

# Melancholia in Latin American studies: a distinct mood disorder for the ICD-11

## Estudos latino-americanos sobre melancolia: um transtorno do humor melhor definido para o CID-11

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### Abstract

**Objective:** Melancholic depression is a lifetime diagnosis, typically with recurrent episodes. Melancholia, a syndrome with a long history and distinctive psychopathological features, is differentiated from major depression by the DSM-IV specifiers and partly described in the International Classification of Diseases – 10<sup>th</sup> edition. Within the present classification, it is frequently seen in severely ill patients with major depression and bipolar disorder. Nevertheless, it has a distinctive psychopathology and biological homogeneity in clinical experience and laboratory test markers, and it is differentially responsive to specific treatment interventions according to international studies. The objective of this study is to review the literature published by Latin American authors about Melancholia. **Method:** We conducted a systematic search to identify scientific literature published by Latin American authors gathering information relevant to the revision of the classification of mental and behavioral disorders in patients with melancholic depression of the International Classification of Diseases – 10<sup>th</sup> edition. The review was specifically focused on literature from Brazil and Latin America in order to examine the specific Latin American contribution for the study of melancholia as a distinct entity. **Results and Conclusion:** Melancholia can be identified as a separate mood disorder with unique psychopathology and psychoneuroendocrinology, worthy of separate attention in the classification systems. We therefore suggest that melancholia be positioned as a distinct, identifiable mood disorder that requires specific treatment.

**Descriptors:** Latin America; Depressive disorder; Diagnosis; International Classification of Diseases; Evaluation studies

### Resumo

**Objetivo:** A depressão melancólica é um diagnóstico psiquiátrico de história de vida, geralmente com episódios recorrentes. Melancolia é uma síndrome com longa duração e características específicas de psicopatologia, insuficientemente diferenciada de depressão maior por um especificador no DSM-IV e parcialmente descrito nos critérios da Classificação Internacional de Doenças-10<sup>a</sup> Edição. Dentro da classificação atual, é frequentemente vista em pacientes gravemente doentes com depressão e transtorno bipolar. No entanto, a melancolia possui uma homogeneidade psicopatológica e biológica distinta na experiência clínica e nos marcadores de testes laboratoriais, e é diferencialmente sensível às intervenções terapêuticas específicas. O objetivo deste estudo é revisar a literatura de artigos publicados por autores latino-americanos sobre a melancolia. **Método:** Realizou-se busca de artigos latino-americanos de informações relevantes para a revisão da Classificação Internacional de Doenças-10<sup>a</sup> Edição de transtornos mentais e comportamentais em pacientes com depressão melancólica. Foi avaliada a qualidade do design de todos os estudos e realizada uma revisão abrangente sobre o assunto, com o objetivo de considerar a contribuição latino-americana para inclusão da melancolia como uma entidade distinta na futura Classificação Internacional de Doenças-11<sup>a</sup> Edição. **Resultados e Conclusão:** Os estudos latino-americanos fundamentam o diagnóstico da melancolia com uma psicopatologia e psiconeuroendocrinologia própria que fundamentam ser reconhecida como um transtorno de humor identificável e merecedor de uma atenção específica nos sistemas de classificação, como um transtorno de humor distinto, identificável e especificamente tratável.

**Descritores:** América Latina; Transtorno depressivo; Diagnóstico; Classificação Internacional de Doenças; Estudos de avaliação

### Introduction

Melancholia is the only condition whose original name survived from the Hippocratic classification of diseases based on the four humors. The humoral theory viewed illnesses as disturbances in the

equilibrium of the humors. Hippocrates thought that melancholia was caused by a humor called "black bile" and that treatment should consist of bloodletting.<sup>1,2</sup> From a historical perspective, there have been

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great changes in diagnostic classification systems, from descriptive-phenomenological approaches like that of Kraepelin, to interpretative-based approaches, such as Freud's.<sup>3</sup> Afterwards, new classifications were proposed, endogenous depressions were included among mood disorders, and the depressive syndrome was divided into endogenous or reactive and cyclothymic disorders.<sup>1</sup> Recently, major depression is sub-divided into multiple sub-groups – some categorical (e.g. psychotic, melancholic, catatonic), some etiological (e.g. postpartum, seasonal), and some dimensional or weighted (involving severity, chronicity, and persistence).<sup>2,4-6</sup>

The results of classification efforts in the 1980s and early 1990s supported the distinction between unipolar (depression) and bipolar (manic-depressive) disorders, which is reflected in recent editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)<sup>4</sup> and the *International Classification of Diseases* (ICD-10).<sup>5</sup> Although the concept of melancholia — a biologically-based, severe depressive syndrome, can be traced back to antiquity, the diagnostic validity of this construct remains uncertain. In particular, there has been extensive discussion on whether non-melancholic and melancholic depression are two separate conditions or reflect differences in the severity of a single syndrome.<sup>6,7</sup> In the section concerning mood and affective disorders of the ICD-10 (F30-39), the authors state that the “relationship between etiology, symptoms, underlying biochemical processes, response to treatment, and outcome of mood [affective] disorders is not yet sufficiently well understood to allow their classification in a way that is likely to meet with universal approval”,<sup>5</sup> and continue explaining that the “main criteria by which the affective disorders have been classified have been chosen for practical reasons, in that they allow common clinical disorders to be easily identified. Single episodes have been distinguished from bipolar and other multiple episode disorders because substantial proportions of patients have only one episode of illness, and severity is given prominence because of implications for treatment and for provision of different levels of health services. It is acknowledged that the symptoms referred to here as ‘somatic’ could also have been called ‘melancholic’, ‘vital’, ‘biological’, or ‘endogenomorphic’, and that the scientific status of this syndrome is in any case somewhat questionable. It is hoped that the result of its inclusion will lead to widespread critical appraisal of the usefulness of its separate identification. The classification is arranged so that this somatic syndrome could be recorded by those who so wish, but can also be ignored without loss of any other information”.<sup>5</sup>

The DSM-III and ICD-10 were expected to bring about advance to nosology, as they consisted of procedures and defined systems based on manifest behaviors. Since then, the core entity of mood disorders became a uniform major depressive disorder with modifiers for differences in subtypes (e.g., psychotic or atypical), and for circumstances presumed to have clinical significance (e.g., seasonal or postpartum depression).<sup>7,8</sup> The early description of major depressive disorder in the DSM-III (preserved in the DSM-IV and DSM-IV-TR) clearly defined the melancholic features of depression; although the DSM-IV criteria for melancholia challenges the recognition of a detailed subcategory of severe patients described by a

specific symptom outline, not triggered by stress, approachable by biological treatment, and related to a greater incidence of organic dysfunctions (for instance, non-suppression in the dexamethasone suppression test and shorter rapid eye movement sleep latency).<sup>9,10</sup> In the DSM, some of the specifiers would appear categorical (as melancholia, for example), but this is less obvious when decision charts are reviewed. For instance, a depressive patient with anhedonia, early insomnia, psychomotor dysfunction and weight change would meet criteria for both major depression and the melancholic subtype. This is irrational if the “specifier” is intended to describe a subtype of depression.

In order to specify melancholic depression, the DSM-IV criteria are more similar to the DSM-III than to the DSM-III-R criteria. Lafer et al. have argued that the DSM-IV criteria for melancholia represent a return to the older, perhaps stricter, DSM-III definition.<sup>11</sup> The key symptoms for a diagnosis of major depression in the DSM-IV are the same, except that the newer version comprises also persistent anhedonia or unreactive mood, while the DSM-III requires both. The DSM-IV criteria for melancholia differ from DSM-III-R criteria in respect to the absence of the item “no significant premorbid personality disturbance, previous response to treatment and prior episode followed by complete recovery,” and to the inclusion of “excessive guilt” and “distinct quality of mood” (Table 1).

Many authors also suggest that the concept of melancholy should be recovered. Ruiz-Doblado, in an interesting non-systematic review named *Sacrificing validity for feasibility in psychopathology: Seeing through a dark glass*, argued that melancholy is one of the few diseases that remained valid over more than two millennia in the psychiatric vocabulary.<sup>12</sup> Since Hippocrates, the term includes melancholic mood disturbances of particular intensity, delusional symptoms and vegetative symptoms (loss of appetite, weight, libido, altered circadian rhythms).<sup>12</sup>

Rush and Weissenburger proposed that “melancholic depression is a type of depression that has not been precipitated by stress; has a biological etiology; goes with unresponsiveness to environmental events; responds to somatic therapies but not psychotherapy; is seen in patients without personality pathology; is characterized by a special symptom pattern”.<sup>9</sup> The symptoms of psychomotor retardation, late insomnia, early morning worsening, weight loss, psychomotor agitation, and guilt are included in most of the diagnostic systems.<sup>9</sup>

The Australian group of Parker et al. has increased the validity of the diagnosis of major depression through various studies over the last two decades.<sup>13</sup> The essential characteristics of melancholy according to these authors include psychomotor retardation and different quality of affect. The group advocates for the recovery of the old concept of melancholy in future classifications and regrets the delay in doing it.<sup>14</sup>

Parker and Brotchie,<sup>15</sup> in a special article for a supplement of the *Revista Brasileira de Psiquiatria*, stated that the features most commonly found were severity, psychomotor retardation, lack of a precipitant, unreactive mood, older age, not immature or hysterical, adequate personality, not hypochondriacal, distinct quality of mood,

**Table 1 – Diagnostic criteria for major depressive episode with melancholia according to the DSM-III-R and DSM-IV**

DSM-III-R	DSM-IV
At least 5 of the following:	Either no. 1 or 2 and at least 3 of no. 3-8:
1. Loss of pleasure in all or almost all activities	1. Loss of pleasure in all or almost all activities
2. Lack of reactivity to usually pleasurable stimuli	2. Lack of reactivity to usually pleasurable stimuli
3. Depression is regularly worse in the morning	3. Depression is regularly worse in the morning
4. Early morning awakening	4. Early morning awakening
5. Marked psychomotor retardation or agitation	5. Marked psychomotor retardation or agitation
6. Significant anorexia or weight loss	6. Significant anorexia or weight loss
7. No significant personality disturbance before first major depressive episode	7. Excessive or inappropriate guilt
8. One or more previous major depressive episodes followed by complete or nearly complete recovery	8. Distinct quality of depressed mood
9. Previous good response to specific and adequate somatic antidepressant treatment	

Adapted from Lafer et al.<sup>11</sup>

diurnal mood variability, delusions/paranoid features, and guilt. Features less consistently related to the endogenous factor across studies were late insomnia, psychomotor agitation, diurnal mood variation, weight loss, and obsessional symptoms or personality.

The DSM-IV structure is mainly dimensional, major depression is mostly differentiated from depressive disorders by severity (for instance, length and number of symptoms differentiate major depression disorder and dysthymia), chronicity, and relapse. Every attempt to describe melancholia as a different entity is likely to fail if DSM-IV diagnostic criteria are used, and thus the validation of melancholia as a significant depressive subtype is discouraged.<sup>13-15</sup>

There is increasing data supporting that depressive disorders include a group of conditions which may be different in regard to the activity of the hypothalamus–pituitary–adrenal (HPA) axis, immune functions, and treatment response. Besides melancholia, a range of disorders may be related to increased activation of the hypothalamic-pituitary-adrenal (HPA) axis.<sup>16</sup> Juruena et al. suggested the hypothesis that “continuous stress system dysfunction, characterized by either hyper- or hypoactivity of the HPA axis, play a role in various pathophysiological conditions”, including melancholic depression and treatment-resistant depression.<sup>10,16</sup> Clinical and biochemical features of depression, especially of the melancholic subtype, closely resemble those that occur during acute stress, which is accompanied by the activation of the sympathetic nervous system and the HPA axis.<sup>2,16,17</sup>

In recent years, an important movement has proposed the

reinstitution of the definition of melancholia, the establishment of a duration criterion, and the inclusion of a secondary criterion associating laboratory findings of non-suppression of cortisol, high nighttime cortisol levels, or decreased REM latency or other characteristic sleep abnormalities.<sup>6-11,13-15,18</sup> (see Table 2).

Our aim is to review Brazilian and Latin American evidence relevant to the revision of the classification of mental and behavioral disorders in patients with melancholic depression in the ICD-10. The purpose of the review is to focus specifically on literature from Latin America and to consider the particular contribution of this region for the inclusion of melancholia as a distinct entity in the ICD- 11.

## Method

Two literature searches were conducted. In the first, the search expression “Melancholy” OR “Melancholia” was entered into the search fields of the following electronic databases: Ovid Medline(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE; Journals@Ovid Full Text; Books@Ovid; BIOS Previews; ISI Web of Knowledge; ISI Proceedings; EMBASE Classic+EMBASE; Medline; PsycINFO; SCOPUS; SciELO; Psych Articles; IBECS; LILACS; BIREME; and the Brazilian Psychiatric Index.

In the second search, the expression “Melancholy” OR “Melancholia” was entered into each of the databases in combination with the names of 12 countries and with “Latin America” (“Argentina OR Bolivia OR Brazil OR Chile OR Colombia OR Costa Rica OR Cuba OR

**Table 2 - Proposed diagnostic criteria for melancholia (all must be present)**

A. An episode of illness with reduced functioning characterized by an unremitting mood of apprehension and gloom that compromises normal daily activities and persists for at least two weeks.
B. Psychomotor disturbance as agitation, retardation (including stupor and catatonia), or both.
C. Vegetative signs (at least two).
D. At least one of the following:
- Abnormal dexamethasone suppression or dexamethasone-suppressed corticotrophin-releasing hormone test (DEX/CRH);
- High nighttime cortisol levels.
- Decreased REM latency or other sleep abnormalities.

Adapted from Shorter,<sup>6</sup> Taylor MA and Fink<sup>7,18</sup>

Mexico OR Paraguay OR Peru OR Uruguay OR Venezuela OR Latin America”). See Figure 1 for details on the search procedures.

## Results

The searches using the expression “Melancholy” OR “Melancholia” in combination with the names of 12 countries and Latin America yielded a total of 177 articles. Search results were refined by analysis of the abstracts of retrieved articles. Repeated references, duplicated data, and articles using a psychoanalytic approach were excluded, together with articles written in languages other than English, Portuguese, and Spanish. Data were systematically extracted from 127 articles entered in a review table. Forty-five articles were selected after filtering with the exclusion criteria (detailed in Figure 1), 12 of which were excluded due to repetition across databases, and a total of 33 articles were included in this review. Selected articles were then assigned to different categories for analysis: History, Classification and Diagnosis, Neurobiology, and Comorbidity.

### 1. History

Vidal described the first case of melancholia in the River Plate.<sup>19</sup> Cabrera’s was the first case of melancholia reported in the history of Latin America. The author argued that melancholia could not have appeared prior to the Renaissance age: it was necessary that Europeans were in a situation to achieve an ample point of individual distinction so that they could feel in charge for their actions by guilt deteriorating into melancholia.<sup>19</sup>

Elferink, in a non-systematic review, studied the occurrence of mental disorders among the Incas in ancient Peru.<sup>20</sup> The absence of written documents of pre-Columbian contacts and the chroniclers’ relative lack of medical knowledge create difficulties in precisely identifying the types of mental disorders that existed among the Incas. Melancholia affected not only the common people, but the family of the Inca emperor as well. The Incas considered all diseases to be the result of a disturbed relation with supernatural forces, and treated mental diseases with a mixture of religious/magic acts and medicinal plants. The dominance of melancholia among the Incas sets them apart from the Spanish and Aztec cultures, where no specific mental disorder preponderated.<sup>20</sup> Silva reviewed the term melancholia and analyzed the difficulties in defining this condition at the beginning of the Modern Age. The author studied the relationship of melancholia with sadness and, mainly, with the production of delirium and fantasies according to the language of the medicine of the soul of the 16th and 17th centuries.<sup>21,22</sup>

Spanemberg and Juruena, in a non-systematic review concerning historical and nosological aspects, described that in “the Greek Hippocratic School, dysthymia was considered as part of the concept of melancholia”.<sup>23</sup> Thus, lethargic, anxious, and insecure individuals were predisposed to melancholic temperament. The review mentioned that Galen of Pergamum (128-201 AD) described melancholy as a chronic and recurrent condition, which could be a primary disease of the brain or secondary to other diseases. Sorano of Ephesus described

melancholic patients with symptoms of injury and as being paranoid and depressed. During the Renaissance, Robert Burton published the classic *The Anatomy of Melancholy* (1621). In this work, Burton listed old age, temperament, and genetic inheritance among the causes of melancholy, and also established it as a secondary cause of diseases of the body. In the 18th century, William Cullen (1710-1790), under the influence of the Enlightenment, associated melancholy with a primary instability of the brain and suggested “constraints” as the best remedy to lessen excitement. The term “depression” appeared in medical dictionaries in 1860 and was widely accepted and increasingly restricted the term “melancholy”. Esquirol (1772-1840) suggested that the word “melancholy” should be left to the use of poets, and Berrius stated that the term “depression” had supplanted the ancient “melancholy” due to the apparent impression of physiological and metaphorical fall of the functions implied.<sup>23</sup>

### 2. Classification and diagnosis

Del Porto, in a non-systematic review, investigated melancholic features.<sup>24</sup> The term “melancholy” has been employed in current classifications, such as the DSM-IV, to designate a subtype previously called “endogenous”, “vital”, “organic”, “somatic” or “endogenomorphic” depression. Considered by many as the prototype or nuclear syndrome of depression, melancholy - unlike other forms of depression - seems to be part of a more homogeneous group of conditions that respond better to biological treatments and in which genetic factors would be the main determinants. The review emphasized studies by Parker et al., which draw attention to the importance of psychomotor changes in melancholy, the main feature of this nosological category according to those authors. The concept of melancholia in the DSM-IV was revised in relation to the DSM-III-R, becoming more accurate and defining the subgroup studied more precisely.<sup>24</sup> In normal mourning, individuals usually retain certain interests and respond positively to the environment when properly stimulated. Psychomotor inhibition characteristic of melancholic states are not observed in mourning. In a literature review concerning depressive states, the item “psychomotor retardation” was the common denominator in nine classification systems as a defining feature of melancholia.<sup>24</sup> The most severe forms of psychotic depression were described by Kraepelin and named “fantastic melancholy”. This condition involved intense delusions and hallucinations, alternating states of arousal with violent stuporous states, along with slight clouding of consciousness. Motor immobility may present as stupor (called “melancholy stupor”) or as catalepsy (waxy flexibility). It should be noted that true melancholic stupor is very seldom observed nowadays.<sup>24</sup>

In a non-systematic review with the title *Sacrificing validity for feasibility in psychopathology: Seeing through a dark glass*<sup>12</sup> Ruiz-Doblado debated the issue of nosological validity as an example of loss of diagnostic accuracy between melancholy and major depression.<sup>12</sup>

Pinzon Sanchez, in a large epidemiologic study conducted in the 1970s in Colombia, reported a high incidence of depressive states in a Colombian psychiatric clinic.<sup>25</sup> The total number of patients was

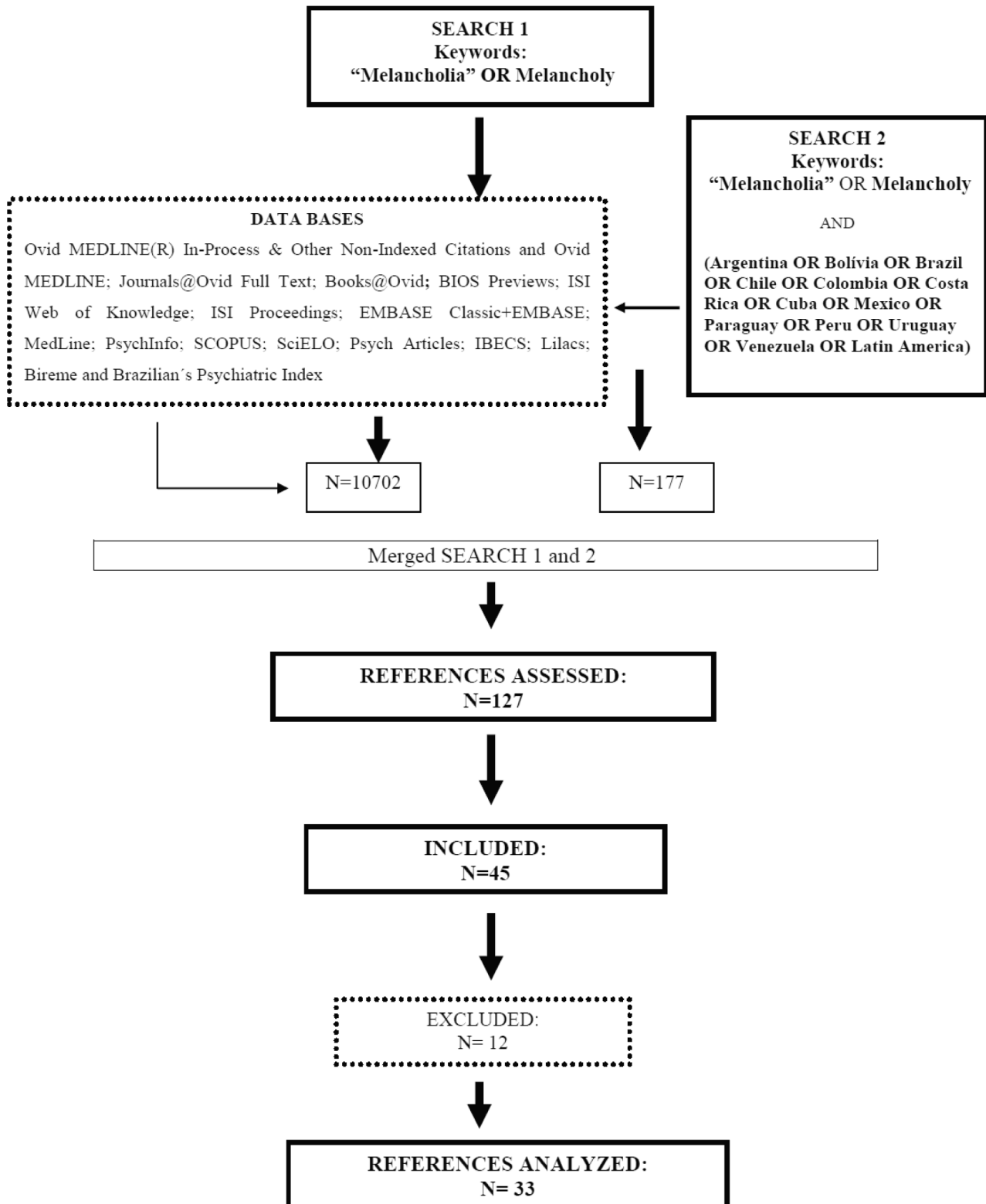


Figure 1 - Chart showing the methodology used to search for and select articles.

48,101, followed over a 2.5-year period, and data were presented in relation to sex, age, marital status, frequency of consultation, and services rendered. Depressive disorders accounted for 75.3% of all cases, and the following problems were found: depressive neurosis (43.2%); involuntary melancholy (13.8%); hypochondriac neurosis (11.9%); and cerebral dysthymia (6.4%). No reasons could be determined for the high incidence of depressive disorders in this geographical area.<sup>25</sup>

Dratcu et al., in a case control study,<sup>26</sup> emphasized the importance of cross-cultural investigations in psychiatry and revealed the need for standardized instruments to diagnose and assess depression. The authors described the first application of the Montgomery-Asberg Depression Rating Scale (MADRS) in Brazilian patients, comparing the results with those obtained with the Hamilton Depression Rating Scale, the Visual Analogue Mood Scale (a self-rating scale), and the global clinical assessment of independent Brazilian psychiatrists. There were correlations between the MADRS and the three other assessment instruments, indicating that it is a useful and operational instrument to evaluate depressed patients. Moreover, all the patients, except one, met the Research Diagnostic Criteria (RDC) criteria for the endogenous subtype of major depressive disorder. In fact, a careful analysis and the practical application of these diagnostic criteria led to the observation of an overlap for the diagnosis of major depressive disorder and its endogenous subtype. In this study, published in the *British Journal of Psychiatry* in 1987,<sup>26</sup> the authors state that the RDC and the DSM-III criteria are still a matter of discussion and controversy, and should not be used as a gold standard for diagnosis. The authors suggested that it is feasible that clinical psychiatrists have emphasized the endogenous features in diagnosing depression, as they are closer to the classical description of melancholia.<sup>26</sup>

Calil, in a non-systematic review, examined the Latin American concept of depression and presented a Brazilian proposal.<sup>27</sup> She argued that the diagnoses of depression have substantially increased over the last decades, thus compromising their validity. Actually, although depressed mood is considered the hallmark of depression, this disorder also involves cognitive, behavioral, and somatic changes. A conceptual model of depression, based on a bidimensional approach to its diagnosis, has been proposed by Sonenreich et al.<sup>28</sup> According to this model, depression refers to the slowness of psychomotor functions (movements, thought, speech, perception) and narrowing of the inner field of experience. Biological, vital slowness ("lentification") is experienced as "heaviness", and thus reflects normal or pathological states. The inner field of experience means the global psychic activity or the synthesis of information processing provided by the body, the environment, and the meanings attributed to their relationships. This model conceives affection as a quality of experiences and not as a psychological function, and allows several research approaches. The relationship between the dimensions of the inner field of experience and the speed/velocity of psychomotor functions yields into separating depression, anxiety (a typical affection for some investigators), and mania. Some studies have attempted to validate this conceptual model.<sup>27,28</sup>

Banzato, in a non-systematic review, investigated classification issues in psychiatry: the move towards the ICD-11 and DSM-V.<sup>29</sup> The

analysis of taxometric studies favored the option for categorical models to explain some disorders (like melancholia and eating disorders) and for dimensional models to others (like depression, generalized anxiety, and posttraumatic stress disorder), supporting therefore a pluralistic view of psychiatric classifications. Besides, as a taxon does not require a biological cause, the author recommends treating the categorical versus dimensional issue and the problem of causation separately.<sup>29</sup>

Lafer et al., using a case control design, studied 176 consecutive outpatients with unipolar depression, of which 40 (22.7%) fulfilled the DSM-III-R diagnostic criteria and 29 (16.5%) met DSM-IV criteria for melancholia specifier.<sup>11</sup> Patients with DSM-IV melancholia had greater mean scores in dimensions of clinical severity as paralleled with those who met the DSM-III-R diagnosis. The data suggested that the diagnostic criteria for melancholia recommended in the DSM-IV are more limiting and define a more severely depressed population than criteria in the DSM-III-R.

Gentil et al., in a case control study, compared the efficacy and tolerability of antidepressants in outpatients with major depression with and without melancholia.<sup>30</sup> This was an eight-week, multicenter, randomized, double-blind, parallel group comparison. Outpatients with DSM-IV major depression, a minimum score of 20 in the 21-item Hamilton Depression Rating Scale (HAM-D), and depressive symptoms for at least one month were enrolled. The primary efficacy variables were the final on-therapy scores on the HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS), and Clinical Global Impression severity scales. One hundred and 16 patients were randomized, and 115 were evaluated. Additional analyses were performed for sub-groups of patients as follows: with or without long duration of current episode (defined as greater or equal to the median: 20 weeks); with or without long duration of depressive illness from the first episode, as determined with the SADS-L (greater or equal to the median: 7 years); and with or without melancholia (according to DSM-IV criteria). The pre-treatment scores in the total HAM-D, MADRS, CGI-severity of illness, and SCL-90 were significantly greater in the sub-group with melancholia ( $p < 0.05$ ).<sup>30</sup>

The Brazilian Medical Association, in a systematic review, proposed guidelines for the treatment of depression, describing prevalence rates, demographics, disability, diagnoses and sub-diagnoses, efficacy of pharmacological and psychotherapeutic treatment, and costs and side-effects of different classes of drugs available in Brazil.<sup>31,32</sup>

In a cross-cultural approach, Fleck et al. applied the Hamilton Rating Scale for Depression to 130 depressed inpatients in France and Brazil.<sup>33</sup> Items were factorized, with three factors obtained in France and four in Brazil. The first factor included the core symptoms of depression (melancholic features) in both samples. Qualitative and quantitative differences between the Brazilian and French samples appeared in relation to the anxiety factor. Insomnia items appeared as another factor for both groups. Principal component analysis for depressive inpatients in these two countries showed a similar structure. The differences observed concerned the way in which anxiety items were distributed.<sup>33</sup>

Caldieraro, in a Master's dissertation, compared the prevalence of psychotic symptoms in non-melancholic and melancholic depression in one hundred eighty-one patients with unipolar major depressive disorder.<sup>34</sup> Melancholia diagnoses were made using both the DSM-IV-TR criteria and the sign-based (CORE) rating system of psychomotor disturbance. Melancholic patients differed from non-melancholic ones in respect to symptom severity, suicidal ideation, axis I comorbidities, personality styles, and parental care measures. The results indicated a much higher percentage of patients with a melancholia diagnosis than did the CORE measure. The prevalence of psychosis was significantly higher in melancholic patients. But there was a gradient in the intensity of depressive symptoms among non-melancholic and melancholic patients, not influenced by psychotic status.<sup>34</sup>

Busnello et al., in a cross-sectional study, evaluated the Version for Primary Care (ICD-10 PC), prepared by the Division of Mental Health of the World Health Organization (WHO).<sup>35</sup> Community general practitioners (CGP) were trained in this version and followed a field trial designed by the WHO. The data about the reliability of mental diagnosis attributed by nine pairs of CGP to 460 patients in their first appointments with Cohen's Kappa for mental disorder diagnoses was 0.79 (CI 95%: 0.69–0.88), but the indices for depression (F31) and mixed anxiety and depression (F 41.2) were lower: 0.66 (CI-95%: 0.57-0.75) and 0.42 (CI-95%: 0.38-0.56).<sup>35</sup>

### 3. Neurobiology

In the pioneering study *A Dualistic Approach to Some Biochemical Problems in Endogenous Depressions*, Bueno and Himwich described vital depression as a syndrome including melancholia, lack of interest, retardation, decreased vitality, and suicidal ideas among delusional ideas of guilt and hopelessness that could be the result of disturbances in the indole metabolites which are increased in inhibited depressions and decreased in the agitated type.<sup>1</sup> Such a dualistic approach may provide an explanation for the conflicting data on monoamine metabolism in endogenous depressions found both in the laboratory and in the clinical field. The clinical actions of the different types of therapy employed in the management of endogenous depressions, such as MAO inhibitors, iminodibenzyl derivatives, and electroconvulsive therapy may also find an explanation in this dualistic conception.<sup>1</sup>

Early studies from the 1980s proposed the use of the dexamethasone suppression test (DST) as an auxiliary tool to diagnose the melancholic subtype of depression and pointed to the high specificity of the DST in melancholia.<sup>10,36</sup> In the 1990s, however, several studies found that the sensitivity of the DST for the diagnosis of the melancholic subtype of major depression as defined by the DSM-III was low (35–45%), although its specificity was high (70–89%).<sup>10,16</sup>

In a prospective study, Dratcu and Calil applied the DST to 40 depressed patients, 40 healthy volunteers, and 40 patients with other psychiatric disorders, and used three different depression rating scales (MADRS, HAM-D, and the Visual Analogue Mood Scale).<sup>37</sup> The authors showed differences between suppressing and non-suppressing

patients concerning severity and treatment response and concluded that HPA axis variations appear to be state-dependent, inclined to improve upon remission of the depressive syndrome.<sup>37</sup>

Juruena et al. described decreased HPA negative feedback leading to high concentrations of cortisol, as observed in melancholia.<sup>38</sup> Consistent with the presence of glucocorticoid receptor (GR) resistance in major depression, the authors described that, despite having higher plasma cortisol concentrations compared to controls, melancholic depressed patients exhibited no increase in plasma sialyltransferase levels. Sialyltransferases are a family of enzymes that participate in the oligosaccharide chain metabolism and are known to be stimulated by glucocorticoids via GR.<sup>16,39</sup>

Mello et al., in a non-systematic review, reported that depression (melancholia) is linked to hypercortisolemia in many patients, but that not all patients present this HPA axis dysfunction.<sup>40</sup> Moreover, the authors concluded that the "dexamethasone suppression test is not the most accurate test to measure the hypothalamic-pituitary-adrenal axis function, and its use in the first published studies probably jeopardized the results".<sup>40</sup> Juruena et al. argued that "hypercortisolemia frequently occurs in patients with severe depression, melancholic, either psychotic or nonpsychotic type; it is linked to the presence of a polymorphism in the promoter of the serotonin transporter gene, with a history of childhood abuse or neglect, or other significant stressful experiences like the loss of a parent during childhood and temperament leading to alterations in the response to stress".<sup>41</sup> The authors concluded that "alterations of the hypothalamic-pituitary-adrenal axis depend on factors like severity and type of depression, genotype, history of exposure to stress, temperament, and probably resilience". All these factors together result in an endophenotype thought to be prone to depression.<sup>41</sup>

In a case control study, Contreras et al. assessed 40 inpatients (19 psychotic and 21 nonpsychotic) with major depressive episode with melancholia according to DSM III-R criteria.<sup>42</sup> The DST, thyroid stimulating hormone response to thyroid releasing hormone (TSH-TRF), and growth hormone response to growth hormone releasing factor (GH-GRF) tests were performed for all 40 inpatients. The data concerning instabilities of the HPA axis demonstrated around 80% of alterations in the 40 patients with melancholia, and that these alterations may be related to the presence of psychotic symptoms. Around 20% of the entire sample (15.8% with psychotic depression and 23.9% with non-psychotic depression) had no disturbances in hormonal axes. In the sample with melancholic patients, 80% had disturbances in at least one hormonal axis, 40% in two axes, and 5% in all the three axes.<sup>42</sup>

Juruena and Cleare, in a non-systematic review of the literature subsequent to the publication of the DSM-IV and ICD-10, concluded that evidence "largely supports the validity of depression with atypical features, as distinct from melancholia and depression with neither atypical nor melancholic features".<sup>43</sup> The authors argued that "those with melancholic depression tend to feel worse in the morning, whereas those with atypical depression feel worse in the evening. While the debate concerning the best clinical criteria for atypical depression continues, the existing data propose that the neuroendocrine

pathophysiology is different and even opposite to that observed in patients with melancholic depression<sup>33</sup> (see details in Table 3). It is known that HPA axis overdrive and hypernoradrenergic function are related to melancholic depression, with elevated plasma cortisol levels and evidence for a strong corticotropin releasing factor (CRF) drive.<sup>44</sup> In addition to HPA axis activity, different alterations of the serotonergic system may also play a significant function in melancholia. The authors argued that “the melancholic subtype with noradrenergic and HPA axis overdrive seems to be associated with reduced 5-HT1A autoreceptor function and, therefore, enhanced serotonergic activation of the HPA axis, as well as an acute phase immune reaction. The latter contributes to HPA axis stimulation and reduces negative feedback inhibition by corticosteroid receptors. The resulting hypercortisolemia can further impair 5-HT1A receptor functions, leading to a vicious circle, which may not be effectively resolved by most of the selective serotonin reuptake inhibitors (SSRI)”.<sup>40,43</sup> It has been suggested that, while typical major depression (melancholic) can be characterized by an excessive activation of the physiological stress systems, the locus coeruleus noradrenergic system, and the hypothalamic-pituitary-

adrenal axis, opposite changes are present in atypical depression.<sup>43</sup> This almost complete opposite neuroendocrine disorder, with reduced HPA activity and CRF secretion, mediated by an increased negative feedback by cortisol and hyponoradrenergic function, was first described more than 15 years ago in atypical depression, and several studies have since substantiated the evidence for HPA hypofunction in this subgroup of depressed patients. While those with melancholic depression fail to suppress cortisol release after dexamethasone, those with atypical depression have an increased suppression of cortisol.<sup>43</sup>

#### 4. Comorbidity

Soares et al., in a systematic review, addressed the historical evolution of the concept of melancholy in relation to the climacteric phase, with its diagnostic inaccuracies, heterogeneity, clinical psychopathology, and repercussions on the proposed therapeutics.<sup>44</sup> In that review, the authors discussed the etiology and correlations with clinical disorders in peri-menopausal periods and models for a better understanding of this phenomenon.

In a cross-sectional study, the group of De Medeiros investigated 354

**Table 3 - Clinical differences between melancholia and atypical depression**

	Melancholia	Atypical depression
<b>Symptoms</b>		
Level of arousal	Hyperaroused	Hypoaroused, apathetic
Anxiety	Anxious	Generally not anxious
Reactivity	Relatively unreactive to environment	Relative to environment
Emotional memory	Predominance of painful emotional memory	Relatively out of touch with past
Cognition	Decreased concentration, perseveration	Loss of focus
Behavior	Shift to relatively well-rehearsed behaviors	Unmotivated, inactive
Strong link to Bipolar II	No	Yes
<b>Neurovegetative</b>		
Sleep	Decreased total sleep; poor quality	Increased total sleep; poor quality
Appetite	Decreased food intake, weight loss	Increased food intake, weight gain
Energy level	Overt energy level variable	Marked lethargy and fatigue
Libido	Diminished	Diminished
Diurnal variation	Worse in the morning	Worse in the evening
<b>Neuroendocrine</b>		
HPA axis	Centrally-activated	Centrally-mediated hypoactivity
Cortisol output	High	Low
CRF	High	Low
Dexamethasone suppression test	Low suppression	High suppression
Response to prednisone	-	Yes
<b>Autonomic</b>		
Sympathetic activity	Increased	Decreased
<b>Body composition</b>		
Body Mass Index (BMI)	Normal	High
Lean body mass	Decreased (sarcopenia)	Normal
Total body fat	Normal or increased	Increased
<b>Immune function</b>		
	Relatively immunosuppressed	Relatively immunoenhanced
<b>Medical sequelae</b>		
Heart disease	Premature ischemic heart disease	Premature ischemic heart disease
Osteoporosis	Premature osteoporosis	Normal bone
Infection/inflammation	Increased susceptibility to infection	Increased susceptibility to inflammation
Neurodegeneration	Hippocampus/medial prefrontal cortex	?

Adapted from Juruena and Cleare<sup>44</sup>



women in menopause.<sup>45</sup> The authors studied gynecological and mental symptomatology and concurrent conditions. Symptoms like hot flashes, anxiety, lack of memory, and low energy were found in nearly 60.0% of the sample. Tearfulness, depression, melancholia, and sleeplessness were recurrent. Menopause, psychosexual, and vasomotor symptoms were the most predominant disorders. Hot flashes were associated with anxiety, lack of memory, tearfulness, depression, and melancholia.<sup>45</sup>

De Lorenzi, in a cross-sectional study concerning factors related to the frequency of sexual activity in 206 postmenopausal women found that menopause symptoms associated with sexual activity were “hot flashes ( $p = 0.05$ ), irritability ( $p = 0.04$ ), melancholy/sadness ( $p = 0.04$ ), arthralgia/myalgia ( $p < 0.01$ ), and weakness/ tiredness ( $p < 0.01$ )”. The authors concluded that their findings “agreed with the hypothesis that sexuality of climacteric women is not only influenced by factors related to hypoestrogenism, but also by psychosocial and cultural aspects associated with aging itself”.<sup>46</sup>

### Conclusion

In light of this literature review, it can be concluded that the inter-examiner and test-retest reliability and internal consistency of the various ICD and DSM diagnostic categories are quite high. Clinicians and researchers around the world can thus communicate more successfully and appropriately, using common assessment tools and a similar nomenclature. However, while reliability does not substantially compromise the validity of nosological categories such as schizophrenia and obsessive-compulsive disorder, many authors do not feel the same way in relation to other new constructs such as major depression, dysthymia, anxiety disorders, and personality disorders. This speaks in favor of the recovery of traditional or classical phenomenological concepts, such as melancholy, providing operational diagnostic criteria able to maintain the high level of agreement reached between clinicians without sacrificing the validity of categories. The lack of correlations between clinical and biological data continues to be, according to several authors, one of the great unsolved problems of psychiatry today, and could be solved by recovering the value of traditional psychopathological analysis based on fundamental and thorough clinical assessment, which should underpin etiological research and treatment decisions.

In order to be diagnosed with major depressive disorder, one has to report depressed mood or loss of interest for pleasure for a period of two weeks, together with other items in a list including nine symptoms (three or more symptoms, if the first two are present). A broad concept certainly does not contribute to test hypotheses about the etiology of depression and response to biological treatments. It does not serve either to assist in the decision to medicate or not those who fulfill these criteria.

The concept of melancholy is much more precise and, therefore, has greater predictive value in the assessment of therapeutic response to antidepressants, for example. The authors conclude that melancholy is a lifetime diagnosis, characteristically with recurrent episodes. In the present classification, it is often seen in severely ill patients

with major depressive disorder and with bipolar affective disorder. As we understand, this refers to the definition of melancholia as a “specifier” in the DSM, which does not provide a clear description of the symptoms that define melancholia as a subtype of major depression symptoms.

Juruena et al. argued that “the key problem in diagnosis is the fact that elaborated classification systems that exist today are solely based on subjective descriptions of symptoms.<sup>47</sup> Such detailed phenomenology includes the description of multiple clinical subtypes; however, there is no biological feature that distinguishes one subtype from another”.<sup>47</sup> The authors believe that “a research approach that describes reliable neurobiological findings based on psychopathological syndromes will be more solid contrasted to a nonetiologic system of classification. Integrative approaches to understanding complex health issues can transcend disciplinary and knowledge boundaries and provide opportunities to view phenomena from diverse perspectives. A future diagnostic criteria system in which etiology and pathophysiology are essential in diagnostic decision making would bring psychiatry closer to other specialties of medicine”.<sup>47</sup>

We conclude that the relationship of melancholia with depressive syndromes is a good illustration of a topic that can be clarified within a comprehensive perspective. Latin American articles describe the clinical features of melancholia that have been validated through physiological tests and treatment response, and offer a historical and more systematic and operationally reliable paradigm for the classification of psychiatric disorders than the current symptom checklists in the ICD-10 and DSM-IV.

**Disclosures**

Writing group member	Employment	Research grant <sup>1</sup>	Other research grant or medical continuous education <sup>2</sup>	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other <sup>3</sup>
Mario F. Juruena	FMRP-USP	FAEPA* CNPq** FAPESP** FAPESP***	Novartis	Pfizer AstraZeneca	-	WHO	-
Helena M. Calil	UNIFESP	AFIP**	Eli-Lilly* Boehringer-Ingelheim* AstraZeneca* Abbot* Torrent* Lundbeck* GSK*	-	-	FAPESP CNPq CAPES CLANP	-
Marcelo P. Fleck	UFRGS	CNPq*** FIPE-HCPA***	CNPq*	-	-	-	-
Jose A. Del Porto	UNIFESP	-	-	-	-	-	-

\* Modest

\*\* Significant

\*\*\* Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

Note: FMRP-USP = Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; UNIFESP = Universidade Federal de São Paulo; UFRGS = Universidade Federal do Rio Grande do Sul; FAEPA = Fundação de Apoio ao Ensino, Pesquisa e Assistência, Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo; AFIP = Associação Fundo de Incentivo à Pesquisa; FIPE-HCPA = Fundo de Incentivo à Pesquisa e Eventos, Hospital de Clínicas de Porto Alegre; CAPES = Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

For more information, see Instructions for Authors.

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