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ORIGINAL ARTICLES

Spanish Consensus on Physical Health of Patients With Bipolar Disorder

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KEY WORDS

Bipolar disorder Physical health Consensus Morbidity Mortality

Abstract

Background and objective: Patients with bipolar disorder have much higher physical morbidity and mortality rates than the general population. In addition to a higher mortality rate from suicide, these patients also have a higher prevalence of physical disorders.

The *aim* of this consensus, promoted by the Spanish Societies of Psychiatry and Biological Psychiatry in collaboration with the General Practitioners' Societies, was to establish practical recommendations on procedures for detection, prevention, and intervention in the somatic diseases that coexist with bipolar disorder in order to improve the quality of life and life expectancy of these patients.

Method: The Spanish Societies of Psychiatry and Biological Psychiatry designated a scientific committee that selected 32 expert psychiatrists and 10 experts from other medical specialties. Working groups were formed for each specialty for the purpose of adapting the guidelines applied in the general population to patients with bipolar disorder. A systematic review of medical comorbidity and mortality in these patients was carried out and 2 multidisciplinary consensus meetings were held.

Results: The literature review revealed an increased risk of hypertension, obesity, smoking, pulmonary diseases, migraine, and HIV infection among patients with bipolar disorder. There was also evidence of higher mortality rates from cardiovascular and respiratory diseases and infections, as well as from suicide. The expert group reached a consensus on a series of basic measures to detect medical comorbidity applicable to the monitoring of these patients. The resulting recommendations will be accepted and disseminated by the promoting societies. Conclusions: The recommendations generated by the Spanish Consensus on the Physical Health od Patients with Bipolar disorders include the most important aspects for the improvement of the psychosocial functioning, quality of life and life expetancy of these patients.

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PALABRAS CLAVE

Trastorno bipolar. Salud física. Consenso. Morbilidad. Mortalidad.

Consenso Español de Salud Física del Paciente con Trastorno Bipolar

Resumen

Introducción y objetivos: Los pacientes con trastorno bipolar presentan una morbilidad física y una mortalidad muy superior a la de la población general. Además de una mayor mortalidad por suicidio, tienen también una mayor prevalencia de enfermedades físicas. El objetivo de este consenso, promovido por las Sociedades Españolas de Psiquiatría y Psiquiatría Biológica, en colaboración con las sociedades de médicos de asistencia primaria, es establecer recomendaciones prácticas sobre los procedimientos de detección, prevención e intervención en las enfermedades somáticas que coexisten con el trastorno bipolar para mejorar la calidad y esperanza de vida de estos pacientes.

Método: Las Sociedades Españolas de Psiquiatría y Psiquiatría Biológica eligieron un Comité Científico que seleccionó a su vez a 32 psiquiatras expertos y 10 médicos expertos en otras especialidades médicas. Se crearon grupos de trabajo para cada especialidad con la finalidad de adaptar las guías aplicadas en la población general a pacientes con trastorno bipolar. Partiendo de una revisión sistemática sobre la comorbilidad médica y la mortalidad en el trastorno bipolar se realizaron dos reuniones para acordar el consenso.

Resultados: En la revisión bibliográfica se detectó un riesgo aumentado, entre los pacientes con trastorno bipolar, de presentar hipertensión arterial, obesidad, tabaquismo, enfermedades pulmonares, migraña e infección por virus de la inmunodeficiencia humana (VIH). También se encontró evidencia de un aumento de mortalidad por enfermedades cardiovasculares, respiratorias e infecciones, además del suicidio. El grupo de expertos alcanzó el consenso en una serie de medidas básicas para la detección de comorbilidad médica aplicables a la monitorización de estos pacientes. Las recomendaciones resultantes serán asumidas y divulgadas por las sociedades promotoras.

Conclusiones: El decálogo generado en el Consenso Español de Salud Física del Paciente con Trastorno Bipolar recoge los aspectos más relevantes para la mejora del funcionamiento psicosocial, la calidad y la esperanza de vida en los pacientes con esta patología.

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Introduction

Bipolar disorder is a serious mental illness that may affect between 2% and 5% of the population. 1,2 It has a great impact on the functioning of the patient, and is ranked sixth among the diseases listed as overall causes of disability.3

Furthermore, there is increasing evidence that bipolar disorder patients suffer from greater physical morbidity and mortality than the general population. The mortality rate due to suicide is double that of the general population and the rate is 10 times higher when other factors are taken into account, such as the increased risk of metabolic syndrome and cardiovascular disease in these patients.⁴⁻⁷

Although there is little research on this topic, available data suggest that several medical diseases (cardiovascular, metabolic, infectious, neurological, and respiratory disorders) have a higher prevalence among these patients. The causes contributing to this are varied. First, difficulties arising from suitable access to prevention services and primary care treatment. Daily habits that include a greater consumption of addictive substances, a sedentary lifestyle, or unsuitable diets, are also risk factors. Furthermore, the presence

of affective symptoms has been associated with immunoinflammatory activation that involves greater organic damage via the so-called allostatic load. ¹⁰ Finally, some of the psychoactive drugs used in the treatment of this disorder can have associated adverse events that may have an impact on physical health. ¹¹

On the other hand, in addition to risks regarding the patient's physical health, these somatic diseases worsen the prognosis of bipolar disorder, hinder its treatment and recovery, and worsen the quality of life of patients. 12 Thus, we can assert that the psychiatric symptoms of bipolar disorder are not the only cause of a negative impact on the overall functional level of the patient.

However, there is a tendency to underdiagnose and undertreat somatic illness in psychiatric patients in general and in bipolar patients in particular. 9,13-15 This situation calls for raising awareness in all health professionals regarding the need to prevent and treat physical illness in these patients. 16

The aim of this project was to reach a consensus on the evaluation of physical health and medical problems in bipolar disorder patients throughout their lives, similar to the one recently carried out by the Spanish Societies of

Psychiatry and Biological Psychiatry on the physical health of patients with schizophrenia, ¹⁷ and establish recommendations on the diagnostic procedures and care interventions needed to detect and modify somatic risk factors that have an impact on the psychosocial functioning of these patients in Spain, as well as on their quality of life and life expectancy. This consensus adds to those developed by other scientific societies in the rest of the world. ^{18,19}

Methods

This consensus document was developed and endorsed by the Spanish Society of Psychiatry (SEP) and the Spanish Society of Biological Psychiatry (SEPB), in collaboration with the Spanish Society of Rural Medicine and General Practitioners (SEMERGEN) and Family and Community Medicine (sem-FYC).

Development Process

The consensus document was developed according to the following steps:

- —The Spanish Societies of Psychiatry and Biological Psychiatry designated a Scientific Committee consisting of 4 members and one coordinator in charge of selecting 32 expert psychiatrists and 10 expert physicians in other medical specialties
- —A systematic review of specialized medical literature on medical comorbidity and mortality in bipolar disorder
- —A review by the specialist consultant physicians of the national and international guidelines on the prevention, diagnosis, and treatment of the different diseases identified as relevant to bipolar disorder patients, after adapting them to the characteristics of bipolar disorder
- —Two multidisciplinary consensus meetings
- —Drafting the final consensus document

Systematic Review of Medical Literature

The aim of the systematic review of the medical literature was to assess the incidence, prevalence, or risk of physical illness, as well as mortality in bipolar disorder patients.

A bibliographic search of the MEDLINE database from 1966 to January 2008 was performed. The search was limited to studies published in Spanish or English. Furthermore, a search was performed of the reference lists of all the primary articles identified and relevant review articles.

Review of National and International Guidelines by Expert Specialist Consultant Physicians

Parallel to the systematic review of the medical literature, the expert specialist consultant physicians reviewed the national and international guidelines and other documentation on the prevention, diagnosis and treatment of the diseases identified above as relevant to bipolar disorder in the systematic review of the medical literature.

Multidisciplinary Consensus Meetings

There were 2 consensus meetings. Both were multidisciplinary and were attended by the Scientific Committee members, representatives of the medical societies and Alcalá de Henares University, and 11 expert consultants from the following medical specialties: primary care (2), gynecology (1), infectious diseases (1), endocrinology (1), circulatory system (1), pharmacology (1), addiction management (1), and mortality prevention (1 expert psychiatrist); and a group of 31 expert psychiatrists participating in the preparation of the consensus.

At the first meeting, the members of the Scientific Committee described the current situation regarding physical health problems in bipolar disorder patients. Subsequently, each expert specialist consultant reviewed the international and national guidelines on diagnosis and follow-up of each of the prevalent diseases selected and then a working group was created for every specialty made up of the corresponding expert specialist consultant and several participating expert psychiatrists. Each group prepared a document with recommendations on diagnostic interventions, monitoring, and preventive and therapeutic interventions adapted to bipolar disorder patients.

At the second meeting a consensus was reached by all participants on the specific recommendations created by each working group that should be incorporated into the final consensus document.

Results

Systematic Review of the Medical Literature

Although the results of the systematic review will be the subject of further publications, the most relevant conclusions extracted from it are summarized below.

Cardiovascular Disease

Number of studies: 14 controlled studies²⁰⁻³³ and 6 uncontrolled studies, ³⁴⁻³⁹

Findings: although 2 studies produced conflicting results, most comparative studies report that bipolar disorder is associated with an increased rate of arterial hypertension (AHT), although prevalence figures vary greatly from one study to another (from 4.6%to 60.8%). Furthermore, a greater risk of AHT has been reported in bipolar disorder patients than in patients with schizophrenia (odds ratio [OR] = 1.13; 95%confidence interval [CI], 1.01-1.26).

No evidence was found that consistently supports bipolar disorder being associated with other different cardiovascular diseases apart from arterial hypertension. Smilar conclusions can be drawn regarding stroke.

Pulmonary Disease

Number of studies: 9 controlled studies $^{20,23,24,26\cdot28,30,33,40}$ and 3 uncontrolled studies. 34,36,37

Findings: a significantly greater risk of asthma was found among bipolar disorder patients compared to the general population. Prevalence figures range between 3% and 17% in bipolar disorder patients versus 2% 10% in the general population or 8% in other reference populations. The lifetime prevalence of asthma in bipolar disorder patients (16.7% 95% CI, 15.1-18.4) was also significantly greater 23 than in the general population (9.7% 95% CI, 9.1-10.3).

Bipolar patients also showed an increased risk of suffering chronic obstructive pulmonary disease (COPD) compared to the general population (lifetime prevalence, 2.7% 95%Cl, 1.9-3.7 vs 1.1% 95%Cl, 0.8-1.3).

Gastrointestinal Disease

Number of studies: 5 controlled studies^{20,26,28,30,41} and 3 uncontrolled studies.³⁶⁻³⁸

Findings: although few data are available, 3 controlled studies suggest that bipolar disorder patients have a higher risk of suffering from peptic ulcer. The prevalence of peptic ulcer in controlled and uncontrolled studies was 0.9%10.8% in bipolar disorder patients versus 0.2%5.0%in reference populations.

Although data on liver disorders are also limited, 2 controlled studies report that bipolar disorder patients had a greater risk of suffering liver disease (OR, 3.97; 95%Cl, 2.84-5.55).

Endocrine-Metabolic Disease

Number of studies: 17 controlled studies $^{20,24,26-28,30-33.35,42-48}$ and 13 uncontrolled studies. $^{34-39,49-55}$

Findings: 6 out of 7 controlled studies that evaluated the prevalence of obesity found significantly greater percentages in bipolar disorder patients (19%53%) than in the general population (9%14%).

Some studies have also found an increase in the prevalence of diabetes, although from a clinical point of view the differences were barely relevant. The data regarding dyslipidemia in bipolar disorder patients are highly variable and lack consistency. Only 1 controlled study evaluated the presence of metabolic syndrome in these patients, and found a prevalence similar to that in patients with schizophrenia (22.5%vs 29.7% P=NS). This prevalence of metabolic syndrome is very similar (22.4%24.7%) to studies conducted in bipolar disorder patients in our setting. 39,56

The association of hypothyroidism with bipolar disorder is highly controversial, and only 1 comparative study has addressed this issue versus the general population. ²⁸ In this study, the prevalence of hypothyroidism in bipolar disorder patients was 9.6% compared to 2.5% in a clinical sample without bipolar disorder (OR, 2.57; 95% CI, 2.27-2.91; P < .0001) This risk seems to increase among patients with rapid cycling bipolar disorder (OR, 3.14; 95% CI, 1.12-8.79; P < .002) compared to those without rapid cycling. ⁴² If

non-comparative studies are included, the prevalence of hypothyroidism among bipolar patients seems to be around 10%

Renal and Genitourinary Disease

Number of studies: 3 controlled studies^{26,28,33} and 3 uncontrolled studies.^{36,38}

Findings: the risk of presenting nephropathies seems to be higher among bipolar disorder patients compared to non-psychiatric patients (OR, 2.78; 95%CI, 1.87-4.14; P<.0001).

Musculoskeletal and Connective Tissue Disease

Number of studies: 6 controlled studies^{20,23,26,28,30,35} and 4 uncontrolled studies.³⁵⁻³⁸

Findings: none of these diseases seem to be associated with bipolar disorder.

Infectious Disease

Number of studies. 5 controlled studies $^{20\text{-}59,57\text{-}59}$ and 3 uncontrolled studies. 36,37,60

Findings: there is a strong association between bipolar disorder and human immunodeficiency virus (HIV) infection. The studies report prevalences fluctuating between 0.1% and 2.6% if studies conducted in African countries with higher prevalences of infection are excluded.

Neurological Disease

Number of studies: 11 controlled studies^{20,23,24,26,28,30,61-65} and 10 uncontrolled studies. ^{34,36-38,49,66-70}

Findings: the prevalence of migraine in bipolar disorder patients is significantly greater than in the general population, (OR, 2.54; 95%CI, 1.59-4.05), is greater in women and has an average prevalence of 25%

Oncological and Hematological Disease

Number of studies: 3 controlled studies 26,28,71 and 2 uncontrolled studies. 36,37

Findings: there is no evidence of increased rates of cancer among bipolar disorder patients.

Dermatological, Ocular, Otorhinolaryngological, and Dental Disease

Number of studies. 3 uncontrolled studies of dermatological disease, ³⁶⁻³⁸ 1 controlled study of ocular disease, ³⁰ and no studies on otorhinolaryngological and dental disease.

Findings: there is no evidence supporting an association with these diseases.

Gynecological and Obstetric Disease

Number of studies: 3 controlled studies 20,28,72 and 1 uncontrolled study. 36

Findings: there is an increased risk of gestational complications among women with bipolar disorder (OR, 1.23; 95% Cl, 1.06-1.44), mainly due to placenta praevia (OR, 2.13; 95%Cl, 1.15-3.94).

Other Medical Disorders

Number of studies: 6 controlled studies^{23,24,26-30} and 1 uncontrolled study.³⁷

Findings: bipolar disorder patients have a significantly greater prevalence of allergies than the general population, with figures ranging between 25% and 40%

It is also associated with chronic fatigue syndrome (4%vs 1%in the general population) and with multiple chemical sensitivity syndrome (4.6%vs 2.3%in the general population; P < .05).

Disorders Related to the Use of Addictive Substances

Number of studies: 10 controlled studies^{21,24-26,28,31,33,64,73,74} and 1 uncontrolled study.⁷⁰

Given the focus of this review, this section only includes articles that provide information on medical comorbidity in relation to the use of addictive substances.

Findings: bipolar disorder patients present a risk of nicotine abuse or dependency more than twice that of the general population (OR, 2.1; 95%Cl, 1.2-4.0), with a prevalence of smoking ranging between 50% and 60%

Smilarly, the risk of alcohol abuse or dependence (OR, 19.63; 95% Cl, 17.9-21.0) and abuse or dependence on other substances (OR, 42.1; 95% Cl, 37.83-48.6) is also very high.

Mortality

Total mortality (from any cause):

Number of studies: 6 studies: 4,6,75-78

Findings: mortality among bipolar disorder patients is at least double in men and 3 times greater in women.

Mortality from non-natural causes:

Number of studies: 10 studies: 4,6,75-82

Findings: mortality due to suicide is more than ten times higher than in the general population (standardized mortality ratio [SMR] between 10 and 18).

Mortality from accidents is also up to three times greater.

Mortality from natural causes:

Number of studies. 5 studies. 75,76,79,80,83

Findings: mortality due to cardiovascular causes is significantly higher and can reach 50% Mortality due to cerebrovascular disease or cancer does not seem to be greater.

Finally, other causes of the increase in mortality are infection—that can be double than expected—and respiratory disorders (SMR between 3 and 7).

Monitoring and Intervention Algorithms Applied to the Physical Health Problems of the Bipolar Disorder Patient

Taking into account the findings obtained from this systematic review of comorbidity in relation to physical disorders among bipolar disorder patients, there follow the consen-

sus recommendations of the Expert Specialist Consultant Physicians Committee and the participating psychiatrists on the diagnostic, preventive and therapeutic interventions regarding the physical health of these patients. All these interventions are summarized in Table 1 (protocol for monitoring the physical health of the bipolar disorder patient). A complete case history should be taken that includes personal and family medical and psychiatric background, including suicide, the consumption of addictive substances, concomitant medication use, and information on diet and lifestyle. They should also be asked about any sexual dysfunction and intentions regarding starting a family. The patients should have a general examination as well as a blood test aimed at assessing given specific disorders that are detailed below.

Cardiovascular Disease

Diagnostic measures: systolic blood pressure (SBP) and diastolic blood pressure (DBP) should be measured at baseline and during each subsequent visit. If blood pressure is normal and visits are frequent, at least one new measurement is recommended at 3 months and every 6 months, subsequently. When values greater than or equal to 140/90 mm Hg are obtained, measurements should be repeated up to 3 times at intervals of 2-3 min. To diagnose AHT, the measurements must be repeated on another 2 days (triple measurements) unless the values on a single occasion are higher than 189/110 mm Ha.

Prevention measures: all the patients should follow a low-salt diet and take exercise appropriate to their physical condition. Weight reduction is fundamental if overweight/obesity is present.

Therapeutic measures: if blood pressure is not controlled (≥ 140/90 mmHg or less in subjects with diabetes or kidney failure) they should be referred to their primary care physician. In this case, it is important to indicate whether the patient is taking antipsychotic drugs and if so, which ones, so that a suitable hypotensive drug can be chosen in each case. It should also be reported whether the patient is being treated with lithium salts to draw attention to possible interactions with some hypotensive drugs (specifically, diuretic and antihypertensive drugs that act on the renin-angiotensin system).

Endocrine and Metabolic Disease

Diagnostic measures: weight, height, body mass index (BMI = weight/height in m^2) and waist circumference should be measured at baseline, as well as blood tests for glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, TSH, and prolactin (only in case of menstrual disorders, sexual dysfunction, or a pediatric population). At every visit, weight should be measured (once a month at most), as well as height if the patient is growing. The remaining measurements should be repeated annually, if they are within the normal range (BMI < 25 kg/ m^2 , HDL-C in men ≥ 40mg/ dL and

women ≥ 50 mg/ dL, triglycerides ≤ 150 mg/ dL, blood glucose < 100 mg/ dL, TSH between 0.3-6 mU/ L, and prolactin < 20 ng/ mL.

If blood glucose is between 100 mg/dL and 126 mg/dL, TSH higher than 6 mU/L, or prolactin > 20 ng/mL then the blood tests should be repeated. In addition, repeat TSH 3 or 6 months after beginning lithium therapy.

If metabolic syndrome is present (defined by at least 3 of the following criteria: waist circumference in men > 102 cm, and in women > 88 cm; HDL-C in men < 40 mg/ dL, and in women < 50 mg/ dL; BP > 130/ 85 mm Hg; triglycerides > 150 mg/ dL; blood glucose > 100 mg/ dL) the parameters should be monitored every 6 months and if the patient has gained weight (more than 4 kg).

Prevention measures: all patients should be recommended diet and exercise, as well as reminding them to maintain a healthy lifestyle.

Therapeutic measures: in case of dyslipidemia (total cholesterol > 250 mg/ dL, triglycerides > 200 mg/ dL), metabolic syndrome or diabetes (blood glucose > 126 mg/ dL), the patient should be referred to primary care, as well as considering an alternative to the pharmacological treatment, especially when the drugs are associated with weight increase. In case of weight gain (> 7%baseline), a change of pharmacological treatment should also be considered and the patient referred to the primary care physician if this gain is accompanied by negative changes in cardiovascular risk factors in line with the criteria mentioned.

When TSH remains elevated the patient should be referred to the endocrinologist. The patient should also be assessed when hyperprolactinemia does not have a pharmacological cause, has a clinical impact or reaches concentrations greater than 200 ng/ mL.

Infectious Disease

Diagnostic measures: the following serological tests should be done at baseline and whenever risk behavior is suspected: anti-HIV antibodies (ELISA), anti-HBV (ELISA), anti-HCV (ELISA), and VDRL/ RPR.

Prevention measures: vaccination against hepatitis Bis recommended in patients who present no evidence of infection.

Therapeutic measures: in the case of a positive result the patient should be referred to the appropriate specialist.

Women of Childbearing Age

Prevention measures: women should be asked about their intentions regarding starting a family, psychoeducation should be provided and planned pregnancy endorsed. If pregnancy is not desired, advice should be given on a suitable contraceptive method and the use of condoms recommended if risky sexual behavior exists. If cytochrome P450 induction is present (eg, due to carbamazepine, topiramate, oxcarbamazepine), use higher doses of estrogens or prescribe alternative contraceptive methods and adjust lamotrigine doses (by evaluating plasma levels) if estrogens

are used. Psychoactive drugs with the lowest teratogenicity risk should be used.

Therapeutic measures: In case of pregnancy, individual risk-benefit should be assessed regarding the desirability of continuing or interrupting psychopharmacological treatment during the first quarter of pregnancy, drawing attention to the possible risks for the mother and the fetus. This should be considered high risk, and thus involves determining plasma values for all possible drugs (especially for lithium, valproate, and carbamazepine) as well as testing for liver and kidney toxicity and ruling out gestational diabetes and thyroid abnormalities. Furthermore, if anticonvulsants or lithium are being used, fetal morphology has to be assessed and screening for neural tube malformations and heart disease (fetal echocardiography) performed.

Treatment during pregnancy should be simplified to the utmost, considering adjusting the dose according to blood dilution during the second and third quarter of the pregnancy. If the patient is taking valproate or carbamazepine, supplements of folic acid should be administered throughout gestation.

Management of Addictions

Diagnostic measures: record substance use at baseline and at each visit. Complete blood count should be performed to determine mean corpuscular volume (MCV) and liver function tests to determine markers of alcohol consumption.

Prevention measures: psychoeducation should be provided on the risks associated with the consumption of substances in relation to the natural history of disease and possible interactions with the treatment.

Therapeutic measures: patients who smoke should be encouraged to follow a smoking cessation program and use nicotine replacement therapy, such as patches or chewing-gum. Assess the effect of the prescribed therapy on substance abuse, such as valproate in the case of alcohol. Consider referring the patient to health care centers specializing in dual pathology.

Mortality/Suicide Prevention

Diagnostic measures: bipolar disorder should be diagnosed as early as possible, and suitable treatment initiated. Take the history of the disorder taking into account that some factors are associated with greater risk of suicide (early onset, depressive polarity or mixed affective episodes, rapid cycling, bipolar type II, etc). Bicit information on any background of personal suicide attempts, as well as substance abuse.

Prevention measures: Explore suicidal ideation at each visit. When necessary prescribe admission.

Other Medical Disorders

Diagnostic measures: gather information on any personal history of peptic ulcers, migraine, respiratory disease and allergies.

Table 1. Protocol for Monitoring Physical Health in Bipolar Disorder Patients	n Bipolar Disorder Patients		
First Visit	At Each Visit	Yearly Visit	Observations
Case History			
Personal background (including physical and psychiatric clinical manifestations of bipolar disorder) Medical and psychiatric family background Tendency to suicide (family background, personal, and current situation) Signs or symptoms indicating organic disease Concomitant medication	Evaluate new signs or symptoms Evaluate suicidal ideation or plans		
Lifestyle (diet and exercise) Ask about sexual dysfunction Ask about/ provide advice on the more suitable contraceptive ^a method Warn about the risk of pharmacological interactions that increase contraceptive failure Ask about intentions regarding childbearing Pre-conception guidance if pregnancy desired		Ask women about intentions regarding childbearing Check that the contraceptive method ^b used does not interfere with the treatment	 Assess levels of lamotrigine if hormonal contraception with estrogens is being used Recommend the use of condoms, if risky sexual behavior is present
Smoking habits (duration, amount, starting age, disposition regarding cessation) Alcohol consumption: frequency and amount Other substance abuse and addiction	Smoking habits (disposition regarding cessation) Alcohol consumption Other addictions		
Physical exploration			
Weight, height, BMI calculation, waist circumference, blood pressure and pulse	Weight, height (if patient is still growing), BMI calculation, blood pressure, and pulse	Waist circumference	

Blood test		
Hemogram including MCV Biochemical study ^a (electrolytes, full lipid profile, renal function, liver function, and blood glucose)	Hemogram including MCV ^D Biochemical study ^D (electrolytes, full lipid profile, renal function, liver function, and blood glucose)	 Certain treatments can alter some parameters. For example, calcium levels should be checked in patients being treated with lithium If initial results are abnormal, there is weight gain > 5% or multiple cardiovascular risk factors present, the levels should be measured more frequently
TSH, ^a prolactin, ^b HIV, HBV, ^c HCV, VDRL ^d	TSH, HIV, HBV, HCV, VDRL	1. Also measure when initiating treatment with lithium and 3-6 months later 2. Perform only if there is clinical evidence of menstrual disorders or sexual dysfunction, repeat subsequently. Perform in pediatric population 3. Hepatitis B vaccination is recommended in patients with no evidence of infection 4. If risky behaviour is suspected 5. If initial serological tests are negative but risky behaviour is suspected
Treatments		
Recommend healthy lifestyle, without alcohol or tobacco consumption Diet Iow in fats and simple sugars! to sustain appropriate weight Daily physical exercise	Recommendations at baseline visit Review of treatment and assessment of adverse reactions Review of treatment compliance	1. Sweets, jams, sweetened fizzy drinks, etc
Reference values for diagnosis: Hypertension: $\geq 140'$ 90 mm Hg. Obesity and $\geq 140'$ 90 mm Hg. Obesity: normal BMI < 25 kg/ m^2 , overweight 25-30 kg/ m^2 and obesity ≥ 30 kg/ m^2 . Metabolic syndrome: at least 3 out of the following 5 criteria: waist circumference ≥ 102 cm in metriglycerides ≥ 150 mg/ dL; glucose ≥ 100 mg/ dL; SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg. Diabetes: if fasting blood glucose ≥ 126 mg/ dL on 2 tests or random blood glucose ≥ 200 mg/ dL. Obysipidemia: Total cholesterol ≥ 200 mg/ dL, HDL-C < 40 mg/ dL, LDL-C ≥ 130 mg/ dL, or triglycerid Subclinical hypothyroidism: if TSH > 6 mU/ L repeat test; if the result is the same, assess the need if serological tests indicate active infection patient should be referred to the specialist. Measuring BMI: weight of the subjects in kilograms divided by the square of their height in meters. Measuring waist circumference: unclothed standing subject. Locate the upper edge of the iliac creto the ground. The reading is taken at the end of a normal expiration.	Reference values for diagnosis: Hypertension: ≥ 140/ 90 mm Hg. Chesity: normal BM < 25 kg/ m², overweight 25-30 kg/ m² and obesity ≥ 30 kg/ m². Wetabolic syndrome: at least 3 out of the following 5 criteria: waist circumference ≥ 102 cm in men or ≥ 88 cm in women; HDL-C < 40 mg/ dL in men or < 50 mg/ dL in women; triglycerides ≥ 150 mg/ dt. SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg. Triglycerides ≥ 150 mg/ dt. SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg. Diabetes: if fasting blood glucose ≥ 126 mg/ dt. DL-C > 130 mg/ dt. Diabetes: if fasting blood glucose ≥ 126 mg/ dt. DL-C > 130 mg/ dt., Dr. C ≥ 130 mg/ dt. Subclinical hypothyroidism: if TSH > 6 mU/ L repeat test; if the result is the same, assess the need to refer to specialist. No absolute criterion for withdrawal of medication. If serological tests indicate active infection patient should be referred to the specialist. Measuring BMI: weight of the subjects in kilograms divided by the square of their height in meters. Measuring waist circumference: undothed standing subject. Locate the upper edge of the iliac crests and surround the waist with a measuring tape above that point, parallel to the ground. The reading is taken at the end of a normal expiration.	-C< 40 mg/dL in men or < 50 mg/dL in women; solute criterion for withdrawal of medication.

Therapeutic measures: take into account possible interactions between lithium and non-steroid antiinflammatory drugs used for the symptomatic treatment of migraine. The presence or onset of kidney failure should be monitored and lithium doses adjusted accordingly. The corticoid steroids used for asthma control and lung diseases can provoke affective episodes.

Consensus Decalogue

- 1. The Spanish Society of Psychiatry (SEP) and the Spanish Society of Biological Psychiatry (SEPB) in collaboration with the Spanish Society of Rural and General Medicine (SEMERGEN) and the Spanish Society of Family and Community Medicine (semFYC) consider that bipolar disorder is associated with a striking deterioration in physical health, and disability due to factors inherent to the disorder itself, less awareness regarding healthy habits and the effect of some of the treatments.
- 2. The Spanish Strategy for Mental Health and the European Strategy for Mental Health, as well as WHO, promote the improvement of physical health in patients with mental illnesses and the use of preventive measures to promote health.
- 3. Bipolar disorder patients present a greater incidence of cardiovascular, metabolic, respiratory, neurological, and infectious diseases than the general population, greater total mortality (cardiovascular, respiratory, and infectious disease), and an increased risk of suicide.
- 4. Access to health care resources needs to be improved for patients with bipolar disorder, as well as the degree of coordination between secondary and primary health services in order to provide better care regarding the mental and physical health of these patients.
- 5. A full clinical history is essential as well as providing integrated treatments that include caring for the physical health of bipolar disorder patients.
- 6. Measures are recommended (protocol for physical health monitoring in bipolar disorder patients) aimed at the prevention, diagnosis, and management of concomitant diseases, factors, and risky behaviour associated with bipolar disorder.
- 7. Monitoring and specific care are required for the most vulnerable patients with bipolar disorder, such as elderly people, children and adolescents and women of childbearing age.
- 8. Psychoeducational programs will incorporate aspects aimed at promoting physical health and improving lifestyles, in addition to those directly related to mental health and relapse prevention.
- 9. In order to improve physical health in bipolar disorder patients, continuous education is needed for clinical psychiatrists, primary care physicians, and other health professionals.
- 10. Finally, the sponsoring societies (SEP, SEPB, SEMER-GEN and semFYC) urge the greatest possible dissemination

of this Spanish Consensus to promote caring for the physical health of bipolar disorder patients as an integral part of their treatment.

Conclusions

This project was promoted by the Spanish Society of Psychiatry (SEP) and the Spanish Society of Biological Psychiatry (SEPB), in collaboration with the Spanish Society of Rural and General Medicine (SEMERGEN) and the Spanish Society of Family and Community Medicine (semFYC), and established a Consensus on the Evaluation of Physical Health and the problems of bipolar disorder patients throughout their lifetime. This consensus decalogue summarizes the most relevant points in this regard, in the hope that its dissemination will have an impact on the psychosocial functioning, quality of life, and life expectancy of these patients in Spain.

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References

- Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord. 1998;50:143-51.
- Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007;64:543-52.
- Murray CJL, Lopez AD, eds. The global burden of disease and injury series, volume 1: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge: Harvard University Press; 1996
- Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34-38 years. J Affect Disord, 2002;68:167-81.
- Baldessarini RJ, Tondo L. Suicide risk and treatments for bipolar disorder patients. JAMA. 2003;290:1517-9.
- Osby U, Brandt L, Correia N, Ekbom A, Sparén P. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry. 2001;58:844-50.
- Torrent C, Amann B, Sánchez-Moreno J, Colom F, Peinares M, Comes M, et al. Weight gain in bipolar disorder: pharmacological treatment as a contributing factor. Acta Psychiatr Scand. 2008;118:4-18.
- Garcia-Portilla MP, Saiz BP, Bascaran MT, Martínez S, Benabarre A, Serra P, et al on behalf of the General Health Status in Bipolar Disorder Collaborative Group. Cardiovascular risk in bipolar disorder patients. J Affect Dis. 2008. In press.
- McIntyre RS, Soczynska JK, Beyer JL, Woldeyohannes HO, Law CW, Miranda A, et al. Medical comorbidity in bipolar disorder: re-prioritizing unmet needs. Curr Opin Psychiatry. 2007;20: 406-16.
- McEwen BS. Mood disorders and allostatic load. Biol Psychiatry. 2003;54:200-7.
- Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209-23.
- Black DW, Winokur G, Bell S, Nasrallah A, Hulbert J. Complicated mania. Comorbidity and immediate outcome in the treatment of mania. Arch Gen Psychiatry. 1988;45:232-6.
- D'Ercole A, Skodol AE, Struening E, Curtis J, Millman J. Diagnosis of physical illness in psychiatric patients using axis III and a standardized medical history. Hosp Community Psychiatry. 1991;42:395-400.
- Koranyi EK. Morbidity and rate of undiagnosed physical illnesses in a psychiatric clinic population. Arch Gen Psychiatry. 1979; 36:414-9.
- Kupfer DJ. The increasing medical burden in bipolar disorder. JAMA. 2005;293:2528-30.
- Kilbourne AM, Post EP, Nossek A, Drill L, Cooley S, Bauer MS. Improving medical and psychiatric outcomes among individuals with bipolar disorder: a randomized controlled trial. Psychiatr Serv. 2008;59:760-8.

- Saiz J, Bobes J, Vallejo J, Giner J, García-Portilla MP. Consenso sobre la salud física del paciente con esquizofrenia de las Sociedades Españolas de Psiquiatría and de Psiquiatría Biológica. Actas Eso Psiquiatr. 2008. In press.
- Fleischhacker WW, Cetkovich-Bakmas M, De Hert M, Hennekens CH, Lambert M, Leucht S, et al. Comorbid somatic illnesses in patients with severe mental disorders: clinical, policy, and research challenges. J Clin Psychiatry. 2008;69:514-9.
- Yatham LN, Kennedy SH, O'Donovan C, Parikh S, MacQueen G, McIntyre R, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of bipolar disorder patients: consensus and controversies. Bipolar Disord. 2005;7 Suppl 3:5-69.
- Ghadirian AM, Engelsmann F. Somatic illness in manic-depressive and schizophrenic patients. J Psychosom Res. 1985; 29:281-6.
- 21. Yates WR, Wallace R. Cardiovascular risk factors in affective disorder. J Affect Disord. 1987;12:129-34.
- Winokur G, Coryell W, Endicott J, Akiskal H. Further distinctions between manic-depressive illness (bipolar disorder) and primary depressive disorder (unipolar depression) Am J Psychiatry. 1993:150:1176-81.
- Calabrese JR, Hirschfeld RM, Reed M, Davies MA, Frye MA, Keck PE, et al. Impact of bipolar disorder on a U.S. community sample. J Clin Psychiatry. 2003;64:425-32.
- Hirschfeld RM, Calabrese JR, Weissman MM, Reed M, Davies MA, Frye MA, et al. Screening for bipolar disorder in the community. J Clin Psychiatry. 2003;64:53-9.
- Nilsson FM, Kessing LV. Increased risk of developing stroke for patients with major affective disorder-a registry study. Eur Arch Psychiatry Clin Neurosci. 2004;254:387-91.
- 26. Kilbourne AM, Cornelius JR, Han X, Pincus HA, Shad M, Salloum I et al. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disord. 2004;6:368-73.
- Oedegaard KJ, Fasmer OB. Is migraine in unipolar depressed patients a bipolar spectrum trait? J Affect Disord. 2005;84: 233-42
- Carney CP, Jones LE. Medical comorbidity in women and men with bipolar disorders: a population-based controlled study. Psychosom Med. 2006;68:684-91.
- Johannessen L, Strudsholm U, Foldager L, Munk-Jørgensen P. Increased risk of hypertension in bipolar disorder patients and patients with anxiety compared to background population and patients with schizophrenia. J Affect Disord. 2006; 95:13-7.
- McIntyre RS, Konarski JZ, Soczynska JK, Wilkins K, Panjwani G, Bouffard B, et al. Medical comorbidity in bipolar disorder: implications for functional outcomes and health service utilization. Psychiatr Serv. 2006;57:1140-4.
- 31. Birkenaes AB, Opjordsmoen S, Brunborg C, Engh JA, Jonsdottir H, Ringen BP, et al. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. J Qin Psychiatry. 2007;68:917-23.
- Kilbourne AM, Brar JS, Drayer RA, Xu X, Post EP: Cardiovascular disease and metabolic risk factors in male patients with schizophrenia, schizoaffective disorder, and bipolar disorder. Psychosomatics. 2007;48:412-7.
- Lin HC, Tsai SY, Lee HC. Increased risk of developing stroke among bipolar disorder patients after an acute mood episode: a six-year follow-up study. J Affect Disord. 2007;100: 49-54
- Strakowski SM, Tohen M, Stoll AL, Faedda GL, Goodwin DC. Comorbidity in mania at first hospitalization. Am J Psychiatry. 1992;149:554-6.
- McEroy SL, Frye MA, Suppes T, Dhavale D, Keck PE Jr, Leverich GS, et al. Correlates of overweight and obesity in 644 bipolar disorder patients. J Clin Psychiatry. 2002;63:207-13.

Beyer J, Kuchibhatla M, Gersing K, Krishnan KR. Medical comorbidity in a bipolar outpatient clinical population. Neuropsychopharmacology. 2005;30:401-4.

- Fenn HH, Bauer MS, Altshuler L, Evans DR, Williford WO, Kilbourne AM et al. VA Cooperative Study #430 Team. Medical comorbidity and health-related quality of life in bipolar disorder across the adult age span. J Affect Disord. 2005;86:47-60.
- Thompson WK, Kupfer DJ, Fagiolini A, Scott JA, Frank E. Prevalence and clinical correlates of medical comorbidities in patients with bipolar I disorder: analysis of acute-phase data from a randomized controlled trial. J Clin Psychiatry. 2006;67: 783-8.
- 39. Garcia-Portilla MP, Saiz BP, Benabarre A, Sierra P, Perez J, Rodriguez A, et al. The prevalence of metabolic syndrome in bipolar disorder patients. J Affect Disord. 2008;106:197-201.
- Strudsholm U, Johannessen L, Foldager L, Munk-Jørgensen P. Increased risk for pulmonary embolism in bipolar disorder patients. Bipolar Disord. 2005;7:77-81.
- Ewald H, Mortensen PB, Mors O. Decreased risk of acute appendicitis in patients with schizophrenia or manic-depressive psychosis. Schizophr Res. 2001;49:287-93.
- Bauer MS, Whybrow PC, Winokur A. Rapid cycling bipolar affective disorder. I. Association with grade I hypothyroidism. Arch Gen Psychiatry. 1990:47:427-32.
- Benazzi F. Clinical differences between bipolar II depression and unipolar major depressive disorder: lack of an effect of age. J Affect Disord. 2003;75:191-5.
- 44. Cassidy F, Ahearn E, Carroll BJ. ⊟evated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry. 1999;156:1417-20.
- Emslie JL, SIverstone JT, Mann JI, Williams SM, Romans SE. Prevalence of overweight and obesity in bipolar patients. J Clin Psychiatry. 2000;61:179-84.
- 46. Lilliker SL. Prevalence of diabetes in a manic-depressive population Compr Psychiatry. 1980;21:270-5.
- Regenold WT, Thapar RK, Marano C, Gavirneni S, Kondapavuluru PV. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use. J Affect Disord. 2002;70:19-26.
- Thomsen AF, Kessing LV. Increased risk of hyperthyroidism among patients hospitalized with bipolar disorder. Bipolar Disord. 2005;7:351-7.
- Blehar MC, DePaulo JR Jr, Gershon ES, Reich T, Smpson SG, Nurnberger JI Jr. Women with bipolar disorder: findings from the NIMH Genetics Initiative sample. Psychopharmacol Bull. 1998:34:239-43.
- Fagiolini A, Frank E, Houck PR, Mallinger AG, Swartz HA, Buysse DJ, et al. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. J Clin Psychiatry. 2002:63:528-33.
- Fagiolini A, Frank E, Scott JA, Turkin S, Kupfer DJ. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. Bipolar Disord. 2005;7:424-30.
- Kupka RW, Nolem WA, Post RM, McErroy SL, Altshuler LL, Denicoff KD, et al. High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. Biol Psychiatry. 2002;51:305-11.
- Valle J, Ayuso-Gutierrez JL, Abril A, Ayuso-Mateos JL. Evaluation of thyroid function in lithium-naive bipolar patients. Eur Psychiatry. 1999;14:341-5.
- Ruzickova M, Saney C, Garnham J, Alda M. Clinical features of bipolar disorder with and without comorbid diabetes mellitus. Can J Psychiatry. 2003;48:458-61.
- Wang PW, Sachs GS, Zarate CA, Marangell LB, Calabrese JR, Goldberg JF, et al. Overweight and obesity in bipolar disorders. J Psychiatr Res. 2006;40:762-4.

- Scras A, Rejas J, Navarro R, Serrat J, Blanca M. Metabolic syndrome in bipolar disorder: a cross-sectional assessment of a Health Management Organization database. Bipolar Disord. 2008; 10:607-16.
- Beyer JL, Taylor L, Gersing KR, Krishnan KR. Prevalence of HIV infection in a general psychiatric outpatient population. Psychosomatics. 2007;48:31-7.
- Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Cole S, Krivogorsky B, et al. Infection with herpes simplex virus type 1 is associated with cognitive deficits in bipolar disorder. Biol Psychiatry. 2004;55:588-93.
- Himelhoch S, McCarthy JF, Ganoczy D, Medoff D, Dixon LB, Blow FC. Understanding associations between serious mental illness and HIV among patients in the VA Health System. Psychiatr Serv. 2007;58:1165-72.
- Nakimuli-Mpungu E, Musisi S, Mpungu SK, Katabira E. Primary mania versus HIV-related secondary mania in Uganda. Am J Psychiatry. 2006;163:1349-54.
- Marchesi C, de Ferri A, Petrolini N, Govi A, Manzini GC, Coiro V, et al. Prevalence of migraine and muscle tension headache in depressive disorders. J Affect Disord. 1989;16:33-6.
- Shulman KI, Tohen M, Satlin A, Mallya G, Kalunian D. Mania compared with unipolar depression in old age. Am J Psychiatry. 1992:149:341-5.
- 63. Fasmer OB. The prevalence of migraine in patients with bipolar and unipolar affective disorders. Cephalalgia. 2001;21:894-9.
- 64. Kessing LV, Nilsson FM. Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. J Affect Disord. 2003;73:261-9.
- Nilsson FM, Kessing LV, Bolwig TG. On the increased risk of developing late-onset epilepsy for patients with major affective disorder. J Affect Disord. 2003;76:39-48.
- Low NC, Du Fort GG, Cervantes P. Prevalence, clinical correlatos, and treatment of migraine in bipolar disorder. Haedache. 2003;43:940-9.
- 67. Mahmood T, Romans S, SIverstone T. Prevalence of migraine in bipolar disorder. J Afffect Disrd. 1999;52:239-41.
- Mukherjee S, Posen AM, Caracci G, Shukla S. Persistent tardive dyskinesia in bipolar patients. Arch Gen Psychiatry. 1986;43: 342-6.
- Snowdon J. A retrospective case-note study of bipolar disorder in old age. Br J Psychiatry. 1991;158:485-90.
- Sajatovic M, Blow FC, Ignacio RV. Psychiatric comorbidity in older adults with bipolar disorder. Int J Geriatr Psychiatry. 2006; 21:582-7
- Hippisley-Cox J, Vinogradova Y, Coupland C, Parker C. Risk of malignancy in patients with schizophrenia or bipolar disorder: nested case-control study. Arch Gen Psychiatry. 2007;64: 1368-76.
- Jablensky AV, Morgan V, Zubrick SR, Coger C, Yellachich LA. Pregnancy, delivery, and neonatal complications in a population cohort of women with schizophrenia and major affective disorders. Am J Psychiatry. 2005;162:79-91.
- Gonzalez-Pinto A, Gutierrez M, Ezcurra J, Aizpuru F, Mosquera F, Lopez P, et al. Tobacco smoking and bipolar disorder. J Clin Psychiatry. 1998;59:225-8.
- Morris CD, Giese AA, Turnbull JJ, Dickinson M, Johnson-Nagel N. Predictors of tobacco use among persons with mental illnesses in a statewide population. Psychiatr Serv. 2006;57:1035-8.
- Weeke A, Vaeth M. Excess mortality of bipolar and unipolar manic-depressive patients. J Affect Disord. 1986;11:227-34.
- Weeke A, Juel K, Vaeth M. Cardiovascular death and manic-depressive psychosis. J Affect Disord. 1987;13:287-92.
- 77. Saku M, Tokudome S, Ikeda M, Kono S, Makimoto K, Uchimura H, et al. Mortality in psychiatric patients, with a specific focus on cancer mortality associated with schizophrenia. Int J Epidemiol. 1995;24:366-72.

- Dutta R, Boydell J, Kennedy N, Van Os J, Fearon P, Murray RM. Suicide and other causes of mortality in bipolar disorder: a longitudinal study. Psychol Med. 2007;37:839-47.
- Tsuang MT, Woolson RF, Fleming JA. Causes of death in schizophrenia and manic-depression. Br J Psychiatry. 1980;136: 239-42.
- 80. Black DW, Winokur G, Nasrallah A. Mortality in patients with primary unipolar depression, secondary unipolar depression, and bipolar affective disorder: a comparison with general population mortality. Int J Psychiatry Med. 1987;17:351-60.
- 81. Kallner G, Lindelius R, Petterson U, Stockman O, Tham A. Mortality in 497 patients with affective disorders attending a lithium clinic or after having left it Pharmacopsychiatry. 2000;33:8-13.
- Høyer EH, Mortensen PB, Olesen AV. Mortality and causes of death in a total national sample of patients with affective disorders admitted for the first time between 1973 and 1993. Br J Psychiatry. 2000;176:76-82.
- Evans NJ, Baldwin JA, Gath D. The incidence of cancer among in-patients with affective disorders. Br J Psychiatry. 1974;124: 518-25.