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# Bipolar disorder associated to substance use disorders (dual diagnosis). Systematic review of the scientific evidence and expert consensus

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The present work focuses on the so-called dual diagnosis (DD): bipolar disorder (BD) associated with substance use disorders (SUD). Although the psychiatrists who treat patients with BD and physicians in charge of patients with SUD frequently find this association with DD, unfortunately there are few scientific works that have studied this association. The Spanish Working Group on Bipolar Disorders in Dual Diagnosis reviewed the published material using a Medline search and selected the most relevant articles. Following this, the work group developed an expert consensus in DD and finally, a survey was performed among a group of experts in this disorder to cover the areas that were not fully addressed by the scientific evidence or in those areas in which the work group was unable to reach a consensus. We conclude that, in view of the above, establishment of a consensus is a valid tool to complement the current scientific evidence.

**Key words:**
Bipolar disorder. Substance dependence. Dual diagnosis. Expert consensus. Scientific evidence.

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## Trastorno bipolar asociado al uso de sustancias adictivas (patología dual). Revisión sistemática de la evidencia científica y consenso entre profesionales expertos

El presente trabajo está focalizado en la llamada patología dual (PD): trastorno bipolar (TB) asociado a un trastorno por uso de sustancias (TUS). A pesar de que tanto los psiquiatras que tratan a pacientes con TB como los médicos que tratan a los pacientes con TUS encuentran frecuentemente esta asociación; lamentablemente las publicaciones que exploran la PD son escasas. El Grupo Español de Trabajo en Patología Dual en Trastorno Bipolar realizó una revisión del material publicado mediante una búsqueda bibliográfica en Medline y seleccionó los artículos relevantes publicados hasta el momento; a continuación se llevó a cabo un consenso de expertos y finalmente se realizó una encuesta a expertos en PD para responder a las áreas que no estaban suficientemente cubiertas por la evidencia científica o en las cuales no se llegó a un consenso dentro del grupo de trabajo. Se concluye que en las actuales circunstancias el establecimiento de un consenso constituye una herramienta muy útil para complementar la evidencia científica existente.

**Palabras clave:**
Trastorno bipolar. Dependencia de sustancias. Patología dual. Consenso de expertos. Evidencia científica.

## INTRODUCTION

The term dual diagnosis indicates the coexistence of two disorders that may or may not be independent, although they must be interactive[1]. It is commonly used to refer to the concomitant presentation of a substance use disorder (SUD) and another mental disorder. The present work studies dual diagnosis related with bipolar disorder (BD).

The prevalence of BD, using the most extensive definition of this disease (bipolar spectrum) would be between 5 % and 7 % of the general population[2]. In relationship with the dual diagnosis associated to this disorder, it has already been described in the study Epidemiologic Catchment Area Survey (ECA) that 60.7 % of the subjects with type I bipolar disorder had a comorbid SUD. This percentage exceeds that of any other psychiatric disorder, including type II bipolar disorder that also has an equally high comorbidity[3], and is only exceeded by antisocial personality disorder. These comorbidity rates significantly increase if the most benign and mild cases of BD or cyclothythmic disorder that often occur subclinically or with sub-threshold symptoms, are taken into account. These affective pictures may occur, and in fact often do, comorbidly with substance use disorders and are generally, in the clinical practice, considered, diagnosed and treated exclusively as substance

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abuse or dependence, overlooking the presence of the affective disorder, which reduces diagnostic and therapeutic possibilities[4]. This indicates the elevated prevalence of dual disorder of BD and SUD, which is why it has clinical and health care importance.

According to the data provided by the European Monitoring Center for Drugs and Drug Addictions[5], the prevalence rate of cocaine use in young adults (from 15 to 34 years) in Europe places Spain practically on the same level as Russia and the United States (4.6%), much above the mean for the European Union (1.8%). Similar data are observed regarding the use of amphetamines, ecstasy or cannabis. This fact could support the special relevance of the problem in our country and indirectly «make it possible to extrapolate» its repercussion on the dual diagnosis.

The causes of this comorbidity have been the object of different hypotheseis, among which impulsivity, considered by different authors as an underlying psychopathology dimension in all the periods of bipolar disease[6], is one of the most relevant. Impulsivity is also identified as a primordial factor in SUD. Furthermore, both disorders, BD and SUD, could represent manifestations of a single genetic diathesis[7].

Patients who suffer this dual diagnosis have worse clinical course, tend to have greater chronicity of both comorbid disorders[8,9], have symptoms that are more difficult to treat, such as those of the mixed affective type, and finally have greater frequency of rapid cycles and hospitalization. On the other hand, these patients have an increased risk of suicide during their lifetime in comparison with BD patients without substance abuse or dependence (39.5% versus 23.8%, respectively)[10]. All these factors underscore the importance of an adequate and complete diagnostic evaluation of this dual diagnosis and of performing an individualized treatment, considering all the comorbid disorders, their interrelationships and prognostic implications[1] with the final objective of achieving a treatment in these patients that would provide the best possible therapeutic effectiveness.

In this context, a clinical guideline was elaborated using the methodology of exhaustive review of the scientific evidence. When there was no factual base for the recommendations, consensus was obtained from the clinical experts on the clinical-therapeutic attitudes in patients where there was coexistence of BD and SUD (abuse or dependence). The present work represents the publication of the results of the document entitled *Guía clínica española para el manejo del paciente con trastorno bipolar asociado al uso de sustancias (patología dual)* («Spanish clinical guidelines for the management of the patient with bipolar disorder associated to the use of substances [dual diagnosis]») and explains, in the first place, the scientific evidence available at present on this disorder. In the second place, it makes recommendations on the clinical-therapeutical management of these patients in our country, both in the care setting, that is considered the common one in the current situation, and in another that may be classified as ideal. Ideal management is understood to be that which is performed by the professional if he or she has the necessary human and financial resources and sufficient time to carry out this activity.

## MATERIAL AND METHODS

A work group with experience in the management of dual diagnosis was formed to conduct this study and a total of three meetings were held. Before each meeting, preparatory work was made to collect all the material. At the end of these, the actions agreed on in the work group were established. During the first meeting, the most important clinical aspects of the dual diagnosis were defined based on the experience itself of the work group and a bibliographic search made prior to the meeting. Furthermore, the articles were discussed based on the scientific evidence they provided. During the second meeting, held two months later, the survey aimed at a selection of professionals with experience in the management of this disorder and based on the points of interest generated during the first meeting was discussed and approved. During the following weeks, the surveys were sent to the professionals and the corresponding statistical analysis was performed. The final meeting was conducted at four months of the second meeting. In it, the results were presented, and analyzed by the work group and the recommendations were incorporated.

It is important to stress that during the three work meetings, whenever there was no consensus, unanimity was always sought in the criteria by agreement of all the group participants. If this consensus could not be obtained after the discussion, the proposal was withdrawn.

### Review of the scientific evidence

The recommendations based on the scientific evidence were obtained through an extensive review of the dual diagnosis bibliography on bipolar disorder from the year 1994 to 2005. In the search made in Medline, the following key words were used: Drug abuse OR substance abuse AND bipolar disorder. Forty articles out of a total of 1,623 abstracts were selected. Of these, those articles that were observational studies or clinical trials that included patients with dual diagnosis were selected.

### Survey methodology

Based on the data obtained in the bibliographic review, a survey was designed that was aimed at specialists in psychiatry, both in the setting of the psychiatric care network and in that of addictive disorders. The objective was to know their opinion on the actions related with the diagnosis, treatment and follow-up of patients with BD and

SUD, in those in which sufficient evidence had not been generated in the bibliographic review. It was also important to know the opinion they had from their experience on the aspects already clarified by the scientific evidence. They were asked about these actions, both in their usual clinical practice and under ideal work conditions, when possible differences could be expected. The survey was reviewed by the same work group, who gave their approval before it was sent to the rest of the specialist.

The work group provided a list of 60 candidates located in centers of the entire Spanish territory. At least two surveys were sent by E-mail to all the professionals proposed explaining the project. A total of 33% responded during the months of July to September of the year 2005. The survey collected the opinions of 20 experts on those clinical questions of great importance, especially on those lacking published scientific evidence (table 4).

Based on the different levels of scientific evidence and the consensus among the experts, the recommendation grades were defined, both in the case of scientific evidence and for recommendations by consensus. In the case of scientific evidence, the recommendation grades came from the methodology proposed by the Centre for Evidence-Based Medicine. The recommendation grade according to the scientific evidence was made up of four categories (A, B, C and D) that correspond in the present article to: A) extremely recommendable; B) favorable recommendation, but not imperative; C) favorable recommendation, but not conclusively, and D) the action was neither recommended nor disapproved.

In the case of the recommendation by consensus, four categories were also established (a, b, c and d) corresponding to: a) extremely recommendable; b) favorable recommendation, but not imperative; c) favorable recommendation, but not conclusively, and d) the action was neither recommended nor disapproved. The criteria detailed for each category of recommendation are presented in tables 1, 2 and 3.

In this document, only those statements that the present work group have considered to correspond at least to grade A, that is, ≥90% of the level of expert consensus and B, 70%-90% of the level of expert consensus, have been included. In addition, regarding scientific evidence, grades A, «extremely recommendable» and B, «favorable recommendation but not imperative», according to the previously presented criteria were included.

## Presentation of results

The results of the work group are presented in different sections according to the availability of results in the following order: first, scientific evidence; second, consensus of experts and third, the results of the survey. When the scientific evidence was solid (evidence A level), it was not considered to be necessary to recur to any type of consensus or survey. For this reason, in certain sections, neither the results of the consensus or survey accompanying the findings of the evidence are included. The conclusions of this project have been stated in form of recommendations that aim to form guidelines that determine the clinical action in the management of the patients who have a concomitant presentation of BD and SUD.

The strength of the recommendations has been classified according to the following criteria: on the one hand, the grade of scientific evidence that supports them (publications) and, on the other hand, when said evidence does not

**Table 1** Evidence of studies on treatment, prevention, etiology and complications

| Grade of recommendation | Source |
|---|---|
| A | Systematic review of randomized clinical trials with homogeneity (that include studies with comparable results and in the same direction) |
| | Individual randomized clinical trial (with intervals of close confidence) |
| | Efficacy demonstrated by the clinical practice and not by experimentation |
| B | Systematic review of cohort studies, with homogeneity (that includes studies with comparable results and inthe same direction) |
| | Study of individual cohorts and low quality randomized clinical trials (<80% of follow-up) |
| | Research of results in health |
| | Systematic review of case-control studies, with homogeneity (that include studies with comparable results and in the same direction) |
| | Individual case control studies |
| C | Series of cases and cohort studies and case-control studies of low quality |
| D | Expert's opinion without explicit critical assessment |

**Table 2** Diagnostic studies

| Grade of recommendation | Source |
|---|---|
| A | Systematic review of level 1 diagnostic studies (high quality, with homogeneity) that include studies with comparable results and in the same direction, rules of diagnostic decision with 1b studies from different clinical sites |
| | 1b studies of cohorts that validate the quality of a specific test, with some good reference standards (independent of the test) or categorization algorithms based diagnosis (diagnostic decision rules) studied in a single site |
| | Diagnostic tests with such a high specificity that a positive result confirms the diagnosis and with such a high sensitivity that a negative result rules out the diagnosis |
| B | Systemic review of level 2 diagnostic studies (median quality) with homogeneity (that includes studies with comparable results and in the same direction) |
| | Exploratory studies which, for example, through a logistic regression, determine what factors are significant with some good reference standards (independent of the test). Categorization algorithm based diagnosis (diagnostic decision rules), derived or validated in separate samples or data bases |
| | Systematic review of case-control studies, with homogeneity (that includes studies with comparable results and in the same direction) |
| | Studies with non-consecutive patients, without reference standards applied consistently |
| C | Low quality cases and controls or without independent standard |
| D | Expert's opinion without explicit critical assessment |

exist or does not fulfill the requirements to be considered as level A or B, according to the clinical opinion of those forming the work group and the survey answered by experts in this dual diagnosis.

A description analysis was made of relative and accumulative frequencies for each one of the questions on the survey. The data were analyzed statistically using the SPSS program (version 12).

## RESULTS

### Diagnosis

*Scientific evidence*

The following three statements have an A level of recommendation. In general, BD is underdiagnosed in primary care; and there is an associated SUD in a significant proportion of the patients diagnosed of BD, which complicates the diagnosis even more[11]. As is known, abuse of certain stimulant substances may cause symptoms that are not differentiated from mania or hypomania during the time that the drug has a pharmacological effect[12]. Finally, the withdrawal itself of some stimulant substances may produce depressive symptoms, as is also seen in alcohol abstinence, in which the depressive symptoms may persist from two to four weeks[13].

**Table 3** Equivalence between grade of recommendation and consensus level

| Grade of recommendation | Consensus level |
|---|---|
| a | >90% |
| b | 70-90% |
| c | 50-70% |
| d | <50% |

#### Depression

*Expert consensus*

Depression in patients with BD and SUD is evaluated with the same instruments and specific scales of depression used in patients with BD (level of evidence - expert consensus [b]).

*Survey*

In the opinion of most of those surveyed, 4 weeks under ideal conditions are needed to rule out that a depression has been produced or induced by any substance in patients with SUD and with no previous background of BD. However, in the common clinical practice, the decision is generally made at 2 weeks. In the presence of BD with dual diagnosis, the periods needed to rule out such association continue to be the same.

**Table 4** List of participants in the survey

| Nombre |
|---|
| 1. Juan Francisco Ramírez. Provincial Service of Drug Dependence. Huelva |
| 2. José Javier Valls Lapica. Hospital Sagrat Cor. Martorell. Barcelona |
| 3. Belén Arranz. Fundació Hospital/Asil de Granollers. Barcelona |
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| 5. Andrés Porcel Torrens. Unidad de Salud Mental del Área 10. Valencia |
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| 7. Luis San. Hospital Sant Rafael. Barcelona |
| 8. Pedro Holgado Madera. Hospital Universitario 12 de Octubre. Madrid |
| 9. Roberto Rodríguez Jiménez. Hospital Universitario 12 de Octubre. Madrid |
| 10. José Manuel Martínez Delgado. Servicio Provincial de Drogodependencias. Cádiz |
| 11. Francisco González-Saiz. Servicio Provincial de Drogodependencias. Cádiz |
| 12. Enriqueta Ochoa Mangado. Hospital Ramón y Cajal. Madrid |
| 13. Valentín JM Conde López. Hospital Universitario de Valladolid |
| 14. Miguel Ángel Landabaso. Centro de Salud Mental (Drogodependencias). Baracaldo. Vizcaia |
| 15. Josep Solé. Hospital de Sant Boi de Llobregat. Barcelona |
| 16. Pedro Sopelana. Centro de Salud Mental de Alcalá de Henares. Madrid |
| 17. Josep Antoni Ramos. Hospital Universitari de la Vall d'Hebron. Barcelona |
| 18. Francisco Árias Horcajada. Hospital Fundación Alcorcón. Madrid |
| 19. Nestor Szerman. Hospital Virgen de la Torre. Madrid |
| 20. José Martínez-Raga. IDYCA, CEU-Universidad Cardenal Herreray Agencia Valenciana de Salud |

To quantify depression in patients with BD and SUD, most of those surveyed use the usual scales for the evaluation of BD.

## Mania

*Expert consensus*

For those patients with grade (b) mania, the following is recommended: that 2 weeks may be necessary to rule out that a mania episode in a patient with SUD, with or without background of BD, is being induced or provoked by the effect of the drugs and the evaluation of the mania episode in patients with BD and SUD should be done using the usual instruments aimed at patients with BD for mania.

*Survey*

A total of 50% of the professionals surveyed stated that the time used to rule out a first episode of mania in SUD patients without a previous background of BD is less than 2 weeks under the usual clinical practice conditions. Under ideal conditions, 60% believe that 2 or more weeks are required. This time did not vary based on the substance (nicotine, cannabis, alcohol, cocaine, heroin and psychostimulants). If the patient has a previous background of BD, at least 50% of the professionals surveyed believe that the time necessary is less than 2 weeks, both under usual conditions as well as ideal ones of the clinical practice.

For the evaluation of mania in a patient with BD and SUD, most of those surveyed use the same scales as those used for mania without SUD.

## Bipolar disorder

*Screening of depression/mania in patients with substance use disorder*

Expert consensus

With grade a, the following is recommended: in patients with SUD without background of BD and who have episodes of depression/mania, the possible previous symptoms of hypomania should be reevaluated since these may have been interpreted as secondary to the SUD.

Survey

It was found that in patient with SUD without a previous background of BD, most of the professionals surveyed generally focus the anamnesis towards the detection of possible backgrounds of mania or depression.

*Screening of substance use disorder in patients with bipolar disorder*

Expert consensus

The expert consensus gave a recommendation b to the following statement: from a theoretical approach, a urine analysis should be obtained to rule out drug consumption in all the patients who consult with BD. In the clinical practice, this is only done when there is a reasonable doubt and it is technically accessible.

Survey

Most of the professionals surveyed would obtain a urine analysis in patients who come with BD. Under usual conditions, this is only done under certain suppositions, generally when there is suspicion of substance usage. The settings to make the urine analysis, under usual conditions, are: hospital admission, emergency services and specialized clinical offices, ruling out primary care. Under ideal conditions, the emergency service is considered to be the best place.

### Additional recommendations of the work group

Rapid diagnosis is fundamental and the symptoms of BD in patients with SUD and vice versa should always be studied.

## Clinical aspects

*Scientific evidence*

The bibliographic review made it possible to obtain the following two recommendations and conclusions on an evidence A level: patients who present BD and SUD comorbidly develop a more severe picture (with anxiety, mixed or dysphoric mania and rapid cycles) than patients who only have BD[14]. Regarding the severity of the symptoms, BD is less severe in patients who begin with alcohol abuse or dependence and then develop BD than in those who begin with BD. In addition, the former tend to recovery faster[7,15].

The following two conclusions were reached with evidence B level: the patients with affective disorders and drug or alcohol dependence have a greater risk of suicide[16] and, as could be expected, the presence of comorbid SUD makes it difficult to achieve clinical stabilization of the bipolar patient and also significantly worsens their global functioning[17].

### Relationship between bipolar disorder and substance use disorder

Scientific evidence

The bibliographic review made it possible to identify three articles on the recommendation A level in which it is deduced that the case-effect relationship between SUD and BD is not conclusive and may vary in each patient[18]. Regarding the concurrent presence of SUD, it complicates both the diagnosis and management of patients with BD[18]. Thus, as has been previously mentioned, SUD associated with alcohol and other drugs is frequent among individuals with BD[3].

Survey

Most of the professionals surveyed consider that there is comorbidity between SUD and BD in more than 20% of the patients who visit with BD or SUD, the substances associated to greater comorbidity being alcohol and nicotine.

### Frecuencia de visita

*Scientific evidence*

With the scientific evidence selected, it can be recommended on an evidence B level that a regime of 2 visits per week during the acute treatment phase (first ten weeks) is adequate[19,20].

*Expert consensus*

With consensus level (a), the work group believes that patients with BD and SUD visit more frequently than those with BD in the care practice. In addition, the experts reached a b level of consensus regarding the following recommendation: under ideal conditions, a patient with dual diagnosis should be visited at least once a week until the maintenance phase.

*Survey*

Under usual conditions, most of those surveyed have visits with patients with BD and SUD more often than patients with only BD until they reach the maintenance phase. More than half of the professionals would see these patients at least once every 2 weeks. In this case, the usual clinical practice coincides with the ideal conditions practice. During the maintenance phase, most of those surveyed would maintain the same frequency of visits under the usual conditions. However, under ideal conditions, 90% of those surveyed would maintain a visit frequency of at least once a week.

### Hospital admission

*Expert consensus*

In a patient with uncontrolled SUD and personal background of BD, a b level recommendation is made that hospital admission is more necessary. Finally, and with recommendation a grade, the experts consider that when there is a suicide attempt, admission of the patient is especially recommended.

*Survey*

In regards to the decision for hospital admission, this would vary for patients with acute BD associated to SUD in relationship to patients with acute BD without SUD. This difference is maintained both under common conditions and in ideal ones. The decision for hospital admission also would vary in most of those surveyed and under ideal conditions based on whether it is an uncontrolled SUD in the presence or absence of a background of BD. Under usual

conditions, there are still many professionals who would vary their decision for admission but the number is less.

Both in the usual clinical practice and in the ideal one, all the professionals surveyed chose admission when there was a suicide attempt in at patient with BD and SUD.

### Integrated care of the patient

*Expert consensus*

Recommendation level (a) was reached in regards to the need for a coordinated approach to the dual diagnosis.

*Survey*

Under ideal conditions, most of those surveyed would prefer attending to the patient with BD and SUD in an integrated way, that is, by a single professional for both diseases and coordination between the professionals attending to the patient. On the other hand, this integration is less frequent in the usual clinical practice.

### Additional recommendations of the work group

*Scientific evidence*

Having a B level recommendation, patients with BD should be warned about the risk of developing an SUD and about the importance of its early detection[12]. In addition, the self-administered questionnaires may be a valid instrument for the detection of substance abuse in BD patient[21].

*Expert consensus*

*a)* Use/abuse of substances may worsen the BD but if the patient continues to consume drugs, above all, it should be attempted that he or she continues with the treatment. In this sense, the educative approach and reduction of harm from the SUD is very important.

*b)* Special care must be taken when examining patients with alcohol abuse since this may often mask a diagnosis of concomitant BD.

## Treatment of the different phases of bipolar disorder

### Manic episode in the context of bipolar disorder

*Expert consensus*

Grade b recommendation is made that is concomitant SUD is detected in the usual clinical practice, both treatment should be initiated at the same time, without giving priority to one over the other. However, if the SUD presents as an acute intoxication or abstinence syndrome, treatment of the manic episode must be adapted. In regards to the best treatment of a manic episode associated or not to acute intoxication or abstinence syndrome, regardless of the SUD causing drug, the work group considers that the medications to be used are atypical antipsychotics and classical anti-seizure drugs (carbamazepine and valporoate). Finally, with grade (a), the work group considers that the antidepressants are an inadequate treatment for a manic episode associated or not to an acute intoxication or abstinence syndrome, regarding of the SUD causing drug.

*Survey*

It was found that most of the professionals surveyed did not give priority to one treatment above another when there was a manic episode in presence of a comorbid SUD. However, 85% of the professionals surveyed did not deal with the manic episode in presence or in absence of acute intoxication or abstinence syndrome in the same way and they would generally reduce the dose without substituting the active ingredient.

In the opinion of those surveyed, treatment of manic episode associated to acute intoxication or abstinence syndrome, independently of the problem drug, atypical antipsychotics and new anti-seizure agents are the ideal option for the treatment, followed by classical anti-seizure drugs and benzodiazepines and that the SSRIs and tricyclic antidepressants are inadequate.

Most of the professionals surveyed would continue the treatment with the same active ingredients to treat the manic episode with a SUD not associated to an acute intoxication or to abstinence syndrome if the patient did not have a SUD. However, almost half of them would modify the dose. The best treatments for the manic episode are atypical antipsychotics and new and classical anti-seizure drugs. This does not vary greatly if the SUD is caused by alcohol or cocaine.

### Depressive episode in the context of bipolar disorder

*Expert consensus*

With an a recommendation, the work group considers that the SSRI (always associated with mood stabilizer), lamotrigine and quetiapine are the adequate treatment for a depressive episode whether they are associated or not to an acute intoxication or abstinence syndrome and regardless of what the SUD causing drug is.

*Survey*

Most of the professionals surveyed did not give priority to treatment of the depression over that of SUD. In any event,

80% of them did not treat the depressive episode the same in presence of acute intoxication or abstinence syndrome.

According to those surveyed, the best treatments of depressive episode, associated or not to acute intoxication or abstinence syndrome are SSRI and new anti-seizure drugs, followed by benzodiazepines, atypical antipsychotics or classical anti-seizure drugs. Tricyclic antidepressants are also adequate in certain occasions.

The SSRI and new anti-seizure drugs, according to those surveyed, are the best drugs for the treatment of depressive episode and SUD not associated to acute intoxication or abstinence syndrome. It is important to stress that the option of combining treatment was not permitted in the survey.

### Rapid cyclers

*Expert consensus*

The work group makes two level (a) recommendations: the first one refers to the obligations of adapting the rapid cycling treatment if the SUD presents as acute intoxication or abstinence syndrome. The second one specifies that the best treatment of rapid cycling associated or not to acute intoxication or abstinence syndrome, regardless of the SUD causing drug, is the atypical antipsychotics and/or anti-seizure drugs.

The experts make the following two grade (b) recommendations: in the first place, if a concomitant SUD is detected in the common clinical practice, both treatments are administered simultaneously, without giving priority of one over the other. In the second place, regardless of the SUD causing drug, tricyclic antidepressants are inadequate treatments against a rapid cycling episode associated or not to an acute intoxication or abstinence syndrome.

*Survey*

Most of the professionals surveyed would not give priority to one treatment over another when rapid cycling and SUD occur together. Furthermore, the majority of these professionals would change the active ingredient or reduce the rapid cycling dose if the SUD presented as acute intoxication or abstinence syndrome. The best treatments, in their opinion, for the rapid cycling episode associated to an acute intoxication or abstinence syndrome are atypical antipsychotics and new and classical anti-seizures. If the episode is not associated to acute intoxication or abstinence syndrome, the treatment would be the same as in the absence of SUD.

In the opinion of most of the professionals surveyed, the best treatments for the episode of rapid cycling not associated to an acute intoxication or abstinence syndrome are the atypical antipsychotics and new and classical anti-seizure drugs.

### Maintenance phase

*Survey*

In general, most of those surveyed would not change the maintenance treatment of the BD, regardless of whether the SUD is not associated to an acute intoxication or abstinence syndrome.

In the opinion of most of the professionals surveyed, the new anti-seizure drugs, followed by atypical antipsychotics, lithium, and classical anti-seizure drugs are the best for the maintenance treatment of BD associated to SUD.

## Principal active ingredients used in treatment of bipolar disorder associated with substance use disorder (dual diagnosis)

### Lithium

*Scientific evidence*

An article having evidence A level was found where treatment with lithium of a group of adolescents with BD and secondary SUD was effective in the approach to both disorders[22]. Additional publications supply an evidence B level in regards to treatment with lithium. They indicate that the presence of a concomitant SUD to BD predicts poor response to lithium[12]. Furthermore, two open-label studies have evaluated the efficacy of lithium in the treatment of BD associated to SUD (cocaine) with contradictory results: Gawin et al. described its efficacy 23 while Nunes et al. found no evidence for it[24].

### Valproate

*Scientific evidence*

There is a publication with evidence A level in which valproate decreases the elevated consumption of alcohol in patients with BD and comorbid alcohol dependence[25]. In two articles that had evidence B level, the utility of valproate in patients with mania during alcohol abstinence syndrome was described[26] while on the other hand, better treatment compliance in patients who took valproate was described in patients with BD associated with SUD who were prescribed lithium and valproate, which was related with the side effects profile of the two drugs[21].

### Carbamazepine

*Scientific evidence*

With evidence B level, the Halikas[27] and Brady[28] studies found that carbamazepine was associated with a reduction in cocaine consumption in cocaine addict patients with affective disorders.

### Gabapentin

*Scientific evidence*

The possibility of the utility of co-adjuvant treatment in patients with BD resistant to treatment with other mood stabilizers, especially when alcohol and comorbid anxiety disorders are associated, has been observed on an evidence B level[29].

### Lamotrigine

*Scientific evidence*

With an evidence B level, it was observed that lamotrigine improved both affective symptoms and craving for cocaine in patients with BD and cocaine dependence[30]. Furthermore, a high frequency of personal and familial background of SUD in bipolar patients who respond to lamotrigine has been observed in at least two studies[31,32].

### Benzodiazepines

*Scientific evidence*

Two publications, with evidence B level, indicate the risk of benzodizepine abuse. In the first one, patients with BD, or with other severe mental disorders and comorbid SUD, present an increased risk of developing benzodiazepine abuse[33]. In the second one, the existence of a very elevated use of benzodiazepines was also observed in patients with severe mental diseases, which was even higher in those with concomitant SUD. The group with concomitant SUD has a greater predisposition to use rapid action and high strength benzodiazepines so that these treatments must be carefully monitored. The added risk of causing or worsening a SUD should be compensated with the need to offer a safe and effective treatment of anxiety, other psychiatric diseases and the adverse effects of the medication[34].

*Expert consensus*

Additional recommendations of the work group regarding the use of benzodiazepines: in general, the use of benzodiazepines in presence of BD and associated SUD is not recommendable. However, if the decision is made to use them, it should be adjusted to the indications of the data sheet and the possible signs and symptoms of abuse should be monitored.

### Atypical antipsychotics

*Scientific evidence*

There are evidence B level works on the use of quetiapine and aripiprazole. Quetiapine has been associated with significant improvements of the psychotic, depressive symptoms and also with a reduction of the craving for cocaine and alcohol in patients with BD and cocaine abuse[35,36]. In addition, a small study with 8 psychotic patients (four of whom had schizophrenia and four had BD) and dependence on cannabis (according to the dependence criteria of DSM-IV) observed a reduction of 97.3% in weekly consumption of cannabis with quetiapine[37]. In regards to aripiprazole, this has been associated with significant improvements in the depressive symptoms, manic symptoms, general psychiatric symptoms and decrease in consumption and craving for alcohol in those patients with comorbid alcohol dependence and reduction of craving of cocaine in those patients with comorbid cocaine abuse[38].

### Antidepressants

*Scientific evidence*

With a B evidence level, it was demonstrated that if the affective disorder is induced by a SUD, there is little evidence that the antidepressants or other medications induce a more rapid or complete resolution of the affective symptoms than that derived from abstinence itself or from the passing of time[39].

### Other potentially useful drugs for which there is not sufficient scientific evidence

- *Topiramate.* Some studies indicate that it may be effective in the treatment of SUD, especially of cocaine[40] and alcohol[41], although its efficacy has not been evaluated in dual bipolar disorder.
- *Oxcarbazepine.* Although there is no evidence that it is effective in the treatment of the dual bipolar disorder, it could be thought that its effectiveness may be similar to that of carbamazepine.
- *Modafinil.* A stimulant of the CNS, it also seems to be effective in the treatment of cocaine dependent patients and, as coadjuvant treatment, seems to improve the depressive symptoms in patients with bipolar disorder, as shown in two randomized and placebo controlled clinical trials[42,43]. However, its efficacy has not been evaluated in dual patients.

## Psychotherapy

*Scientific evidence*

With evidence A level, it is observed that psychoeducative, cognitive and behavioral therapies in patients with BD constitute psychological interventions that have been demonstrated to be effective in the prophylaxis of new recurrences. A combination of psychotherapy and drug therapy may allow the patients to achieve a faster improvement of their symptoms[44].

*Expert consensus*

The experts grant an (a) value to the following three statements: first, psychotherapy with a psychoeducative approach is recommended to achieve better understanding of the disease. Second, psychotherapy is considered adequate for the maintenance of abstinence, prevention of relapses and to improve drug treatment compliance. Third, integral treatment of the dual patient requires both a psychopharmacological and psychotherapeutical approach.

*Survey*

More than 50% of those surveyed consider psychotherapy adequate for maintenance of abstinence, prevention of relapses, treatment of depression, improvement of drug treatment compliance and as emotional support.

## CONCLUSIONS

Considering the comorbidity of BD associated to SUD (dual diagnosis) and the few publications existing on it (with reduced sample sizes), the present publication is a first effort to define some action guidelines in the management of this dual diagnosis. However, the authors admit that given the importance and incidence of this dual disorder, it is necessary to continue to study its nosological description in greater depth and also that of the action of its clinical-therapeutic approach. Thus, the recommendations included herein should be up-dated in future reviews.

It is known that BD and comorbid SUDs (dual diagnosis) are frequently found in the common psychiatric practice. This combination of entities is characterized by frequent relapses, suicide attempts, elevated impulsivity, poor adherence and poor response to treatment. The substances that were most frequently associated to SUD in the survey were alcohol, nicotine and cocaine. It has been possible to find some practical aspects thanks to the survey such as the recommendation of a frequency of visits of every 2 weeks, hospital admission in patients with uncontrolled SUD and BD and integral care to these patients. The latter point is supported in a recent pilot study conducted in 45 patients with this dual diagnosis, in which specific integral group therapy was carried out with significant success in regards to the percentage of patients in abstinence versus those who had not followed an integrated therapy. Consequently, it seems to be a viable alternative to reduce substance abuse in patients with BD[45]. Of course, it is important to warm patients with BD about the risk of developing SUD and to stress the importance of early detection and treatment.

In regards to treatment with drug agents, there is abundant bibliography regarding the use of lithium and valproate in dual diagnosis, especially with alcohol abuse. Equally, literature and series of studies, although with unequal results, are found in relationship to the use of carbamazepine, gabapentin, topiramate, lamotrigine and atypical antipsychotics, among others. The existence of so many treatment alternatives may be due to the lack of conclusive studies in this disorder. Thus, it is recommendable to conduct controlled studies that include sufficiently large patient studies. This statement coincides with that made by Dr. Salloum during the Seventh International Conference on Bipolar Disorder (Pittsburgh, USA, 2007)[46]. He stressed the scarce evidence and scarce soundness of the publications related with the treatment of dual diagnosis. In his opinion, anti-seizure agents are profiled as the most promising treatments. In addition, there is an increase in the use of atypical antipsychotics, although there are no double blind, controlled studies and the role of the adjuvant therapy for alcohol and SUD must still be evaluated. Therefore, this author insists on the need to conduct large, prolonged and controlled studies that include sufficiently large samples of patients in this complex condition. However, it is unlikely that a single therapy will be developed in the near future due to the heterogeneity of patients with BD and SUD, although it is possible to identify the most appropriate therapies based on scientific evidence. Until this evidence is reached, the establishment of a consensus constitutes a very useful tool to complement the existing scientific evidence.

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