satisfacción alto, lleno de energía, en el que se necesita dormir menos, en el que los pensamientos se aceleran, en el que se tienen muchas ideas, en el que aumenta la productividad, la creatividad, la motivación o el comportamiento impulsivo. SI **SÍ**:	NO	SÍ	1
	b	¿En este momento se siente «exaltado», «eufórico», o lleno de energía?	NO	SÍ	2
D2	a	¿Ha estado usted alguna vez persistentemente irritado durante varios días, de tal manera que tenía discusiones, peleaba o le gritaba a personas fuera de su familia? ¿Ha notado usted o los demás, que ha estado más irritable o que reacciona de una manera exagerada, comparado a otras personas, en situaciones que incluso usted creía justificadas? SI **SÍ:**	NO	SÍ	3
	b	¿En este momento se siente excesivamente irritable?	NO	SÍ	4
		¿CODIFICÓ **SÍ** EN **D1a** O EN **D2a**?	NO ➡	SÍ	
D3		SI **D1b** O **D2b = SÍ:** EXPLORAR SOLAMENTE EL EPISODIO **ACTUAL** SI **D1b** Y **D2b = NO:** EXPLORAR EL EPISODIO **PASADO** MÁS SINTOMÁTICO **Durante el tiempo en el que se sentía exaltado, lleno de energía, o irritable notó que:**			
	a	¿Sentía que podía hacer cosas que otros no podían hacer, o que usted era una persona especialmente importante?	NO	SÍ	5
	b	¿Necesitaba dormir menos (p. ej., se sentía descansado con pocas horas de sueño)?	NO	SÍ	6
	c	¿Hablaba usted sin parar o tan deprisa que los demás tenían dificultad para entenderle?	NO	SÍ	7
	d	¿Sus pensamientos pasaban tan deprisa por su cabeza que tenía dificultades para seguirlos?	NO	SÍ	8
	e	¿Se distraía tan fácilmente, que la menor interrupción le hacía perder el hilo de lo que estaba haciendo o pensando?	NO	SÍ	9
	f	¿Estaba tan activo, tan inquieto físicamente que los demás se preocupaban por usted?	NO	SÍ	10
	g	¿Quería involucrarse en actividades tan placenteras, que ignoró los riesgos o consecuencias (p. ej., se embarcó en gastos descontrolados, condujo imprudentemente o mantuvo actividades sexuales indiscretas)?	NO	SÍ	11
		¿CODIFICÓ **SÍ** EN **3** O MÁS RESPUESTAS DE **D3** (O **4** O MÁS RESPUESTAS SI **D1a** ES **NO** [EPISODIO PASADO] O SI **D1b** ES **NO** [EPISODIO ACTUAL])?	NO ➡	SÍ	

MINI 5.0.0 (1 de enero de 2000)

D4 ¿Duraron estos síntomas al menos 1 semana y le causaron problemas que estaban fuera de su control, en la casa, en el trabajo, en la escuela, o fue usted hospitalizado a causa de estos problemas?

NO SÍ 12

EL EPISODIO EXPLORADO ERA:

↓ ☐ *HIPOMANÍACO*

↓ ☐ *MANÍACO*

¿CODIFICÓ **NO** EN **D4**?

NO	SÍ
EPISODIO HIPOMANÍACO	
ACTUAL	☐
PASADO	☐

ESPECIFICAR SI EL EPISODIO ES ACTUAL O PASADO.

¿CODIFICÓ **SÍ** EN **D4**?

NO	SÍ
EPISODIO MANÍACO	
ACTUAL	☐
PASADO	☐

ESPECIFICAR SI EL EPISODIO ES ACTUAL O PASADO.

MINI 5.0.0 (1 de enero de 2000)

E. Trastorno de angustia

(➡ SIGNIFICA: RODEAR CON UN CÍRCULO **NO** EN **E5** Y PASAR DIRECTAMENTE A **F1**)

E1	a	¿En más de una ocasión, tuvo una crisis o ataques en los cuales se sintió **súbitamente** ansioso, asustado, incómodo o inquieto, incluso en situaciones en la cual la mayoría de las personas no se sentirían así?	➡ NO	SÍ	1
	b	¿Estas crisis o ataques alcanzan su máxima expresión en los primeros 10 minutos?	➡ NO	SÍ	2
E2		¿Alguna vez estas crisis o ataques o ocurrieron de una manera inesperada o espontánea u ocurrieron de forma impredecible o sin provocación?	NO	SÍ	3
E3		¿Ha tenido una de estas crisis seguida por un período de un mes o más en el que temía que otro episodio recurriera o se preocupaba por las consecuencias de la crisis?	NO	SÍ	4
E4		**Durante la peor crisis que usted puede recordar:**			
	a	¿Sentía que su corazón le daba un vuelco, latía más fuerte o más rápido?	NO	SÍ	5
	b	¿Sudaba o tenía las manos húmedas?	NO	SÍ	6
	c	¿Tenía temblores o sacudidas musculares?	NO	SÍ	7
	d	¿Sentía la falta de aliento o dificultad para respirar?	NO	SÍ	8
	e	¿Tenía sensación de ahogo o un nudo en la garganta?	NO	SÍ	9
	f	¿Notaba dolor o molestia en el pecho?	NO	SÍ	10
	g	¿Tenía náuseas, molestias en el estómago o diarreas repentinas?	NO	SÍ	11
	h	¿Se sentía mareado, inestable, aturdido o a punto de desvanecerse?	NO	SÍ	12
	i	¿Le parecía que las cosas a su alrededor eran irreales, extrañas, indiferentes, o no le parecían familiares, o se sintió fuera o separado de su cuerpo o de partes de su cuerpo?	NO	SÍ	13
	j	¿Tenía miedo de perder el control o de volverse loco?	NO	SÍ	14
	k	¿Tenía miedo de que se estuviera muriendo?	NO	SÍ	15
	l	¿Tenía alguna parte de su cuerpo adormecida o con hormigueos?	NO	SÍ	16
	m	¿Tenía sofocaciones o escalofríos?	NO	SÍ	17
E5		¿CODIFICÓ **SÍ** EN **E3** Y EN POR LO MENOS **4** DE **E4**?	NO	SÍ ***Trastorno de angustia de por vida***	
E6		SI **E5 = NO**, ¿CODIFICÓ **SÍ** EN ALGUNA RESPUESTA DE **E4**? SI **E6 = SÍ**, PASAR A **F1**.	NO	SÍ ***Crisis actual con síntomas limitados***	
E7		¿En el pasado mes, tuvo estas crisis en varias ocasiones (2 o más), seguidas de miedo persistente a tener otra?	NO	SÍ ***Trastorno de angustia actual***	18

MINI 5.0.0 (1 de enero de 2000)

F. Agorafobia

F1	¿Se ha sentido particularmente incómodo o ansioso en lugares o situaciones donde podría tener una crisis o ataque, o síntomas de una crisis como los que acabamos de discutir, o situaciones donde no dispondría de ayuda o escapar pudiera resultar un tanto difícil: como estar en una multitud, permanecer en fila, estar solo fuera de casa, permanecer solo en casa, viajar en autobús, tren o automóvil?	NO	SÍ	19

SI **F1 = NO**, RODEE CON UN CÍRCULO **NO** en **F2**.

F2	¿Teme tanto estas situaciones que las evita, sufre en ellas o necesita estar acompañado para enfrentarlas?	NO	SÍ *Agorafobia actual*	20

¿CODIFICÓ **NO** EN **F2** (AGORAFOBIA ACTUAL)

Y

CODIFICÓ **SÍ** EN **E7** (TRASTORNO DE ANGUSTIA ACTUAL)?

NO **SÍ**

TRASTORNO DE ANGUSTIA sin agorafobia ACTUAL

¿CODIFICÓ **SÍ** EN **F2** (AGORAFOBIA ACTUAL)

Y

CODIFICÓ **SÍ** EN **E7** (TRASTORNO DE ANGUSTIA ACTUAL)?

NO **SÍ**

TRASTORNO DE ANGUSTIA con agorafobia ACTUAL

¿CODIFICÓ **SÍ** EN **F2** (AGORAFOBIA ACTUAL)

Y

CODIFICÓ **NO** EN **E5** (TRASTORNO DE ANGUSTIA DE POR VIDA)?

NO **SÍ**

AGORAFOBIA ACTUAL sin historial de trastorno de angustia

MINI 5.0.0 (1 de enero de 2000)

G. Fobia social (trastorno de ansiedad social)

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, RODEAR CON UN CÍRCULO **NO** EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

G1	¿En el pasado mes, tuvo miedo o sintió vergüenza de que lo estén observando, de ser el centro de atención o temió una humillación? Incluyendo cosas como el hablar en público, comer en público o con otros, el escribir mientras alguien le mira o el estar en situaciones sociales.	➡ NO	SÍ	1
G2	¿Piensa usted que este miedo es excesivo o irracional?	➡ NO	SÍ	2
G3	¿Teme tanto estas situaciones sociales que las evita, o sufre en ellas?	➡ NO	SÍ	3
G4	¿Este miedo interfiere en su trabajo normal o en el desempeño de sus actividades sociales o es la causa de intensa molestia?	**NO**	**SÍ**	**4**

***FOBIA SOCIAL (trastorno de ansiedad social)* ACTUAL**

MINI 5.0.0 (1 de enero de 2000)

H. Trastorno obsesivo-compulsivo

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, MARCAR CON UN CÍRCULO **NO** Y CONTINUAR CON EL SIGUIENTE MÓDULO)

H1	¿Este último mes, ha estado usted molesto con pensamientos recurrentes, impulsos o imágenes no deseadas, desagradables, inapropiadas, intrusas o angustiosas? (p. ej., la idea de estar sucio, contaminado o tener gérmenes, **o** miedo de contaminar a otros, **o** temor de hacerle daño a alguien sin querer, **o** temor que actuaría en función de algún impulso, **o** tiene temores o supersticiones de ser el responsable de que las cosas vayan mal, **o** se obsesiona con pensamientos, imágenes o impulsos sexuales; **o** acumula o colecciona sin control, **o** tiene obsesiones religiosas) (NO INCLUIR PREOCUPACIONES EXCESIVAS POR PROBLEMAS DE LA VIDA COTIDIANA. NO INCLUIR OBSESIONES DIRECTAMENTE RELACIONADAS CON TRASTORNOS DE LA ALIMENTACIÓN, CONDUCTAS SEXUALES, PROBLEMAS PATOLÓGICOS RELACIONADOS CON EL JUEGO, ALCOHOL O ABUSO DE DROGAS, PORQUE EL PACIENTE PUDIERA DERIVAR PLACER DE LA ACTIVIDAD Y PUDIERA QUERER EVITARLA SIMPLEMENTE POR LAS CONSECUENCIAS NEGATIVAS)	NO ➡ H4	SÍ	1
H2	¿Estos pensamientos volvían a su mente aun cuando trataba de ignorarlos o de librarse de ellos?	NO ➡ H4	SÍ	2
H3	¿Cree usted que estos pensamientos son producto de su propia mente y que no le son impuestos desde el exterior?	NO	SÍ obsesiones	3
H4	¿En el pasado mes, ha hecho usted algo repetidamente, sin ser capaz de evitarlo, como lavar o limpiar en exceso, contar y verificar las cosas una y otra vez o repetir, coleccionar, ordenar las cosas o realizar otros rituales supersticiosos?	NO	SÍ compulsiones	4
	¿CODIFICÓ **SÍ** EN **H3** O EN **H4**?	➡ NO	SÍ	
H5	¿Reconoce usted que estas ideas obsesivas o actos compulsivos son irracionales, absurdos o excesivos?	➡ NO	SÍ	5
H6	¿Estas obsesiones o actos compulsivos interfieren de manera significativa con sus actividades cotidianas, con su trabajo, con sus relaciones sociales, o le ocupan más de una hora diaria?	**NO**	**SÍ**	**6**

TRASTORNO OBSESIVO/ COMPULSIVO ACTUAL

MINI 5.0.0 (1 de enero de 2000)

I. Estado por estrés postraumático (opcional)

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, RODEAR CON UN CÍRCULO **NO** Y CONTINUAR CON EL SIGUIENTE MÓDULO)

I1		¿Ha vivido o ha sido testigo de un acontecimiento extremadamente traumático, en el cual otras personas han muerto y/u otras personas o usted mismo han estado amenazadas de muerte o en su integridad física? EJEMPLOS DE ACONTECIMIENTOS TRAUMÁTICOS: ACCIDENTES GRAVES, ATRACO, VIOLACIÓN, ATENTADO TERRORISTA, SER TOMADO DE REHÉN, SECUESTRO, INCENDIO, DESCUBRIR UN CADÁVER, MUERTE SÚBITA DE ALGUIEN CERCANO A USTED, GUERRA O CATÁSTROFE NATURAL	➡ NO	SÍ	1
I2		¿Durante el pasado mes, ha revivido el evento de una manera angustiosa (p. ej., lo ha soñado, ha tenido imágenes vívidas, ha reaccionado físicamente o ha tenido memorias intensas)?	➡ NO	SÍ	2
I3		**En el último mes:**			
	a	¿Ha evitado usted pensar en este acontecimiento, o en todo aquello que se lo pudiese recordar?	NO	SÍ	3
	b	¿Ha tenido dificultad recordando alguna parte del evento?	NO	SÍ	4
	c	¿Ha disminuido su interés en las cosas que le agradaban o en las actividades sociales?	NO	SÍ	5
	d	¿Se ha sentido usted alejado o distante de otros?	NO	SÍ	6
	e	¿Ha notado que sus sentimientos están adormecidos?	NO	SÍ	7
	f	¿Ha tenido la impresión de que su vida se va a acortar debido a este trauma o que va a morir antes que otras personas?	NO	SÍ	8
		¿CODIFICÓ **SÍ** EN **3** O MÁS RESPUESTAS DE **I3**?	➡ NO	SÍ	
I4		**Durante el último mes:**			
	a	¿Ha tenido usted dificultades para dormir?	NO	SÍ	9
	b	¿Ha estado particularmente irritable o le daban arranques de coraje?	NO	SÍ	10
	c	¿Ha tenido dificultad para concentrarse?	NO	SÍ	11
	d	¿Ha estado nervioso o constantemente en alerta?	NO	SÍ	12
	e	¿Se ha sobresaltado fácilmente por cualquier cosa?	NO	SÍ	13
		¿CODIFICÓ **SÍ** EN **2** O MÁS RESPUESTAS DE **I3**?	➡ NO	SÍ	
I5		¿En el transcurso de este mes, han interferido estos problemas en su trabajo, en sus actividades sociales o han sido causa de gran ansiedad?	**NO**	**SÍ**	**14**

ESTADO POR ESTRÉS POSTRAUMÁTICO ACTUAL

MINI 5.0.0 (1 de enero de 2000)

J. Abuso y dependencia de alcohol

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, RODEAR CON UN CÍRCULO **NO** EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

J1		¿En los últimos 12 meses, ha tomado 3 o más bebidas alcohólicas en un período de 3 horas en tres o más ocasiones?	➡ NO	SÍ	1
J2		**En los últimos 12 meses:**			
	a	¿Necesitaba beber más para conseguir los mismos efectos que cuando usted comenzó a beber?	NO	SÍ	2
	b	¿Cuando reducía la cantidad de alcohol, temblaban sus manos, sudaba, o se sentía agitado? ¿Bebía para evitar estos síntomas o para evitar la resaca (p. ej., temblores, sudoraciones o agitación)? CODIFICAR **SÍ**, SI CONTESTÓ **SÍ** EN ALGUNA.	NO	SÍ	3
	c	¿Durante el tiempo en el que bebía alcohol, acababa bebiendo más de lo que en un principio había planeado?	NO	SÍ	4
	d	¿Ha tratado de reducir o dejar de beber alcohol pero ha fracasado?	NO	SÍ	5
	e	¿Los días en los que bebía, empleaba mucho tiempo en procurarse alcohol, en beber y en recuperarse de sus efectos?	NO	SÍ	6
	f	¿Pasó menos tiempo trabajando, disfrutando de sus pasatiempos, o estando con otros, debido a su consumo de alcohol?	NO	SÍ	7
	g	¿Continuó bebiendo a pesar de saber que esto le causaba problemas de salud, físicos o mentales?	NO	SÍ	8
		¿CODIFICÓ **SÍ** EN **3** O MÁS RESPUESTAS DE **J2**?	**NO**	➡ **SÍ**	
				DEPENDENCIA DE ALCOHOL ACTUAL	
J3		**En los últimos 12 meses:**			
	a	¿Ha estado usted varias veces intoxicado, embriagado, o con resaca en más de una ocasión, cuando tenía otras responsabilidades en la escuela, el trabajo o la casa? ¿Esto le ocasionó algún problema? CODIFIQUE **SÍ** SÓLO SI ESTO LE HA OCASIONADO PROBLEMAS.	NO	SÍ	9
	b	¿Ha estado intoxicado en alguna situación en la que corría un riesgo físico, por ejemplo conducir un automóvil, una motocicleta, una embarcación, utilizar una máquina, etc.)?	NO	SÍ	10
	c	¿Ha tenido problemas legales debido a su uso de alcohol, por ejemplo un arresto, perturbación del orden público?	NO	SÍ	11
	d	¿Ha continuado usted bebiendo a pesar de saber que esto le ocasionaba problemas con su familia u otras personas?	NO	SÍ	12
		¿CODIFICÓ **SÍ** EN **1** O MÁS RESPUESTAS DE **J3**?	**NO**	**SÍ**	
				ABUSO DE ALCOHOL ACTUAL	

MINI 5.0.0 (1 de enero de 2000)

K. Trastornos asociados al uso de sustancias psicoactivas no alcohólicas

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, RODEAR CON UN CÍRCULO **NO** EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

Ahora le voy a enseñar/leer una lista de sustancias ilícitas o medicinas.

K1 a **¿En los últimos 12 meses,** tomó alguna de estas sustancias, en más de una ocasión, para sentirse mejor o para cambiar su estado de ánimo? ➡ NO SÍ

RODEE CON UN CÍRCULO TODAS LAS SUSTANCIAS QUE HAYA USADO:

Estimulantes: anfetaminas, *speed*, cristal, dexedrina, ritalina, píldoras adelgazantes.
Cocaína: inhalada, intravenosa, crack, *speedball*.
Narcóticos: heroína, morfina, Dilaudid, opio, Demerol, metadona, codeína, Percodan, Darvon.
Alucinógenos: LSD (ácido), mescalina, peyote, PCP (polvo de ángel, *peace pill*), *psilocybin*, STP, hongos, éxtasis, MDA, MDMA.
Inhalantes: pegamento, éter, óxido nitroso (*laughing gas*), *amyl* o *butyl nitrate (poppers)*.
Marihuana: hachís, THC, pasto, hierba, mota, *reefer*.
Tranquilizantes: Qualude, Seconal («reds»), Valium, Xanax, Librium, Ativan, Dalmane, Halción, barbitúricos, «Miltown», Tranquimazin, Lexatin, Orfidal.
Otras sustancias: esteroides, pastillas dietéticas o para dormir sin receta. ¿Cualquier otra sustancia?
ESPECIFIQUE LA/S SUSTANCIA/S MÁS USADA/S: _____

b. SI EXISTE USO CONCURRENTE O SUCESIVO DE VARIAS SUSTANCIAS O DROGAS, ESPECIFIQUE QUÉ DROGA/CLASE DE DROGA VA A SER EXPLORADA EN LA ENTREVISTA A CONTINUACIÓN:

SÓLO UNA DROGA/CLASE DE DROGA HA SIDO UTILIZADA. ☐

SÓLO LA CLASE DE DROGA MÁS UTILIZADA ES EXPLORADA. ☐

CADA DROGA ES EXAMINADA INDIVIDUALMENTE. (FOTOCOPIAR K2 Y K3 SEGÚN SEA NECESARIO.) ☐

K2 **Considerando su uso de** (NOMBRE DE LA DROGA/CLASE DE DROGAS SELECCIONADA), **en los últimos 12 meses:**

a ¿Ha notado que usted necesitaba utilizar una mayor cantidad de (NOMBRE DE LA DROGA/CLASE DE DROGA SELECCIONADA) para obtener los mismos efectos que cuando comenzó a usarla? NO SÍ 1

b ¿Cuándo redujo la cantidad o dejó de utilizar (NOMBRE DE LA DROGA/CLASE DE DROGA SELECCIONADA) tuvo síntomas de abstinencia? (dolores, temblores, fiebre, debilidad, diarreas, náuseas, sudaciones, palpitaciones, dificultad para dormir, o se sentía agitado, ansioso, irritable o deprimido)? Utilizó alguna/s droga/s para evitar enfermarse (síntomas de abstinencia) o para sentirse mejor? NO SÍ 2

CODIFICAR **SÍ**, SI CONTESTÓ **SÍ** EN ALGUNA

c ¿Ha notado que cuando usted usaba (NOMBRE DE LA DROGA/CLASE DE DROGA SELECCIONADA) terminaba utilizando más de lo que en un principio había planeado? NO SÍ 3

d ¿Ha tratado de reducir o dejar de tomar (NOMBRE DE LA DROGA/CLASE DE DROGA SELECCIONADA) pero ha fracasado? NO SÍ 4

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	e	¿Los días que utilizaba (NOMBRE DE LA DROGA/CLASE DE DROGA SELECCIONADA) empleaba mucho tiempo (> 2 horas) en obtener, consumir, recuperarse de sus efectos, o pensando en drogas?	NO	SÍ	5
	f	¿Pasó menos tiempo trabajando, disfrutando de pasatiempos, estando con la familia o amigos debido a su uso de drogas?	NO	SÍ	6
	g	¿Ha continuado usando (NOMBRE DE LA DROGA/CLASE DE DROGA SELECCIONADA) a pesar de saber que esto le causaba problemas mentales o de salud?	NO	SÍ	7

¿CODIFICÓ **SÍ** EN **3** O MÁS RESPUESTAS DE **K2**?
ESPECIFICAR LA/S DROGA/S: _____

NO	➡ SÍ
DEPENDENCIA DE SUSTANCIAS ACTUAL	

Considerando su uso de (NOMBRE DE LA CLASE DE DROGA SELECCIONADA), **en los últimos 12 meses:**

K3	a	¿Ha estado intoxicado o con resaca a causa de (NOMBRE DE LA DROGA/CLASE DE DROGA SELECCIONADA), en más de una ocasión, cuando tenía otras responsabilidades en la escuela, en el trabajo o en el hogar? ¿Esto le ocasionó algún problema? (CODIFIQUE **SÍ**, SÓLO SI LE OCASIONÓ PROBLEMAS)	NO	SÍ	8
	b	¿Ha estado intoxicado con (NOMBRE DE LA DROGA/CLASE DE DROGA SELECCIONADA) en alguna situación en la que corriese un riesgo físico (p. ej., conducir un automóvil, una motocicleta, una embarcación, o utilizar una máquina, etc.)?	NO	SÍ	9
	c	¿Ha tenido algún problema legal debido a su uso de drogas, por ejemplo, un arresto o perturbación del orden público?	NO	SÍ	10
	d	¿Ha continuado usando (NOMBRE DE LA DROGA/CLASE DE DROGA SELECCIONADA) a pesar de saber que esto le causaba problemas con su familia u otras personas?	NO	SÍ	11

¿CODIFICÓ **SÍ** EN **1** O MÁS RESPUESTAS DE **K3**?
ESPECIFICAR LA/S DROGA/S: _____

NO	SÍ
ABUSO DE SUSTANCIAS ACTUAL	

MINI 5.0.0 (1 de enero de 2000)

L. Trastornos psicóticos

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, RODEAR CON UN CÍRCULO **NO** EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

PIDA UN EJEMPLO PARA CADA PREGUNTA CONTESTADA AFIRMATIVAMENTE. CODIFIQUE **SÍ** SOLAMENTE PARA AQUELLOS EJEMPLOS QUE MUESTRAN CLARAMENTE UNA DISTORSIÓN DEL PENSAMIENTO O DE LA PERCEPCIÓN O SI NO SON CULTURALMENTE APROPIADOS. ANTES DE CODIFICAR, INVESTIGUE SI LAS IDEAS DELIRANTES CALIFICAN COMO «EXTRAÑAS» O RARAS.

LAS IDEAS DELIRANTES SON «EXTRAÑAS» O RARAS SI: SON CLARAMENTE ABSURDAS, IMPROBABLES, INCOMPRENSIBLES, Y NO PUEDEN DERIVARSE DE EXPERIENCIAS DE LA VIDA COTIDIANA.

LAS ALUCINACIONES SON «EXTRAÑAS» O RARAS SI: UNA VOZ HACE COMENTARIOS SOBRE LOS PENSAMIENTOS O LOS ACTOS DE LA PERSONA, O DOS O MÁS VOCES CONVERSAN ENTRE SÍ.

		Ahora le voy a preguntar acerca de experiencias poco usuales que algunas personas pueden tener.			EXTRAÑOS	
L1	a	¿Alguna vez ha tenido la impresión de que alguien le espiaba, o conspiraba contra usted, o que trataban de hacerle daño? **NOTA:** PIDA EJEMPLOS PARA DESCARTAR UN VERDADERO ACECHO.	NO	SÍ	SÍ	1
	b	**Si SÍ:** ¿Actualmente cree usted esto?	NO	SÍ	SÍ ➡ L6	2
L2	a	¿Ha tenido usted la impresión de que alguien podía leer o escuchar sus pensamientos, o que usted podía leer o escuchar los pensamientos de otros?	NO	SÍ	SÍ	3
	b	**Si SÍ:** ¿Actualmente cree usted esto?	NO	SÍ	SÍ ➡ L6	4
L3	a	¿Alguna vez ha creído que alguien o que una fuerza externa haya metido pensamientos ajenos en su mente o le hicieron actuar de una manera no usual en usted? Alguna vez ha tenido la impresión de que está poseído? ENTREVISTADOR/A: PIDA EJEMPLOS Y DESCARTE CUALQUIERA QUE NO SEA PSICÓTICO.	NO	SÍ	SÍ	5
	b	**Si SÍ:** ¿Actualmente cree usted esto?	NO	SÍ	SÍ ➡ L6	6
L4	a	¿Alguna vez ha creído que le envían mensajes especiales a través de la radio, el televisor o el periódico, o que una persona que no conocía personalmente se interesaba particularmente por usted?	NO	SÍ	SÍ	7
	b	**Si SÍ:** ¿Actualmente cree usted esto?	NO	SÍ	SÍ ➡ L6	8
L5	a	¿Consideran sus familiares o amigos que algunas de sus creencias son extrañas o poco usuales? ENTREVISTADOR/A: PIDA EJEMPLOS. CODIFIQUE **SÍ** SÓLO SI LOS EJEMPLOS SON **CLARAMENTE** IDEAS DELIRANTES NO EXPLORADAS EN LAS PREGUNTAS L1 A L4, POR EJEMPLO, DELIRIOS SOMÁTICOS, RELIGIOSOS O DE GRANDEZA, CELOS, CULPA, RUINA O DESTITUCIÓN, ETC.	NO	SÍ	SÍ	9
	b	**Si SÍ:** ¿Actualmente, consideran los demás sus ideas como extrañas?	NO	SÍ	SÍ	10
L6	a	¿Alguna vez ha escuchado cosas que otras personas no podían escuchar, como voces?	NO	SÍ		11
		LAS ALUCINACIONES SON CODIFICADAS COMO «EXTRAÑAS» SOLAMENTE SI EL PACIENTE CONTESTA **SÍ** A LO SIGUIENTE:				
		Si SÍ: ¿Escuchó una voz que comentaba acerca de sus pensamientos o sus actos, o escuchó dos o más voces conversando entre sí?			SÍ	
	b	**Si SÍ:** ¿Ha escuchado estas cosas en el pasado mes?	NO	SÍ	SÍ ➡ L8b	12

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L7	a	¿Alguna vez, estando despierto, ha tenido visiones o ha visto cosas que otros no podían ver? ENTREVISTADOR/A: INVESTIGUE SI ESTAS VISIONES SON CULTURALMENTE INAPROPIADAS.	NO	SÍ	13
	b	**Si SÍ:** ¿Ha visto estas cosas el pasado mes?	NO	SÍ	14
		BAJO EL PUNTO DE VISTA DEL ENTREVISTADOR/a:			
L8	b	¿PRESENTA EL PACIENTE ACTUALMENTE UN LENGUAJE DESORGANIZADO, INCOHERENTE O CON MARCADA PÉRDIDA DE LAS ASOCIACIONES?	NO	SÍ	15
L9	b	¿PRESENTA EL PACIENTE ACTUALMENTE UN COMPORTAMIENTO DESORGANIZADO O CATATÓNICO?	NO	SÍ	16
L10	b	¿HAY SÍNTOMAS NEGATIVOS DE ESQUIZOFRENIA PROMINENTES DURANTE LA ENTREVISTA (UN APLANAMIENTO AFECTIVO SIGNIFICATIVO, POBREZA DEL LENGUAJE [ALOGIA] O INCAPACIDAD PARA INICIAR O PERSISTIR EN ACTIVIDADES CON UNA FINALIDAD DETERMINADA)?	NO	SÍ	17
L11		¿CODIFICÓ **SÍ EXTRAÑO** EN 1 O MÁS PREGUNTAS «b»? o ¿CODIFICÓ **SÍ** (EN VEZ DE **SÍ EXTRAÑO**) EN 2 O MÁS PREGUNTAS «b»?	**NO**	**SÍ** ***TRASTORNO PSICÓTICO* ACTUAL**	
L12		¿CODIFICÓ **SÍ EXTRAÑO** EN 1 O MÁS PREGUNTAS «a»? o ¿CODIFICÓ **SÍ** (EN VEZ DE **SÍ EXTRAÑO**) EN 2 O MÁS PREGUNTAS «a»? VERIFIQUE QUE LOS DOS SÍNTOMAS OCURRIERAN DURANTE EL MISMO PERÍODO DE TIEMPO o ¿CODIFICÓ **SÍ** EN **L11**?	**NO**	**SÍ** 18 ***TRASTORNO PSICÓTICO* DE POR VIDA**	
L13	a	¿CODIFICÓ **SÍ** EN 1 O MÁS PREGUNTAS DE **L1b** A **L7b** Y CODIFICÓ **SÍ** EN EPISODIO DEPRESIVO MAYOR (ACTUAL) o EPISODIO MANÍACO (ACTUAL O PASADO)?	➡ NO	SÍ	
	b	SI CODIFICÓ SÍ EN L1EA: Anteriormente me dijo que usted tuvo un período/s en el que se sintió (deprimido[a]/exaltado[a]/particularmente irritable). Estas creencias o experiencias que me acaba de describir (SÍNTOMAS CODIFICADOS SÍ DE **L1b** a **L7b**) ¿Se limitaban exclusivamente a los períodos en los que se sintió deprimido(a)/exaltado(a)/irritable?	**NO**	**SÍ** 19 **TRASTORNO DEL ESTADO DE ÁNIMO** *CON SÍNTOMAS PSICÓTICOS* **ACTUAL**	

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M. Anorexia nerviosa

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, RODEAR CON UN CÍRCULO **NO** EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

M1	a	¿Cuál es su estatura?	☐ pies ☐ ☐ pulgadas ☐ ☐ ☐ cm	
	b	¿En los últimos 3 meses, cuál ha sido su peso más bajo?	☐ ☐ ☐ libras ☐ ☐ ☐ kg	
	c	¿ES EL PESO DEL PACIENTE INFERIOR AL PESO MÍNIMO CORRESPONDIENTE A SU ESTATURA (VER TABLA A CONTINUACIÓN)?	➡ NO	SÍ

En los últimos 3 meses:

M2		¿A pesar de su bajo peso, evitaba engordar?	➡ NO	SÍ	1
M3		¿A pesar de estar bajo peso, temía ganar peso o ponerse gordo/a?	➡ NO	SÍ	2
M4	a	¿Se consideraba gordo, o que una parte de su cuerpo era demasiado gorda?	NO	SÍ	3
	b	¿Influyó mucho su peso o su figura en la opinión que usted tenía de sí mismo?	NO	SÍ	4
	c	¿Pensaba usted que su bajo peso era normal o excesivo?	NO	SÍ	5
M5		¿CODIFICÓ **SÍ** EN UNA O MÁS RESPUESTAS DE **M4**?	➡ NO	SÍ	
M6		SÓLO PARA MUJERES: ¿En los últimos 3 meses, dejó de tener todos sus períodos menstruales, aunque debió tenerlos (cuando no estaba embarazada)?	➡ NO	SÍ	6

PARA MUJERES: ¿CODIFICÓ **SÍ** EN **M5** Y **M6**?

PARA HOMBRES: ¿CODIFICÓ **SÍ** EN **M5**?

NO	SÍ
ANOREXIA NERVIOSA ACTUAL	

TABLA UMBRAL DE ESTATURA/PESO MÍNIMO (estatura sin zapatos; peso sin ropa)

Mujer estatura/peso

Pies/pulgadas	4,9	4,10	4,11	5,0	5,1	5,2	5,3	5,4	5,5	5,6	5,7	5,8	5,9	5,10
Libras	84	85	86	87	89	92	94	97	99	102	104	107	110	112
cm	144,8	147,3	149,9	152,4	154,9	157,5	160,0	162,6	165,1	167,6	170,2	172,7	175,3	177,8
kg	38	39	39	40	41	42	43	44	45	46	47	49	50	51

Hombre estatura/peso

Pies/pulgadas	5,1	5,2	5,3	5,4	5,5	5,6	5,7	5,8	5,9	5,10	5,11	6,0	6,1	6,2	6,3
Libras	105	106	108	110	111	113	115	116	118	120	122	125	127	130	133
cm	154,9	157,5	160,0	162,6	165,1	167,6	170,2	172,7	175,3	177,8	180,3	182,9	185,4	188,0	190,5
kg	47	48	49	50	51	51	52	53	54	55	56	57	58	59	61

Los umbrales de pesos anteriormente mencionados son calculados con un 15 % por debajo de la escala normal de la estatura y sexo del paciente como es requerido por el DSM-IV. Esta tabla refleja los pesos con un 15 % por debajo del límite inferior de la escala de distribución normal de la *Metropolitan Life Insurance Table of Weights*.

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N. Bulimia nerviosa

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, RODEAR CON UN CÍRCULO **NO** EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

N1	¿En los últimos 3 meses, se ha dado usted atracones, en los cuales comía grandes cantidades de alimentos en un período de 2 horas?	➡ NO	SÍ	7
N2	¿En los últimos 3 meses, se ha dado usted al menos 2 atracones por semana?	➡ NO	SÍ	8
N3	¿Durante estos atracones, se siente descontrolado comiendo?	➡ NO	SÍ	9
N4	¿Hace usted algo para compensar o evitar ganar peso como consecuencia de estos atracones, como vomitar, ayunar, practicar ejercicio, tomar laxantes, enemas, diuréticos (pastillas de agua) u otros medicamentos?	➡ NO	SÍ	10
N5	¿Influye grandemente en la opinión que usted tiene de sí mismo su peso o la figura de su cuerpo?	➡ NO	SÍ	11
N6	¿CUMPLEN LOS SÍNTOMAS DEL PACIENTE CON LOS CRITERIOS DE ANOREXIA NERVIOSA?	NO ↓ Ir a N8	SÍ	
N7	¿Ocurren estos atracones solamente cuando está por debajo de (_____libras/kg)? (ENTREVISTADOR/A: ESCRIBA EN EL PARÉNTESIS EL PESO MÍNIMO DE ESTE PACIENTE EN RELACIÓN A SU ESTATURA, BASADO EN LA TABLA DE ESTATURA/PESO QUE SE ENCUENTRA EN EL MÓDULO DE ANOREXIA NERVIOSA.)	NO	SÍ	12

N8	¿CODIFICÓ **SÍ** EN **N5** O CODIFICÓ **NO** EN **N7** O SALTÓ A **N8**?	**NO**	**SÍ** → ***BULIMIA NERVIOSA*** **ACTUAL**
	¿CODIFICÓ **SÍ** EN **N7**?	**NO**	**SÍ** → ***ANOREXIA NERVIOSA*** *TIPO COMPULSIVO/PURGATIVO* **ACTUAL**

MINI 5.0.0 (1 de enero de 2000)

O. Trastorno de ansiedad generalizada

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, RODEAR CON UN CÍRCULO **NO** EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

O1	a	¿Se ha sentido excesivamente preocupado o ansioso debido a varias cosas durante los últimos 6 meses?	➡ NO	SÍ	1
	b	¿Se presentan estas preocupaciones casi todos los días?	➡ NO	SÍ	2
		CODIFICAR SÍ, SI LA ANSIEDAD DEL PACIENTE ES RESTRINGIDA EXCLUSIVAMENTE, O MEJOR EXPLICADA POR CUALQUIERA DE LOS TRASTORNOS PREVIAMENTE DISCUTIDOS.	NO	➡ SÍ	3
O2		¿Le resulta difícil controlar estas preocupaciones o interfieren para concentrarse en lo que hace?	➡ NO	SÍ	4
O3		CODIFIQUE **NO** SI LOS SÍNTOMAS SE LIMITAN A RASGOS DE CUALQUIERA DE LOS TRASTORNOS PREVIAMENTE EXPLORADOS.			
		En los últimos 6 meses cuando estaba ansioso, casi todo el tiempo:			
	a	¿Se sentía inquieto, intranquilo o agitado?	NO	SÍ	5
	b	¿Se sentía tenso?	NO	SÍ	6
	c	¿Se sentía cansado, flojo o se agotaba fácilmente?	NO	SÍ	7
	d	¿Tenía dificultad para concentrarse, o notaba que la mente se le quedaba en blanco?	NO	SÍ	8
	e	¿Se sentía irritable?	NO	SÍ	9
	f	¿Tenía dificultad durmiendo (dificultad para quedarse dormido, se despertaba a media noche o demasiado temprano, o dormía en exceso)?	NO	SÍ	10
		¿CODIFICÓ **SÍ** EN **3** O MÁS RESPUESTAS DE **O3**?	**NO**	**SÍ**	
				TRASTORNO DE ANSIEDAD GENERALIZADA ACTUAL	

MINI 5.0.0 (1 de enero de 2000)

P. Trastorno antisocial de la personalidad (opcional)

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS Y RODEAR CON UN CÍRCULO **NO**)

P1		**Antes de cumplir los 15 años:**			
	a	¿Faltaba a la escuela o se escapaba y dormía fuera de casa con frecuencia?	NO	SÍ	1
	b	¿Mentía, hacía trampa, estafaba o robaba con frecuencia?	NO	SÍ	2
	c	¿Iniciaba peleas o incitaba a otros, los amenazaba o los intimidaba?	NO	SÍ	3
	d	¿Destruía cosas deliberadamente o empezaba fuegos?	NO	SÍ	4
	e	¿Maltrataba a los animales o a las personas deliberadamente?	NO	SÍ	5
	f	¿Forzó a alguien a tener relaciones sexuales con usted?	NO	SÍ	6
		¿CODIFICÓ **SÍ** EN **2** O MÁS RESPUESTAS DE **P1**?	NO ➡	SÍ	
		NO CODIFIQUE **SÍ**, SI LA CONDUCTA ES SÓLO POR MOTIVOS POLÍTICOS O RELIGIOSOS.			
P2		**Después de cumplir los 15 años:**			
	a	¿Se ha comportado repetidamente de una forma que otros considerarían irresponsable, como no pagar sus deudas, ser deliberadamente impulsivo o deliberadamente no trabajar para mantenerse?	NO	SÍ	7
	b	¿Ha hecho cosas que son ilegales incluso si no ha sido descubierto (p. ej., destruir la propiedad, robar artículos en las tiendas, hurtar, vender drogas o cometer algún tipo de delito)?	NO	SÍ	8
	c	¿Ha participado repetidamente en peleas físicas (incluyendo las peleas que tuviera con su cónyuge o con sus hijos)?	NO	SÍ	9
	d	¿Ha mentido o estafado a otros con el objetivo de conseguir dinero o por placer, o mintió para divertirse?	NO	SÍ	10
	e	¿Ha expuesto a otros a peligros sin que le importara?	NO	SÍ	11
	f	¿No ha sentido culpabilidad después de hacerle daño a otros, maltratarlos, mentirles o robarles, o después de dañar la propiedad de otros?	NO	SÍ	12

¿CODIFICÓ **SÍ** EN **3** O MÁS RESPUESTAS DE **P2**?

NO	SÍ
TRASTORNO ANTISOCIAL DE LA PERSONALIDAD **DE POR VIDA**	

MINI 5.0.0 (1 de enero de 2000)

ANNEX 4. MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW PLUS (MINI PLUS)

Nombre del paciente: _____ *Número de protocolo:* _____

Fecha de nacimiento: *Hora en que inició la entrevista:*

Nombre del entrevistador: _____ *Hora en que terminó la entrevista:* _____

Fecha de la entrevista: _____ *Duración total:* _____

	MÓDULOS	PERÍODO EXPLORADO	CUMPLE LOS CRITERIOS	DSM-IV	ICD-10
A	EPISODIO DEPRESIVO MAYOR	Actual (2 semanas)	❑	296.20-296.26 Unico	F32.x
		Pasado	❑	296.30-296.36 Recidivante	F33.x
	TRASTORNO DEL ESTADO DEL ÁNIMO DEBIDO	Actual	❑	293.83	F06.xx
	A UNA ENFERMEDAD MÉDICA	Pasado	❑	293.83	F06.xx
	TRASTORNO DEL ESTADO DEL ÁNIMO	Actual	❑	29x.xx	none
	INDUCIDO POR SUSTANCIAS	Pasado	❑	29x.xx	none
	EDM CON SÍNTOMAS MELANCÓLICOS	Actual (2 semanas)	❑	296.20-296.26 Unico 296.30-296.36 Recurrente	F32.x F33.x
B	TRASTORNO DISTÍMICO	Actual (Últimos 2 años)	❑	300.4	F34.1
		Pasado	❑	300.4	F34.1
C	RIESGO DE SUICIDIO	Actual (Último mes)	❑	ninguno	ninguno
		Riesgo: ❑ Leve ❑ Moderado ❑ Alto			
D	EPISODIO MANÍACO	Actual	❑	296.00-296.06	F30.x-F31.9
		Pasado	❑	296.00-296.06	F30.x-F31.9
	EPISODIO HIPOMANÍACO	Actual	❑	296.80-296.89	F31.8-F31.9/F34.0
		Pasado	❑	296.80-296.89	F31.8-F31.9/F34.0
	BIPOLAR II DISORDER	Actual	❑	296.89	F31.8
		Pasado	❑	296.89	F31.8
	EPISODIO MANÍACO DEBIDO A UNA ENFERMEDAD MÉDICA	Actual	❑	293.83	F06.30
		Pasado	❑	293.83	F06.30
	EPISODIO HIPOMANÍACO DEBIDO A UNA ENFERMEDAD MÉDICA	Actual	❑	293.83	ninguno
		Pasado	❑	293.83	ninguno
	EPISODIO MANÍACO INDUCIDO POR SUSTANCIAS	Actual	❑	291.8-292.84	ninguno
		Pasado	❑	291.8-292.84	ninguno
	EPISODIO HIPOMANÍACO INDUCIDO POR SUSTANCIAS	Actual	❑	291.8-292.84	ninguno
		Pasado	❑	291.8-292.84	ninguno
E	TRASTORNO DE ANGUSTIA	Actual (Último mes)	❑	300.01/300.21	F40.01-F41.0
		De por Vida	❑	300.01/300.21	F40.01-F41.0
	TRASTORNO DE ANSIEDAD CON CRISIS DE ANGUSTIA DEBIDO A UNA ENFERMEDAD MÉDICA	Actual	❑	293.89	F06.4
	TRASTORNO DE ANSIEDAD CON CRISIS DE ANGUSTIA INDUCIDO POR SUSTANCIAS	Actual	❑	291.8-292.89	ninguno
F	AGORAFOBIA	Actual	❑	300.22	F40.00
G	FOBIA SOCIAL (Trastorno de Ansiedad Social)	Actual (Último mes)	❑	300.23	F40.1
H	FOBIA ESPECÍFICA	Actual	❑	300.29	F40.2
I	TRASTORNO OBSESIVO-COMPULSIVO (TOC)	Actual (Último mes)	❑	300.3	F42.8
	TOC DEBIDO A UNA ENFERMEDAD MÉDICA	Actual	❑	293.89	F06.4
	TOC INDUCIDO POR SUSTANCIAS	Actual	❑	291.8-292.89	none
J	ESTADO POR ESTRES POSTRAUMÁTICO	Actual (Último mes)	❑	309.81	F43.1
K	DEPENDENCIA DE ALCOHOL	Últimos 12 Meses	❑	303.9	F10.2x
	DEPENDENCIA DE ALCOHOL	De por Vida	❑	303.9	F10.2x
	ABUSO DE ALCOHOL	Últimos 12 Meses	❑	305.00	F10.1
	ABUSO DE ALCOHOL	De por Vida	❑	305.00	F10.1
L	DEPENDENCIA DE SUSTANCIAS (No-alcohólicas)	Últimos 12 Meses	❑	304.00-.90/305.20-.90	F11.0-F19.1
	DEPENDENCIA DE SUSTANCIAS (No-alcohólicas)	De por Vida	❑	304.00-.90/305.20-.90	F11.0-F19.1
	ABUSO DE SUSTANCIAS (No-alcohólicas)	Últimos 12 Meses	❑	304.00-.90/305.20-.90	F11.0-F19.1
M	TRASTORNOS PSICOTICOS	De por Vida	❑	295.10-295.90/297.1/	F20.xx-F29
		Actual	❑	297.3/293.81/293.82/ 293.89/298.8/298.9	
	TRASTORNO DEL ESTADO DEL ÁNIMO CON SÍNTOMAS PSICÓTICOS	Actual	❑	296.24	F32.3/F33.3
	ESQUIZOFRENIA	Actual	❑	295.10-295.60	F20.xx
		De por Vida	❑	295.10-295.60	F20.xx
	TRASTORNO ESQUIZOAFECTIVO	Actual	❑	295.70	F25.x
		De por Vida	❑	295.70	F25.x
	TRASTORNO ESQUIZOFRENIFORME	Actual	❑	295.40	F20.8
		De por Vida	❑	295.40	F20.8
	TRASTORNO PSICÓTICO BREVE	Actual	❑	298.8	F23.80-F23.81
		De por Vida	❑	298.8	F23.80-F23.81

	TRASTORNO DELIRANTE	Actual	❑	297.1	F22.0
		De por Vida	❑	297.1	F22.0
	TRASTORNO PSICÓTICO DEBIDO A UNA ENFERMEDAD MÉDICA	Actual	❑	293.xx	F06.0-F06.2
		De por Vida	❑	293.xx	F06.0-F06.2
	TRASTORNO PSICÓTICO INDUCIDO POR SUSTANCIAS	Actual	❑	291.5-292.12	none
		De por Vida	❑	291.5-292.12	none
	TRASTORNO PSICÓTICO NO ESPECIFICADO	Actual	❑	298.9	F29
		De por Vida	❑	298.9	F29
	TRASTORNO DEL ESTADO DEL ÁNIMO CON SÍNTOMAS PSICÓTICOS	De por Vida	❑		F31.X3/F31.X2/F31.X5
	TRASTORNO DEL ESTADO DEL ÁNIMO NO ESPECIFICADO	De por Vida	❑	296.90	F39
	EPISODIO DEPRESIVO MAYOR CON SÍNTOMAS PSICÓTICOS	Actual	❑	296.24	F33.X3
		Pasado	❑	296.24	F33.X3
	TRASTORNO BIPOLAR I CON SÍNTOMAS PSICÓTICOS	Actual	❑	296.04-296.64	F31.X2/F31.X5
		Pasado	❑	296.04-296.64	F31.X2/F31.X5
N	ANOREXIA NERVIOSA	Actual (Últimos 3 Meses)	❑	307.1	F50.0
O	BULIMIA NERVIOSA	Actual (Últimos 3 Meses)	❑	307.51	F50.2
	BULIMIA NERVIOSA TIPO PURGATIVO	Actual	❑	307.51	F50.2
	BULIMIA NERVIOSA TIPO NO-PURGATIVO	Actual	❑	307.51	F50.2
	ANOREXIA NERVIOSA, TIPO COMPULSIVO/PURGATIVO	Actual	❑	307. 1	F50.0
	ANOREXIA NERVIOSA, TIPO RESTRICTIVO	Actual	❑	307. 1	F50.0
P	TRASTORNO DE ANSIEDAD GENERALIZADA	Actual (Últimos 6 Meses)	❑	300.02	F41.1
	TRASTORNO DE ANSIEDAD GENERALIZADA DEBIDO A UNA ENFERMEDAD MÉDICA	Actual	❑	293.89	F06.4
	TRASTORNO DE ANSIEDAD GENERALIZADA INDUCIDO POR SUSTANCIAS	Actual	❑	291.8-292.89	none
Q	TRASTORNO ANTISOCIAL de la PERSONALIDAD	De por Vida	❑	301.7	F60.2
R	TRASTORNO DE SOMATIZACIÓN	De por Vida	❑	330.81	F45.0
		Actual	❑		
S	HIPOCONDRÍA	Actual	❑	300.7	F45.2
T	TRASTORNO DISMÓRFICO CORPORAL	Actual	❑	300.7	F45.2
U	TRASTORNO POR DOLOR	Actual	❑	300.89/307.8	F45.4
V	TRASTORNO DE LA CONDUCTA (DISOCIAL)	Últimos 12 Meses	❑	312.8	F91.8
W	TRASTORNO POR DÉFICIT DE ATENCIÓN CON HIPERACTIVIDAD (Niños/Adolescentes)	Últimos 6 Meses Actual	❑	314.00/314.01	F90.0/F90.9/ F98.8
	TRASTORNO POR DÉFICIT DE ATENCIÓN CON HIPERACTIVIDAD (Adultos)	De por Vida Actual	❑ ❑	314.00/314.01	F90.0/F98.8
X	TRASTORNOS ADAPTATIVOS	Actual	❑	309.xx	F43.xx
Y	TRASTORNO DISFÓRICO PREMENSTRUAL	Actual	❑		
Z	TRASTORNO MIXTO DE ANSIEDAD y DEPRESIÓN	Actual	❑		

A. EPISODIO DEPRESIVO MAYOR

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, CIRCULAR NO EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

PARA PACIENTES QUE PAREZCEN ESTAR PSICÓTICOS ANTES DE COMENZAR LA ENTREVISTA, O DE LOS QUE SE SOSPECHE QUE TENGAN ESQUIZOFRENIA, POR FAVOR SIGA EL SIGUIENTE ORDEN PARA ADMINISTRAR LOS MÓDULOS.

1) PARTE 1 DEL MÓDULO M (TRASTORNOS PSICÓTICOS M1–M18).
2) SECCIONES A-D (DEPRESIÓN A (HIPO)MANÍACO).
3) PARTE 2 MÓDULO M (TRASTORNOS PSICÓTICOS M19–M23).
4) TODOS LOS DEMÁS MÓDULOS EN LA SECUENCIA USUAL.

SI EL MÓDULO M YA HA SIDO EXPLORADO Y HA IDENTIFICADO SÍNTOMAS PSICÓTICOS (M1 A M10B), EXAMINE CADA RESPUESTA POSITIVA A LAS SIGUIENTES PREGUNTAS SI LOS SÍNTOMAS DE DEPRESIÓN NO SON MEJOR EXPLICADOS POR LA PRESENCIA DE UN TRASTORNO PSICÓTICO Y CODIFIQUE DE ACUERDO.

A1 a.	¿**Alguna vez**, se ha sentido consistentemente deprimido o decaído la mayor parte del día, casi todos los días, por un período de por lo menos dos semanas?	NO	SÍ
	SI **A1a = SÍ:**		
b.	¿En las últimas dos semanas, se ha sentido deprimido o decaído la mayor parte del día, casi todos los días?	NO	SÍ
A2 a.	¿**Alguna vez**, ha perdido el interés en la mayoría de las cosas o ha disfrutado menos de las cosas que usualmente le agradaban por un período de por lo menos dos semanas?	NO	SÍ
	SI **A2a = SÍ**		
b.	¿En las últimas dos semanas, ha perdido el interés en la mayoría de las cosas o ha disfrutado menos de las cosas que usualmente le agradaban?	NO	SÍ
	¿MARCÓ SÍ EN **A1a** O EN **A2a**?	➡ NO	SÍ

SI ESTÁ DEPRIMIDO EN LA ACTUALIDAD (**A1b** O **A2b** = SÍ): EXPLORE ÚNICAMENTE EL EPISODIO ACTUAL
SI NO: EXPLORE EL EPISODIO PASADO MAS SINTOMÁTICO

A3 **En las últimas dos semanas, cuando se sentía deprimido o sin interés en las cosas:**

		Episodio Actual		Episodio Pasado	
a	¿Disminuyó o aumentó su apetito casi todos los días? ¿Perdió o ganó peso sin intentarlo (ej. variaciones en el último mes de ± 5% de su peso corporal ó ± 8 libras ó ± 3.5 kgr., para una persona de 160 libras/ 70 kgr.)? MARCAR **SÍ**, SI CONTESTÓ **SÍ** EN ALGUNA	NO	SÍ	NO	SÍ
b	¿Tenía dificultad para dormir casi todas las noches (dificultad para quedarse dormido, se despertaba a media noche, se despertaba temprano en la mañana o dormía excesivamente)?	NO	SÍ	NO	SÍ
c	¿Casi todos los días, hablaba o se movía usted más lento de lo usual, o estaba inquieto o tenía dificultades para permanecer tranquilo?	NO	SÍ	NO	SÍ
d	¿Casi todos los días, se sentía la mayor parte del tiempo fatigado o sin energía?	NO	SÍ	NO	SÍ
e	¿Casi todos los días, se sentía culpable o inútil?	NO	SÍ	NO	SÍ

SI **A3e =SÍ**: PIDA UN EJEMPLO.
LOS EJEMPLOS SON CONSISTES CON IDEAS DELIRANTES. ❑ NO ❑ SI

f	¿Casi todos los días, tenía dificultad para concentrarse o tomar decisiones?	NO	SÍ	NO	SÍ
g	¿En varias ocasiones, deseó hacerse daño, se sintió suicida, o deseó estar muerto?	NO	SÍ	NO	SÍ
A4	¿MARCÓ **SÍ** EN **3** O MAS RESPUESTAS DE **A3** (O **4** RESPUESTAS DE **A3**, SI MARCÓ **NO** EN **A1a** O **A2a** PARA EPISODIO PASADO O SI MARCÓ **NO** EN **A1b** OR **A2b** PARA EPISODIO ACTUAL)?	NO	SÍ	NO	SÍ

VERIFIQUE QUE LOS SINTOMAS MARCA DOS COMO POSITIVOS OCCURRIERON DURANTE EL MISMO PERIODO DE 2 SEMANAS.

SI MARCÓ **NO** EN **A4** PARA EPISODIO ACTUAL ENTONCES EXPLORE DE **A3a** A **A3g** PARA EL EPISODIO PASADO MAS SINTOMATICO.

A5	¿Estos síntomas depresivos le causaron un malestar significativo o dificultaron su capacidad laboral, social, o de alguna otra forma importante?	NO	SÍ
A6	¿Estos síntomas se deben totalmente a la pérdida de un ser querido (duelo) y son similares en gravedad, nivel de deterioro y duración, a lo que padecerían la mayoría de las personas en circunstancias similares?		
	¿SE HA EXCLUÍDO UN DUELO NO COMPLICADO?	NO	SÍ

A7 a ¿Había tomado algún tipo de droga o medicamento, justo antes del comienzo de estos síntomas?
❒ No ❒ Sí

b ¿Había padecido alguna enfermedad médica, justo antes del comienzo de estos síntomas?
❒ No ❒ Sí

A JUICIO DEL ENTREVISTADOR/A: ¿ES ALGUNA DE ESTAS POSIBLEMENTE LA CAUSA DIRECTA DE LA DEPRESION DEL PACIENTE? SI ES NECESARIO HAGA PREGUNTAS ADICIONALES.

A7 (RESUMEN): ¿SE HA DESCARTADO ALGUNA CAUSA ORGÁNICA? NO SÍ INCIERTO

		NO	SI
A8	MARCAR **SÍ**, SI **A7 (RESUMEN) = SÍ** O **INCIERTO**. ESPECIFIQUE SI EL EPISODIO ES ACTUAL O PASADO.	*Episodio Depresivo Mayor*	
		Actual	❑
		Pasado	❑

		NO	SI
A9	MARCAR **SÍ**, SI **A7b = SÍ** Y **A7 (RESUMEN) = NO**. ESPECIFIQUE SI EL EPISODIO ES ACTUAL O PASADO.	*Trastorno del Estado del Ánimo Debido a una enfermedad médica*	
		Actual	❑
		Pasado	❑

		NO	SI
A10	MARCAR **SÍ**, SI **A7a = SÍ** Y **A7 (RESUMEN) = NO**. ESPECIFIQUE SI EL EPISODIO ES ACTUAL O PASADO.	*Trastorno del Estado del Ánimo Inducido por sustancias*	
		Actual	❑
		Pasado	❑

CRONOLOGÍA

A11	¿Que edad tenía cuando comenzó a tener síntomas de depresión?	☐ edad
A12	¿A lo largo de su vida cuántas veces ha tenido estos síntomas depresivos (diariamente por al menos 2 semanas)?	☐

C. RIESGO DE SUICIDIO

Durante este último mes:

C1	¿Ha pensado que estaría mejor muerto, o ha deseado estar muerto?	NO	SÍ	1
C2	¿Ha querido hacerse daño?	NO	SÍ	2
C3	¿Ha pensado en suicidarse?	NO	SÍ	3
C4	¿Ha planeado en como suicidarse?	NO	SÍ	4
C5	¿Ha intentado suicidarse?	NO	SÍ	5
	En el transcurso de su vida:			
C6	¿Alguna vez ha intentado suicidarse?	NO	SÍ	6

¿MARCÓ SÍ EN POR LO MENOS 1 RESPUESTA?

SI AFIRMATIVO, SUME EL NÚMERO TOTAL DE PUNTOS DE LAS RESPUESTAS (C1-C6) MARCAR CON UN CIRCULO "SÍ" Y ESPECIFICAR EL NIVEL DE RIESGO DE SUICIDIO

NO **SÍ**

RIESGO DE SUICIDIO

1-5 puntos Leve ☐
6-9 puntos Moderado ☐
≥10 puntos Alto ☐

D. EPISODIO (HIPO) MANÍACO

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, CIRCULAR NO EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

PARA PACIENTES QUE PARECEN ESTAR PSICÓTICOS ANTES DE COMENZAR LA ENTREVISTA, O DE LOS QUE SE SOSPECHE QUE TENGAN ESQUIZOFRENIA, POR FAVOR SIGA EL SIGUIENTE ORDEN PARA ADMINISTRAR LOS MÓDULOS.

1) PARTE 1 DEL MÓDULO M (TRASTORNOS PSICÓTICOS M1–M18).
2) SECCIONES A-D (DEPRESIÓN A (HIPO)MANÍACO).
3) PARTE 2 MÓDULO M (TRASTORNOS PSICÓTICOS M19–M23).
4) TODOS LOS DEMÁS MÓDULOS EN LA SECUENCIA USUAL.

SI EL MÓDULO M YA HA SIDO EXPLORADO Y HA IDENTIFICADO SÍNTOMAS PSICÓTICOS (M1 A M10B), EXAMINE CADA RESPUESTA POSITIVA A LAS SIGUIENTES PREGUNTAS SI LOS SÍNTOMAS (HIPO)MANÍACOS NO SON MEJOR EXPLICADOS POR LA PRESENCIA DE UN TRASTORNO PSICÓTICO Y MARQUE DE ACUERDO.

D1	a	¿**Alguna vez**, ha tenido un período de tiempo en el que se ha sentido exaltado, eufórico, o tan lleno de energía, o seguro de sí mismo, que esto le ha ocasionado problemas u otras personas han pensado que usted no estaba en su estado habitual? (No considere períodos en el que estaba intoxicado con drogas o alcohol)	NO	SÍ	1
		SI AFIRMATIVO EN **D1a**:			
	b	¿**Actualmente** se siente "exaltado", "eufórico", o lleno de energía?	NO	SÍ	2
		SI EL PACIENTE PARECE CONFUNDIDO O NO ENTIENDE A LO QUE SE REFIERE CON "EXALTADO" O "EUFORICO", CLARIFIQUESELO DE LA SIGUIENTE MANERA: LO QUE QUEREMOS DECIR CON "EXALTADO" O "EUFORICO" ES; UN ESTADO DE SATISFACCION ALTO, LLENO DE ENERGIA, EN EL QUE SE NECESITA DORMIR MENOS, EN EL QUE LOS PENSAMIENTOS SE ACELERAN, EN EL QUE SE TIENEN MUCHAS IDEAS, EN EL QUE AUMENTA LA PRODUCTIVIDAD, LA CREATIVIDAD, LA MOTIVACION O EL COMPORTAMIENTO IMPULSIVO.			
D2	a	¿Ha estado usted **alguna vez** persistentemente irritado por varios días, de tal manera que tenía discusiones, peleaba o le gritaba a personas fuera de su familia? ¿Ha notado usted, o los demás, que ha estado mas irritable o que reacciona de una manera exagerada, comparado a otras personas en situaciones que incluso usted creía justificadas?	NO		3
		SI AFIRMATIVO EN **D2a**:			
	b	¿**Actualmente** se siente excesivamente irritable?	NO	SÍ	4
			➡		
		¿MARCÓ SÍ EN **D1a** O EN **D2a**?	NO	SÍ	

D3 SI **D1b O D2b = SÍ**: EXPLORAR SOLAMENTE EL EPISODIO **ACTUAL**
SI **D1b O D2b = NO**: EXPLORAR EL EPISODIO **PASADO** MAS SINTOMÁTICO

Durante el tiempo en el que se sentía exaltado, lleno de energía, o irritable notó qué:

		Episodio Actual		Episodio Pasado		
a	¿Sentía que podía hacer cosas que otros no podían hacer, o que usted era una persona especialmente importante? SI SI, PIDA EJEMPLOS. LOS EJEMPLOS SON CONSISTENTES CON UNA IDEA DELIRANTE. ❒ No ❒ Sí	NO	SÍ	NO	SÍ	5
b	¿Necesitaba dormir menos (ej. se sentía descansado con pocas horas de sueño)?	NO	SÍ	NO	SÍ	6
c	¿Hablaba usted sin parar o tan deprisa que los demás tenían dificultad para entenderle?	NO	SÍ	NO	SÍ	7
d	¿Sus pensamientos pasaban tan deprisa por su cabeza que tenía dificultades para seguirlos?	NO	SÍ	NO	SÍ	8
e	¿Se distraía tan fácilmente, que la menor interrupción le hacía perder el hilo de lo que estaba haciendo o pensando?	NO	SÍ	NO	SÍ	9
f	¿Estaba tan activo, tan inquieto físicamente que los demás se preocupaban por usted?	NO	SÍ	NO	SÍ	10
g	¿Quería involucrarse en actividades tan placenteras, que ignoró los riesgos o consecuencias (por ejemplo, se embarcó en gastos descontrolados, condujo imprudentemente, o mantuvo actividades sexuales indiscretas)?	NO	SÍ	NO	SÍ	11
	D3 (RESUMEN): ¿MARCÓ **SÍ** EN **3** O MAS RESPUESTAS DE **D3**? (O **4** SI **D1a** ES **NO** PARA EPISODIO PASADO O **D1b** ES **NO** PARA EPISODIO ACTUAL)? REGLA: EXALTADO/EUFORICO REQUIERE SOLAMENTE TRES SINTOMAS DE D3 MIENTRAS QUE ESTADO DEL ANIMO IRRITABLE POR SI SOLO REQUIERE **4** DE LOS SINTOMAS DE **D3**. VERIFIQUE SI LOS SINTOMAS OCURRIERON DURANTE EL MISMO PERIODO TIEMPO.	NO	SÍ	➡ NO	SÍ	

D4 a ¿Había tomado algún tipo de droga o medicamento, justo antes del comienzo de estos síntomas?
❒ No ❒ Sí

b ¿Había padecido de alguna enfermedad médica, justo antes del comienzo de estos síntomas?
❒ No ❒ Sí

A JUICIO DEL ENTEVISTADOR/A[123]: ¿ES ALGUNA DE ESTAS POSIBLEMENTE LA CAUSA DIRECTA DEL EPISODIO (HIPO)MANÍACO DEL PACIENTE? SI ES NECESARIO HAGA PREGUNTAS ADICIONALES.

D4 (RESUMEN): ¿SE HA DESCARTADO UNA CAUSA ORGÁNICA?	NO	SÍ	INCIERTO	12

D5 ¿Duraron estos síntomas por menos una semana y le causaron problemas que estaban fuera de su control, en la casa, en el trabajo, en la escuela, o fué usted hospitalizado a causa de estos problemas? NO SÍ | NO SÍ 13

SI MARCÓ **NO** EN **D5** PARA EPISODIO ACTUAL, ENTONCES EXPLORE **D3, D4** Y **D5** PARA EL EPISODIO PASADO MAS SINTOMÁTICO.

D6

SI **D3 (RESUMEN) = SÍ** Y **D4 (RESUMEN) = SÍ** O **INCIERTO** Y **D5 = NO**, Y NO DESCRIBIÓ UNA IDEA DELIRANTE EN **D3a**, MARQUE **SÍ** PARA EPISODIO HIPOMANÍACO.

ESPECIFIQUE SI EL EPISODIO IDENTIFICADO ES ACTUAL O PASADO.

NO	SÍ
EPISODIO HIPOMANÍACO	
Actual	❑
Pasado	❑

D7 SI **D3 (RESUMEN) = SÍ** Y **D4 (RESUMEN) = SÍ** O **INCIERTO** Y **D5 = SÍ** O DESCRIBIÓ UNA IDEA DELIRANTE EN **D3a**, MARQUE **SÍ** PARA EPISODIO MANÍACO.

ESPECIFIQUE SI EL EPISODIO IDENTIFICADO ES ACTUAL O PASADO.

NO	SÍ
EPISODIO MANÍACO	
Actual	❑
Pasado	❑

D8 MARQUE **SÍ**, SI **D3 (RESUMEN)** Y **D4b** Y **D5 = SÍ** Y **D4 (RESUMEN) = NO**

ESPECIFIQUE SI EL EPISODIO IDENTIFICADO ES ACTUAL O PASADO.

NO	SÍ
Episodio (Hipo) Maníaco Debido a una Enfermedad Médica	
Actual	❑
Pasado	❑

D9 MARQUE **SÍ**, SI **D3 (RESUMEN)** Y **D4a** Y **D5 = YES** Y **D4 (RESUMEN)= NO**

ESPECIFIQUE SI EL EPISODIO IDENTIFICADO ES ACTUAL O PASADO.

NO	SÍ
Episodio (Hipo) Maníaco Inducido por Sustancias	
Actual	❑
Pasado	❑

SI **D8** O **D9 = SÍ**, PASE AL SIGUIENTE MÓDULO.

SUBTIPOS

Ciclos Rápidos

En los últimos 12 meses, ¿Ha tenido cuatro o más episodios en los cuales se ha alterado su estado de ánimo?

NO	SÍ
Ciclos Rápidos	

Episodio Mixto

SI EL PACIENTE CUMPLE CRITERIOS TANTO DE UN EPISODIO MANÍACO COMO PARA UN EPISODIO DEPRESIVO MAYOR CASI TODOS LOS DÍAS, AL MENOS POR UN PERÍODO DE UNA SEMANA.

NO	SÍ
Episodio Mixto	

Patrón Estacional
EL COMIENZO Y REMISION, O EL CAMBIO DE DEPRESION A MANIACO O HIPOMANIACO CONSISTENTEMENTE OCURRE EN UNA EPOCA ESPECIFICA DEL AÑO.

NO	SÍ
Con Patrón Estacional	

Con recuperación interepisódica total.

¿Se recuperó totalmente entre los dos episodios mas recientes?

NO	SÍ
Con Recuperación Interepisódica Total	

CIRCULE UNA

EL EPISODIO MAS RECIENTE ERA **MANÍACO / HIPOMANÍACO / MIXTO / DEPRESIVO**

SEVERIDAD

X1	Leve	❑
X2	Moderado	❑
X3	Grave sin síntomas psicóticos	❑
X4	Grave con síntomas psicóticos	❑
X5	En remisión parcial	❑
X6	En remisión total	❑

CRONOLOGÍA

D10 ¿Qué edad tenía cuando comenzó a tener síntomas maníacos/hipomaníacos? ☐ edad

D11 ¿Desde el inicio de los síntomas, en cuántas ocasiones tuvo síntomas significativos maníacos/hipomaníacos? ☐

E. TRASTORNO DE ANGUSTIA (TRASTORNO DE ATAQUE DE PANICÓ)

(➡ SIGNIFICA: PASAR A E6, E7 Y E8, CIRCULAR NO EN TODAS Y CONTINUAR CON EL SIGUIENTE MÓDULO)

E1	a	¿En más de una ocasión, tuvo una crisis o ataques en los cuales se sintió súbitamente ansioso, asustado, incómodo o inquieto incluso en situaciones en la cual la mayoría de las personas no se sentirían así?	➡ NO	SÍ
	b	¿Estas crisis o ataques, alcanzan su máximo nivel en los primeros 10 minutos?	➡ NO	SÍ
E2		¿Alguna vez estas crisis o ataques ocurrieron de una manera inesperada o espontánea u ocurrieron de forma inesperada o sin provocación?	➡ NO	SÍ
E3		¿Ha tenido una de estas crisis seguida por un periodo de un mes o más en el que temía que otro episodio recurriera o se preocupaba por las consecuencias de la crisis?	NO	SÍ
E4		Durante la peor crisis que usted puede recordar:		
	a	¿Sentía que su corazón saltaba latidos, latía más fuerte o más rápido?	NO	SÍ
	b	¿Sudaba o tenía las manos húmedas?	NO	SÍ
	c	¿Tenía temblores o sacudidas musculares?	NO	SÍ
	d	¿Sentía la falta de aliento o dificultad para respirar?	NO	SÍ
	e	¿Tenía sensación de ahogo o un nudo en la garganta?	NO	SÍ
	f	¿Notaba dolor o molestia en el pecho?	NO	SÍ
	g	¿Tenía náuseas, molestias en el estómago o diarreas repentinas?	NO	SÍ
	h	¿Se sentía mareado, inestable, aturdido o a punto de desvanecer?	NO	SÍ
	i	¿Le parecía que las cosas a su alrededor eran irreales, extrañas, indiferentes, o no le parecían familiares, o se sintió fuera o separado de su cuerpo o de partes de su cuerpo?	NO	SÍ
	j	¿Tenía miedo de perder el control o de volverse loco?	NO	SÍ
	k	¿Tenía miedo de que se estaba muriendo?	NO	SÍ
	l	¿Tenía alguna parte de su cuerpo adormecida o con hormigueos?	NO	SÍ
	m	¿Tenía una sensacion de calor en el cuerpo o en la cara, o escalofríos?	NO	SÍ
		E4 (RESUMEN): ¿MARCÓ SI EN 4 O MAS RESPUESTAS DE E4?	NO	SÍ

E5 a ¿Había tomado algún tipo de droga o medicamento, justo antes del comienzo de estos síntomas?
❒ No ❒ Sí

b ¿Había padecido de alguna enfermedad médica, justo antes del comienzo de estos síntomas?
❒ No ❒ Sí

A JUICIO DEL ENTREVISTADOR/A: ¿ES ALGUNA DE ESTAS POSIBLEMENTE LA CAUSA DIRECTA DEL TRASTORNO DE ANGUSTIA DEL PACIENTE?

E5 (RESUMEN): ¿SE HA DESCARTADO UNA CAUSA ORGÁNICA? NO SÍ
SI MARCÓ **NO** EN **E5 (RESUMEN)**, SALTE A **E9**.

E6 ¿MARCÓ **SÍ E3 Y E4 (RESUMEN) Y E5 (RESUMEN)**? NO SÍ
TRASTORNO DE ANGUSTIA **DE POR VIDA**

E7 SI **E6 = NO**, ¿MARCÓ **SÍ** EN 1, 2 O 3 SÍNTOMAS DE **E4a-m**? NO SÍ
CRISIS CON SÍNTOMAS LIMITADOS **ACTUAL**

E8 ¿En el pasado mes, tuvo estas crisis en varias ocasiones (2 o más), seguidas de miedo a que recurrieran? NO SÍ
TRASTORNO DE ANGUSTIA **ACTUAL**

(SI ESTO ES NEGADO POR EL PACIENTE—VERIFIQUE REPASANDO LOS SÍNTOMAS ENDOSADOS EN **E4**).

E9 ¿MARCÓ **SÍ** EN **E3** Y **E4 (RESUMEN)** Y EN **E5b** Y MARCÓ **NO** EN **E5 (RESUMEN)**?

NO	SÍ
Trastorno de Ansiedad con Crisis de Angustia Debido a una Enfermedad Médica ACTUAL	

E10 ¿MARCÓ **SÍ** EN **E3** Y **E4 (RESUMEN)** Y EN **E5a** Y MARCÓ **NO** EN **E5 (RESUMEN)**?

NO	SÍ
Trastorno de Ansiedad con Crisis de Angustia Inducido por Sustancias ACTUAL	

CRONOLOGÍA

E11 ¿Qué edad tenía cuando comenzó a tener los primeros síntomas de crisis de angustia? ☐ edad

E12 ¿Durante el pasado año, qué tanto por ciento del tiempo tuvo síntomas significativos de crisis de angustia o la preocupación de tener otro ataque? ☐

I. TRASTORNO OBSESIVO-COMPULSIVO

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, CIRCULAR NO EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

I1	¿Este último mes, ha estado usted molesto con pensamientos recurrentes, impulsos o imágenes no deseadas, desagradables, inapropiadas, intrusas o angustiosas? (ej. la idea de estar sucio, contaminado o tener microbios, o miedo de contaminar a otros, o temor de hacerle daño a alguien sin querer, o temor que actuaría en forma impulsiva, o tiene temores o supersticiones de ser el responsable de que las cosas vayan mal, o se obsesiona con pensamientos imágenes o impulsos sexuales; o acumula o colecciona sin control, o tiene obsesiones religiosas.) (NO INCLUIR PREOCUPACIONES EXCESIVAS POR PROBLEMAS DE LA VIDA COTIDIANA. NO INCLUIR OBSESIONES DIRECTAMENTE RELACIONADAS CON TRASTORNOS ALIMENTICIOS, CONDUCTAS SEXUALES, PROBLEMAS PATOLOGICOS RELACIONADOS CON EL JUEGO, ALCOHOL O ABUSO DE DROGAS, PORQUE EL PACIENTE PUDIERA DERIVAR PLACER DE LA ACTIVIDAD Y PUDIERA QUERER EVITARLA SIMPLEMENTE POR LAS CONSECUENCIAS NEGATIVAS.)	NO ➡ Ir a I4 SÍ
I2	¿Estos pensamientos volvían a su mente aún cuando trataba de ignorarlos o de librarse de ellos?	NO ➡ Ir a I4 SÍ
I3	¿Cree usted que estos pensamientos son producto de su propia mente y que no le son impuestos desde el exterior?	NO SÍ obsesiones
I4	¿En el pasado mes, ha hecho usted algo repetidamente, sin ser capaz de evitarlo, como el lavar o limpiar en exceso, el contar y verificar las cosas una y otra vez o el repetir, el coleccionar, el ordenar las cosas o el realizar otros rituales supersticiosos?	NO SÍ compulsiones
	¿MARCÓ SÍ EN I3 O EN I4?	➡ NO SÍ
I5	¿Reconoce usted que estas ideas obsesivas o actos compulsivos son irracionales, absurdos o excesivos?	➡ NO SÍ
I6	¿Estas obsesiones o actos compulsivos interfieren de una manera significativa con sus actividades cotidianas, con su trabajo, con sus relaciones sociales, o le ocupan más de una hora diaria?	NO SÍ
I7 a	¿Había tomado algún tipo de droga o medicamento, justo antes del comienzo de estos síntomas? ❒ No ❒ Sí	
b	¿Había padecido de alguna enfermedad médica, justo antes del comienzo de estos síntomas? ❒ No ❒ Sí	
	A JUICIO DEL ENTREVISTADOR/A: ¿ES ALGUNA DE ESTAS POSIBLEMENTE LA CAUSA DIRECTA DEL TRASTORNO OBSESIVO COMPULSIVO DEL PACIENTE?	
	I7 (RESUMEN): ¿SE HA DESCARTADO UNA CAUSA ORGÁNICA?	NO SÍ

¿MARCÓ SÍ EN I6 Y I7 (RESUMEN)?

NO	SÍ

Trastorno Obsesivo Compulsivo ACTUAL

I8 ¿MARCÓ SÍ EN I6 Y EN I7b Y MARCÓ NO EN I7 (RESUMEN)?

NO	SÍ

Trastorno Obsesivo Compulsivo ACTUAL Debido a una Enfermedad Médica

I9 ¿MARCÓ SÍ EN I6 Y EN I7a Y MARCÓ NO EN I7 (RESUMEN)?

NO	SÍ

Trastorno Obsesivo Compulsivo Inducido por Sustancias Actual

CRONOLOGÍA

I10 ¿Qué edad tenía cuando comenzó a tener síntomas obsesivo-compulsivos? ☐ edad

I11 ¿Durante el pasado año, por cuantos meses tuvo síntomas obsesivo-compulsivos? ☐

M. TRASTORNOS PSICÓTICOS - Parte 1

PIDA UN EJEMPLO PARA CADA PREGUNTA CONTESTADA AFIRMATIVAMENTE. CODIFIQUE SÍ SOLAMENTE PARA AQUELLOS EJEMPLOS QUE MUESTRAN CLARAMENTE UNA DISTORSIÓN DEL PENSAMIENTO O DE LA PERCEPCIÓN, O SI NO SON CULTURALMENTE APROPIADOS. ANTES DE MARCAR, INVESTIGUE SI LAS IDEAS IMAGINAREAS CALIFICAN COMO "EXTRAÑAS" O RARAS.

LAS IDEAS IMAGINAREAS SON "EXTRAÑAS" O RARAS SI: SON CLARAMENTE ABSURDAS, IMPROBABLES, INCOMPRENSIBLES, Y NO PUEDEN DERIVARSE DE EXPERIENCIAS DE LA VIDA COTIDIANA.

LAS ALUCINACIONES SON "EXTRAÑAS" O RARAS SI: UNA VOZ HACE COMENTARIOS SOBRE LOS PENSAMIENTOS O LOS ACTOS DE LA PERSONA, O DOS O MAS VOCES CONVERSAN ENTRE SÍ.

TODAS LAS RESPUESTAS DEL PACIENTE DEBEN SER MARCA DAS EN LA COLUMNA A. UTILIZE LA COLUMNA A JUICIO DEL ENTREVISTADOR/A (COLUMNA B) SOLO SI EL CLÍNICO SABE POR EVIDENCIA EXTERNA (POR EJEMPLO, INFORMACIÓN PROVISTA POR LA FAMILIA) QUE LOS SÍNTOMAS ESTÁN PRESENTES PERO SON NEGADOS POR EL PACIENTE.

Ahora le voy a preguntar acerca de experiencias poco usuales que algunas personas pueden tener.

			COLUMNA A Respuesta del Paciente			COLUMNA B A Juicio del Entrevistador/a (si es necesario)		
					EXTRAÑOS		EXTRAÑOS	
M1	a	¿Alguna vez, ha tenido la impresión de que alguien le espiaba, o conspiraba contra usted, o que trataban de hacerle daño?	NO	SÍ	SÍ	SÍ	SÍ	1
	b	SI AFIRMATIVO: ¿Actualmente cree usted esto? NOTA: PIDA EJEMPLOS PARA DESCARTAR UN VERDADERO ACECHO.	NO	SÍ	SÍ →M6	SÍ	SÍ →M6	2
M2	a	¿Ha tenido usted la impresión de que alguien podía leer o escuchar sus pensamientos, o que usted podía leer o escuchar los pensamientos de otros?	NO		SÍ		SÍ	3
	b	SI AFIRMATIVO: ¿Actualmente cree usted esto?	NO		SÍ →M6		SÍ →M6	4
M3	a	¿Alguna vez ha creído, que alguien o que una fuerza externa haya metido pensamientos en su mente o le hicieron actuar de una manera no usual en usted? ¿Alguna vez ha tenido la impresión de que está poseído? ENTREVISTADOR/A: PIDA EJEMPLOS Y DESCARTE CUALQUIERA QUE NO SEA PSICOTICO.	NO		SÍ		SÍ	5
	b	SI AFIRMATIVO: ¿Actualmente cree usted esto?	NO		SÍ →M6		SÍ →M6	6
M4	a	¿Alguna vez ha creído que le envían mensajes especiales a través de la radio, el televisor, o el periódico, o que una persona que no conocía personalmente se interesaba particularmente por usted?	NO	SÍ	SÍ	SÍ	SÍ	7
	b	SI AFIRMATIVO: ¿Actualmente cree usted esto?	NO	SÍ	SÍ →M6	SÍ	SÍ →M6	8

M5	a	¿Consideran sus familiares o amigos que algunas de sus creencias son extrañas o poco usuales? ENTREVISTADOR/A: PIDA EJEMPLOS. MARCAR SI SOLO SI LOS EJEMPLOS SON **CLARAMENTE** IDEAS IMAGINAREAS (POR EJEMPLO, DE GRANDIOSIDAD, HYPOCONDRIA, RUINA, CULPA U OTROS NO EXPLORADOS DE **M1 A M4**).	NO	SÍ	SÍ		SÍ	SÍ		9
	b	SI AFIRMATIVO: ¿Actualmente, consideran los demás sus ideas como extrañas?	NO	SÍ	SÍ		SÍ	SÍ		10
M6	a	¿Alguna vez, ha escuchado cosas que otras personas no podían escuchar, como voces? LAS ALUCINACIONES SON MARCADAS COMO "EXTRAÑAS" SOLO SI EL PACIENTE CONTESTA SI A LO SIGUIENTE:	NO	SÍ			SÍ	SÍ		11
		SI AFIRMATIVO: ¿Escuchó una voz que comentaba acerca de sus pensamientos o sus actos, o escuchó dos o más voces conversando entre sí?			SÍ					
	b	SI AFIRMATIVO: ¿Ha escuchado estas cosas en el pasado mes? CODIFIQUE "SI EXTRAÑO" SI EL PACIENTE ESCUCHO UNA VOZ COMENTANDO ACERCA DE SUS PENSAMIENTOS O SUS ACTOS O DOS O MAS VOCES CONVERSAN ENTRE SI.	NO	SÍ	SÍ →M8		SÍ	SÍ →M8		
M7	a	¿Alguna vez, estando despierto, ha tenido visiones o ha visto cosas que otros no podían ver? ENTREVISTADOR/A: INVESTIGUE SI ESTAS VISIONES SON CULTURALMENTE INAPROPIADAS.	NO	SÍ			SÍ			
	b	SI AFIRMATIVO: ¿Ha visto estas cosas el pasado mes?	NO	SÍ			SÍ			

BAJO EL PUNTO DE VISTA DEL ENTREVISTADOR (A):

M8	b	¿PRESENTA EL PACIENTE ACTUALMENTE UN LENGUAJE DESORGANIZADO , INCOHERENTE O CON MARCADA PERDIDA DE LAS ASOCIACIONES.	NO	SÍ
M9	b	¿PRESENTA EL PACIENTE ACTUALMENTE UN COMPORTAMIENTO DESORGANIZADO O CATATÓNICO?	NO	SÍ
M10	b	¿HAY SINTOMAS NEGATIVOS DE ESQUIZOFRENIA PROMINENTES DURANTE LA ENTREVISTA, POR EJEMPLO,UN APLANAMIENTO AFECTIVO SIGNIFICATIVO, POBREZA DEL LENGUAJE (ALOGIA) O INCAPACIDAD PARA INICIAR O PERSISTIR EN ACTIVIDADES CON UNA FINALIDAD DETERMINADA?	NO	SÍ
M11	a	¿MARCÓ "SÍ" EN POR LO MENOS UNA DE **M1** A **M10b**?	NO	SÍ

M11 b

¿SON LOS UNICOS SINTOMAS PRESENTES AQUELLOS IDENTIFICADOS POR EL ENTREVISTADOR DE **M1** A **M7** (COLUMNA B) Y DE **M8b** O **M9b** O **M10b**?

SI AFIRMATIVO ESPECIFIQUE SI EL ÚLTIMO EPISODIO ES ACTUAL (MARCÓ "SÍ" EN POR LO MENOS UNA PREGUNTA "b" DE **M1** A **M10b**) Y/O DE POR VIDA (CUALQUIER PREGUNTA ES MARCADA SÍ DE **M1** A **M10b**) Y CONTINUE CON LA SIGUIENTE SECCION DIAGNOSTICA.

SI **NO**, CONTINÚE.

NO	SÍ

TRASTORNO PSICÓTICO NO ESPECIFICADO*

Actual ❑
De por vida ❑

*** Diagnóstico provisional debido a que no hay suficiente información disponible en este momento.**

ADVERTENCIA: SI MARCÓ "SÍ" EN POR LO MENOS UNA PREGUNTA "b", CODIFIQUE **M11c** Y **M11d**.
SI MARCÓ NO EN TODAS LAS PREGUNTAS "b", CODIFIQUE SOLO **M11d**.

M11c

DE **M1** A **M10b**: ¿MARCÓ "SI **EXTRAÑO**" EN UNA O MAS PREGUNTAS "b"

O

MARCÓ "SI" EN DOS O MAS PREGUNTAS "b" PERO NO "SI **EXTRAÑO**"?

NO
Entonces el Criterio "A" de Esquizofrenia No se cumple actualmente

SÍ
Entonces el Criterio "A" de Esquizofrenia Se cumple actualmente

M11d DE **M1** A **M10b**: ¿MARCÓ "SI **EXTRAÑO**" EN UNA O MAS PREGUNTAS "a"

O

MARCÓ "SÍ" EN DOS O MAS PREGUNTAS "a" PERO NO "SÍ **EXTRAÑO**"?
(VERIFIQUE QUE LOS 2 ITEMS OCURRIERON DURANTE EL MISMO PERIODO DE TIEMPO.)

NO
Entonces el Criterio "A" de Esquizofrenia No se cumple De Por Vida

O ¿MARCÓ "SI" EN **M11c**?

SÍ
Entonces el Criterio "A" de Esquizofrenia Se cumple De Por Vida

M12 a ¿Había tomado algún tipo de droga o medicamento, justo antes del comienzo de estos síntomas? 18
❒ No ❒ Sí

b ¿Había padecido de alguna enfermedad médica, justo antes del comienzo de estos síntomas? 19
❒ No ❒ Sí

c BAJO EL JUICIO DEL ENTREVISTADOR/A, ¿ES ALGUNA DE ESTAS LA CAUSA DIRECTA DE LA PSICOSIS DEL PACIENTE? 20
(SI ES NECESARIO HAGA PREGUNTAS ADICIONALES.)
❒ No ❒ Sí

d ¿SE HA DESCARTADO UNA CAUSA ORGÁNICA? NO SÍ INCIERTO 21

SI **M12d = NO**: CALIFIQUE **M13 (a, b)** Y PASE AL SIGUIENTE TRASTRONO
SI **M12d = SÍ**: CODIFIQUE **NO** EN **M13 (a, b)** Y PASE A **M14**
SI **M12d = INCIERTO**: CODIFIQUE **INCIERTO** EN **M13 (a, b)** Y PASE A **M14**

M13a ¿MARCÓ **NO** EN **M12d** DEBIDO A UNA ENFERMEDAD MÉDICA?

SI SÍ, ESPECIFIQUE SI EL ÚLTIMO EPISODIO ES

ACTUAL (MARCÓ SÍ EN POR LO MENOS UNA PREGUNTA "b" DE **M1** A **M10b**) Y/O DE POR VIDA ("a" O "b") MARCÓ SÍ EN CUALQUIER PREGUNTA DE **M1** A **M10b**.

22

NO SÍ

TRASTORNO PSICÓTICO
Debido a una Enfermedad Médica
Actual ❑
De Por Vida ❑
Incierto, codifique luego ❑

M13b ¿MARCÓ **NO** EN **M12d** DEBIDO A USO DE DROGAS?

SI SÍ, ESPECIFIQUE SI EL ÚLTIMO EPISODIO ES

ACTUAL (MARCÓ SÍ EN POR LO MENOS UNA PREGUNTA "b" DE **M1** A **M10b**) Y/O DE POR VIDA (MARCÓ SÍ EN CUALQUIER PREGUNTA DE **M1** A **M10b**).

23

NO SÍ

TRASTORNO PSICÓTICO
Inducido por Sustancias
Actual ❑
De Por Vida ❑
Incierto, codifique luego ❑

M14 ¿Cuál fue el período más largo durante el cual tuvo esas creencias o experiencias? _____ 24
SI <1 DIA, IR A LA SIGUIENTE SECCION.

M15 a Durante o después de un período en el cual tuvo estas creencias o experiencias, ¿tuvo dificultad trabajando o relacionándose con otros, o cuidándose a usted mismo? NO SÍ 25

b SI SÍ, ¿Cuánto duraron estas dificultades? _____ 26
SI ≥6 MESES, IR A **M16**.

c ¿Ha sido tratado con medicamentos o ha sido hospitalizado debido a estas creencias o experiencias , o por las dificultades causadas por estos problemas ? NO SÍ 27

d SI SÍ, ¿Cuál ha sido el período de tiempo más largo que ha sido tratado con medicamentos o ha sido hospitalizado por estos problemas? _____ 28

M16 a EL PACIENTE INFORMO INCAPACIDAD (**MARCÓ SI EN M15a**) O FUE TRATADO U HOSPITALIZADO POR PSICÓSIS (**M15c = Sí**). NO SÍ 29

b BAJO EL JUICIO DEL ENTREVISTADOR/A: CONSIDERANDO SU EXPERIENCIA, CALIFIQUE LA INCAPACIDAD DE POR VIDA DEL PACIENTE CAUSADA POR LA PSICOSIS. 30

ausente ❑ 1
leve ❑ 2
moderada ❑ 3
severa ❑ 4

M17 ¿CUAL FUE LA DURACION TOTAL DE LA PSICOSIS, TOMANDO ENCUENTA LA FASE ACTIVA (**M14**) Y LAS DIFICULTADES ASOCIADAS (**M15b**) Y LOS TRATAMIENTOS PSIQUIATRICOS (**M15d**)?
1 ❑ ≥1 día a <1 mes
2 ❑ ≥1 mes a <6 meses
3 ❑ ≥6 meses
31

CRONOLOGÍA

M18 a ¿Qué edad tenía cuando comenzó a tener estas creencias o experiencias poco usuales? ☐ edad 32

b ¿Desde el inicio de los síntomas, cuántas veces ha tenido episodios significativos de creencias o experiencias poco usuales? ☐ 33

P. TRASTORNO DE ANSIEDAD GENERALIZADA

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, CIRCULAR NO EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

P1	a	¿Se ha sentido excesivamente preocupado o ansioso debido a varias cosas durante los últimos 6 meses?	➡ NO	SÍ	1
	b	¿Se presentan estas preocupaciones casi todos los días?	➡ NO	SÍ	2
		MARCAR SÍ, SI LA ANSIEDAD DEL PACIENTE SE RESTRINGE EXCLUSIVAMENTE, O ES MEJOR EXPLICADA POR CUALQUIERA DE LOS TRASTORNOS PREVIAMENTE DISCUTIDOS.	NO	➡ SÍ	3
P2		¿Le resulta difícil controlar estas preocupaciones o interfieren para concentrarse en lo que hace?	➡ NO	SÍ	4
P3		MARQUE NO SI LOS SÍNTOMAS SE LIMITAN A RASGOS DE CUALQUIERA DE LOS TRASTORNOS PREVIAMENTE EXPLORADOS.			
		En los últimos seis meses cuando estaba ansioso, casi todo el tiempo:			
	a	¿Se sentía inquieto, intranquilo o agitado?	NO	SÍ	5
	b	¿Se sentía tenso?	NO	SÍ	6
	c	¿Se sentía cansado, flojo o se agotaba fácilmente?	NO	SÍ	7
	d	¿Tenía dificultad para concentrarse, o notaba que la mente se le quedaba en blanco?	NO	SÍ	8
	e	¿Se sentía irritable?	NO	SÍ	9
	f	¿Tenía dificultad durmiendo (dificultad para quedarse dormido, se despertaba a media noche o demasiado temprano, o dormía en exceso)?	NO	SÍ	10
		RESUMEN DE P3: ¿MARCÓ SÍ EN 3 O MÁS RESPUESTAS DE P3?	➡ NO	SÍ	
P4		¿Le causaron estos síntomas de ansiedad mucha angustia, o le afectaron para funcionar en el trabajo, socialmente o de cualquier manera importante?	➡ NO	SÍ	11
P5	a	¿Había tomado algún tipo de droga o medicamento, justo antes del comienzo de estos síntomas? ❒ No ❒ Sí			
	b	¿Había padecido de alguna enfermedad médica, justo antes del comienzo de estos síntomas? ❒ No ❒ Sí			
		A JUICIO DEL ENTREVISTADOR/A: ¿ES ALGUNA DE ESTAS POSIBLEMENTE LA CAUSA DIRECTA DEL TRASTORNO DEL TRASTORNO DE ANSIEDAD GENERALIZADA DEL PACIENTE?			
		P5 (RESUMEN): ¿SE HA DESCARTADO UNA CAUSA ORGÁNICA?	NO	SÍ	12

¿MARCÓ NO EN P5 (RESUMEN)?

NO	SÍ
Trastorno de Ansiedad Generalizada ACTUAL	

P6 ¿MARCÓ NO EN P5 (RESUMEN) Y MARCÓ SÍ EN P5b?

NO	SÍ
Actual *Ansiedad Generalizada* Debido a una Enfermedad Médica	

P7 ¿MARCÓ NO EN P5 (RESUMEN) Y MARCÓ SÍ EN P5a?

NO	SÍ
Actual *Trastorno de Ansiedad Generalizada* Inducido por Sustancias	

CRONOLOGÍA

P8 ¿Qué edad tenía cuando comenzó a tener síntomas de ansiedad generalizada? ☐ edad

P9 ¿Durante el pasado año, por cuantos meses ha tenido síntomas significativos de ansiedad generalizada? ☐

ANNEX 5. PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

CUESTIONARIO SOBRE LA SALUD DEL PACIENTE-9 (PHQ-9)

Durante las últimas 2 semanas, ¿qué tan seguido le han afectado cualquiera de los siguientes problemas? *(Marque con una "✔" para indicar su respuesta)*	**Para nada**	**Varios días**	**Más de la mitad de los días**	**Casi todos los días**
1. Poco interés o placer en hacer las cosas	0	1	2	3
2. Se ha sentido decaído(a), deprimido(a), o sin esperanzas	0	1	2	3
3. Dificultad para dormir o permanecer dormido(a), o ha dormido demasiado	0	1	2	3
4. Se ha sentido cansado(a) o con poca energía	0	1	2	3
5. Con poco apetito o ha comido en exceso	0	1	2	3
6. Se ha sentido mal con usted mismo(a) – o que es un fracaso o que ha quedado mal con usted mismo(a) o con su familia	0	1	2	3
7. Ha tenido dificultad para concentrarse en cosas tales como leer el periódico o ver televisión	0	1	2	3
8. ¿Se ha estado moviendo o hablando tan lento que otras personas podrían notarlo?, o por el contrario – ha estado tan inquieto(a) o agitado(a), que se ha estado moviendo mucho más de lo normal	0	1	2	3
9. Ha pensado que estaría mejor muerto(a) o se le ha ocurrido lastimarse de alguna manera	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

Si usted marcó cualquiera de estos problemas, ¿qué tan difícil fue hacer su trabajo, las tareas del hogar o llevarse bien con otras personas debido a tales problemas?

Para nada difícil	**Un poco difícil**	**Muy difícil**	**Extremadamente difícil**
☐	☐	☐	☐

Desarrollado por los Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke y colegas, con una beca educacional por parte de Pfizer Inc. No se requiere permiso para reproducir, traducir, mostrar o distribuir.

ANNEX 6. MINI MENTAL STATE EXAMINATION (MMSE)

MINI MENTAL STATE EXAMINATION (MMSE)

Basado en Folstein et al. (1975), Lobo et al. (1979)

NOMBRE:
FECHA:
ESTUDIOS/PROFESIÓN: F. NACIMIENTO: VARÓN / MUJER
OBSERVACIONES: N.Hª: EDAD:

¿En qué año estamos?	0 - 1	ORIENTACIÓN TEMPORAL (Máx.5)	
¿En qué estación?	0 - 1		
¿En qué día(fecha)?	0 - 1		
¿En qué mes?	0 - 1		
¿En qué día de la semana?	0 - 1		

¿En qué hospital (o lugar) estamos?	0 - 1	ORIENTACIÓN ESPACIAL (Máx.5)	
¿En qué piso (o planta, sala, servicio)?	0 - 1		
¿En qué pueblo (ciudad)?	0 - 1		
¿En qué provincia estamos?	0 - 1		
¿En qué país (o nación, autonomía)?	0 - 1		

Nombre tres palabras Peseta-Caballo-Manzana (o Balón- Bandera-Árbol) a razón de 1 por segundo. Luego se pide al paciente que las repita. Esta primera repetición otorga la puntuación. Otorgue 1 punto por cada palabra correcta, pero continúe diciéndolas basta que el sujeto repita las 3, hasta un máximo de 6 veces. **Peseta** 0-1 **Caballo** 0-1 **Manzana** 0-1 (**Balón** 0-1 **Bandera** 0-1 **Arbol** 0-1)	Nº de repeticiones necesarias FIJACIÓN-Recuerdo Inmediato (Máx.3)	

Si tiene 30 pesetas y me va dando de tres en tres, ¿Cuántas le van quedando?. Detenga la prueba tras 5 sustraciones. Si el sujeto no puede realizar esta prueba, pídale que deletree la palabra MUNDO al revés. **30** 0-1 **27** 0-1 **24** 0-1 **21** 0-1 **18** 0-1 **O** 0-1 **D** 0-1 **N** 0-1 **U** 0-1 **M** 0-1	ATENCIÓN-CÁLCULO (Máx.5)	

Preguntar por las tres palabras mencionadas anteriormente **Peseta** 0-1 **Caballo** 0-1 **Manzana** 0-1 (**Balón** 0-1 **Bandera** 0-1 **Arbol** 0-1)	RECUERDO diferido(Máx.3)	

· **DENOMINACIÓN.** Mostrarle un lápiz o un bolígrafo y preguntar ¿qué es esto?. Hacer lo mismo con un reloj de pulsera. **Lápiz** 0-1 **Reloj** 0-1 . · **REPETICIÓN.** Pedirle que repita la frase: "ni si, ni no, ni pero" (o "En un trigal había 5 perros") 0-1 · **ÓRDENES.** Pedirle que siga la orden: "coja un papel con la mano derecha, dóblelo por la mitad, y póngalo en el suelo". **Coje con mano** 0-1 **Dobla por mitad** 0-1 **Pone en suelo** 0-1 · **LECTURA.** Escriba legiblemente en un papel "Cierre los ojos". Pídale que lo lea y haga lo que dice la frase 0-1 · **ESCRITURA.** Que escriba una frase (con sujeto y predicado) 0-1 · **COPIA.** Dibuje 2 pentágonos intersectados y pida al sujeto que los copie tal cual. Para otorgar un punto deben estar presentes los 10 ángulos y la intersección. 0-1	LENGUAJE (Máx.9)	

Puntuaciones de referencia	27 ó más= normal 24 ó menos = sospecha patológica 12-24= deterioro 9-12 = demencia	Puntuación TOTAL: (Máx.30puntos)	

ANNEX 7. PATIENT INFORMATION SHEET

FULL D'INFORMACIÓ PER AL PACIENT

Estudi: *Effects of menstrual cycle phase in glucocorticoid-induced neuropsychiatric disorders: a cohort study.*

Investigadors principals: Dr. Domènec Serrano Sarbosa i Esther Vadillo González.

Benvolguda,

Ens adrecem a vostè per convidar-la a participar en un estudi d'investigació portat a terme pel Servei d'Interconsulta de Psiquiatria de l'Hospital Santa Caterina i l'Hospital Josep Trueta. Aquest estudi ha estat prèviament aprovat pel Comitè d'Ètica d'Investigació Clínica de Girona (CEIC Girona), conforme a la legislació vigent.

Aquest document té la intenció de transmetre-li la informació necessària sobre l'estudi perquè pugui decidir sobre la seva participació. Li preguem que el llegeixi atentament i en cas que tingui algun dubte ens ho consulti als membres de l'equip investigador.

OBJECTIUS DE L'ESTUDI

Els glucocorticoides són un tractament amplament estès. Entre les seves complicacions, i especialment quan s'utilitzen dosis altes, hi figura la possible aparició d'una sèrie de trastorns neuropsiquiàtrics, com ara ansietat, depressió, mania, hipomania, psicosi, etc.

A dia d'avui encara no existeixen estratègies eficaces de prevenció. Fins ara, coneixem alguns factors de risc, com ara el sexe femení. Les dones tenen el doble de risc, i es pensa que això es podria deure a la influència de factors com la interacció entre hormones.

Segons estudis previs, les respostes del cortisol (hormona de la qual els glucocorticoides en són anàlegs sintètics) a l'estrès psicosocial són similars entre homes i dones a la fase lútia del cicle menstrual (aquella que va des de la meitat del cicle fins l'inici d'una nova menstruació), però diferents a la fase fol·licular del cicle (aquella que va des de l'inici de la menstruació fins la meitat del cicle).

A partir d'aquesta idea, l'objectiu principal de l'estudi és valorar l'associació entre la fase del cicle menstrual en què la pacient inicia el tractament amb glucocorticoides a dosis

altes i l'aparició d'algun trastorn neuropsiquiàtric induït per glucocorticoides. També volem saber si depenent de la fase hi ha més incidència d'algun trastorn o algun altre, i si les pacients que desenvolupen algun trastorn tenen més o menys dels altres factors de risc, i més o menys necessitat d'ús de tractaments farmacològics pel maneig del trastorn, en base a la fase del cicle menstrual en què la pacient inicia el tractament.

DESCRIPCIÓ DE L'ESTUDI

L'estudi es realitzarà en l'hospital en el qual vostè ha rebut la prescripció de tractament, durant un període de màxim 6 mesos. Com és un estudi observacional, no se li realitzarà cap intervenció addicional i el maneig del seu cas no serà gaire diferent al d'un pacient que no hi participi.

Si decideix participar, se li programarà una visita amb un psiquiatra el dia després de la prescripció, i se li demanarà que comenci el tractament el dia de la visita.

En aquesta primera visita se li donaran tests de detecció de LH en orina (tests d'ovulació) per tal que es faci un cada dia fins a obtenir un resultat positiu o comenci una nova menstruació, i això ens ajudi a determinar la fase del cicle menstrual en què es trobava quan va començar el tractament. Se li donaran instruccions per a comunicar a l'equip investigador el resultat positiu. A més, en totes les visites se li farà una entrevista psiquiàtrica. A la primera visita també se li realitzarà una analítica sanguínia per valorar altres paràmetres descrits com a factors de risc.

BENEFICIS I RISCOS DE L'ESTUDI

L'estudi està enfocat a proporcionar un coneixement útil per a plantejar futures estratègies de prevenció, de manera que es podria proporcionar en un futur un benefici general per a totes les dones que hagin d'iniciar un tractament amb glucocorticoides a dosis altes. No obtindrà un benefici personal directe per la seva participació.

Com que es tracta d'un estudi observacional, els procediments que es realitzaran no difereixen dels utilitzats en la pràctica clínica diària i, per tant, la seva participació no comporta un risc afegit.

CONFIDENCIALITAT I PROTECCIÓ DE DADES

La informació que s'obtingui de la realització de l'estudi serà totalment confidencial i serà gestionada de forma anònima i utilitzada només amb fins d'investigació, d'acord amb la *Llei Orgànica 3/2018, de 5 de desembre, de protecció de dades personals i garantia dels drets digitals*, i el Reglament 2016/679 del Parlament i el Consell Europeu.

Per garantir la màxima confidencialitat, a l'inici de l'estudi se li assignarà un codi numèric mitjançant el qual s'identificaran les seves dades. L'accés a aquestes quedarà restringit a l'equip investigador.

PARTICIPACIÓ EN L'ESTUDI I COMPENSACIÓ ECONÒMICA

La participació en l'estudi és totalment voluntària. Si accepta participar, tindrà el dret de revocar el seu consentiment en qualsevol moment, sense necessitat d'explicar-ne els motius, i sense que això repercuteixi en la seva assistència mèdica.

No s'ofereix cap compensació econòmica per participar en l'estudi i tampoc li suposarà cap cost addicional. Els investigadors tampoc rebran cap compensació econòmica.

RESULTATS DE LA INVESTIGACIÓ

El pacient està en el seu dret de ser informat dels resultats de la investigació. En cas que es publiquin els resultats de l'estudi en publicacions o congressos, mai es farà de forma individualitzada, assegurant per tant la no identificació dels pacients.

CONTACTE

Pot posar-se en contacte amb l'investigador principal i els altres membres de l'equip investigador si al llarg de l'estudi li sorgeixen nous dubtes o precisa de més informació.

Telèfon:_____ Correu electrònic:_____

Gracies per la seva atenció.

Atentament,

L'equip investigador

ANNEX 8. INFORMED CONSENT DOCUMENT

CONSENTIMENT INFORMAT

Estudi: *Effects of menstrual cycle phase in glucocorticoid-induced neuropsychiatric disorders: a cohort study.*

Investigadors principals: Dr. Domènec Serrano Sarbosa i Esther Vadillo González.

Jo,_____,

amb DNI/NIE _____, declaro que:

- He llegit i comprès el Full d'Informació per al Pacient que se m'ha entregat en relació als objectius de l'estudi.
- He pogut formular totes les preguntes que he considerat oportunes sobre l'estudi i aquestes han estat respostes satisfactòriament per l'investigador responsable.
- Estic conforme amb la quantitat d'informació facilitada sobre l'estudi.
- He estat informada per l'investigador _____ de les implicacions i finalitats de l'estudi.
- Entenc que la meva participació és voluntària i no remunerada.
- Entenc que en qualsevol moment puc revocar consentiment de participació en l'estudi, sense haver de donar justificacions i sense afectar la meva assistència sanitària.
- Dono permís perquè les meves dades i la meva història clínica puguin ser utilitzades per l'equip investigador amb finalitats relacionades amb l'estudi.
- Entenc que es respectarà la confidencialitat de les meves dades personals i que puc sol·licitar la retirada i eliminació d'aquestes en qualsevol moment de l'estudi.
- Dono permís perquè els investigadors contactin amb mi per telèfon mòbil si soc apte per entrar a l'estudi. Seguidament indico el meu número de contacte: _____.
- Declaro que se m'ha donat una còpia del Full d'Informació per al Pacient i una còpia d'aquest document signat.

En conseqüència, DONO EL MEU CONSENTIMENT a participar en aquest estudi i estic d'acord en que la informació obtinguda pugui ser utilitzada en investigacions futures.

Signatura de la pacient Signatura de l'investigador/a

Lloc i data: _____, _____ de _____ de 20___.

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo, _____,
amb DNI/NIE _____, revoco el consentiment prèviament signat per a participar en l'estudi: *Effects of menstrual cycle phase in glucocorticoid-induced neuropsychiatric disorders: a cohort study.*

Signatura del pacient Signatura de l'investigador/a

Lloc i data: _____, _____ de _____ de 20___.
