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The Journal of Mood Disorders publishes original articles stemming from research studies, reviews of current topics, clinical trials, brief reports, letters to the editor, and personal papers. It accepts papers from areas related to psychiatry and psychopathology, and incorporates topics from professionals associated with the field of mental health.

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EDITORIAL

We inform our readers about the news of the Mood Disorders Unit of the University Psychiatric Clinic (CPU), North Faculty of Medicine, University of Chile.

At the time of writing these lines, the final phase of the diploma course on mood disorders for psychiatrists is being reached. The second version of the diploma course on mood disorders for psychologists, whose first version achieved the goals we had set with great interest on the part of these professionals, has begun. They are now exercising their professional work with a deeper perspective and with knowledge that will undoubtedly be of benefit to the numerous patients with mood disorders in our country.

In addition, Víctor Gómez, an outstanding psychologist who, together with his colleague José Luis Rossi, is a permanent member of the teaching team and organizer of the diploma for psychologists, which lasts approximately one year, has been incorporated as a permanent member of the mood disorders unit. The best research papers of both diplomas will be published in this magazine to share them with our readers.

It is worth mentioning that our unit has also incorporated Dr. Ana María Soza, who leads a research project on neuro vestibular stimulation for the treatment of mood disorders. This stimulator consists of a high-cost equipment that is already installed at the C.P.U. and is operating regularly with patients attending the CPU. We must mention that this novel technique places our country in the world vanguard together with a few other countries that already make use of neuro vestibular stimulation. We await with particular interest the results of these studies that will surely innovate our interventions. Our mood disorders unit is also working closely with the Clinical Hospital of the University of Chile and performs intravenous ketamine treatments. Ketamine clinics have already proliferated in several countries and ours already has trained anesthesiologists performing this procedure.

The present issue of this journal contains several papers of interest. Reviewing pharmacological alternatives in the treatment of anxiety comorbid with bipolar disorders is of relevance in this frequent comorbidity and often maintained for long periods in our patients....

A review on the concept of lebenswelt is included with emphasis on the contributions of Hubert Tellembach, an outstanding professor from Heidelberg who made memorable trips to our country, influencing numerous academics and clinicians who translated his important texts into Spanish. We must remember that his ideas are still valid in the psychopathological analysis of patients.

Depression in the elderly, its etiology and clinical approach is becoming more and more frequent as the population ages, due to the greater longevity of our population. The causal and treatment factors are analyzed in this population, which is increasingly consulted in our health care services and clinical practice.

The issue of the predominant polarity in bipolar disorder constitutes a way of approaching not only clinical but also treatment of bipolar subjects. There are controversies about this situation, so this article will undoubtedly review the real importance of considering the dominant pole of clinical presentation of bipolar disorders.

The issue of mixed depression is of utmost importance to diagnose this condition and treat it adequately, since it is a serious condition with high mortality and often requires hospitalization along with a particular pharmacological management.

The role of thyroid hormones is of importance for the treatment of numerous symptoms that appear in mood disorders, where a differential diagnosis has to be carried out. Recognizing the functioning of the hypothalamo-thyroid axis and the use of thyroid hormones is described by the authors for clarity on this subject.

A case of depression linked to a vascular disorder is presented. The etiological or concomitant factors are necessary to be clarified for this comorbidity. We have chosen a clinical case as a form of depression together with a finished analysis of this situation.

The editors

Pharmacological Alternatives in Anxiety Treatment Comorbid with Bipolar Disorder.

Fernando Ramírez N.[1], Paulina Cortés U.[2]

ABSTRACT

Introduction: *The comorbidity of bipolar disorder with other psychiatric disorders is frequent, with higher prevalence anxious disorders and substance abuse disorder. The objective of this review was to identify pharmacological alternatives that could be useful in cases of bipolar disorder with anxious symptoms or anxious disorders due to the great impact they have on the course of the former.*

Methodology: *A search was performed through Pubmed with the key terms: Bipolar disorder, comorbidity, anxiety disorder, and treatment, with the goal of identifying articles related to the objective of this study. After limiting the search, 18 articles included in this review were entered.*

Results. There is little evidence with respect to specific treatments for this frequent comorbidity, suggesting, in the various articles reviewed, the use of Benzodiazepines, SSRS, Valproate, Pregabalin, Gabapentin, the combination of Olanzapine/Fluoxetine or Olanzapine/Lamotrigine.

Conclusions: *Although there is no specific pharmacological alternative for the treatment of bipolar disorder with anxious disorder comorbidity, there are various medications with anxiolytic effect that can be selected according to the patient's symptomatological profile, considering that the main approach must be to achieve mood stability. More studies are needed for new pharmacological strategies considering the high prevalence of this comorbidity in bipolar disorder.*

Keywords: *bipolar disorder, anxiety disorder, comorbidity*

INTRODUCTION

It has been reported that psychiatric comorbidities are common in patients with bipolar disorder, with anxiety disorders and substance abuse disorders appearing as the most prevalent comorbidities[(1)].

Anxiety disorders have been associated with suicidal behavior in the general population and in individuals with other psychiatric disorders[(2)].

Reported lifetime rates of psychiatric comorbidity in bipolar disorder are greater than 50%[(3)]. In particular, anxiety disorders have a high comorbidity with this mood disorder, reporting up to 86-89% with comorbidity reports varying according to the study consulted[(4, 5)]. Bipolar disorder patients frequently experience comorbid anxiety symptoms and anxiety disorders (generalized anxiety disorder, panic disorder, post-traumatic stress disorder, and others)[(6)]. Compared with patients without concomitant anxiety disorders, those who have comorbid anxiety disorders would have an

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earlier onset of the disease[7] in addition to being associated with a greater number of mood episodes and depressive symptoms, including suicidality and sleep disorders, and greater alteration in psychosocial functioning and quality of life[6, 8], so evaluation and treatment are recommended[4].

Anxious symptoms are often persistent between episodes and can contribute to mood instability[4]. According to several studies, Generalized Anxiety Disorder is one of the most common conditions that appears concomitantly with bipolar disorder[1].

Prospective studies have shown that suicide attempts and suicidal ideation during the follow-up period are more common in patients with bipolar disorder and major depressive disorder with comorbid anxiety than in those without comorbidity[2]. Lifetime presence of comorbid anxiety disorders had a significant association in 8 of the 13 studies reviewed in the meta-analysis of suicidal attempt in bipolar disorder in the presence of comorbid anxiety disorder by Schaffer et al, with an OR of 1.81 (95% CI: 1.66–1.97, $p < 0.0001$)[4]. In addition, previous studies have described that these patients have higher rates of mixed states, depressive symptoms, and alcohol abuse[7].

Considering what is presented in this introduction, and because the pharmacological choice in these cases becomes more complex, it is considered important to perform a review of the medications that could be useful in the management of anxiety symptoms in patients with bipolar disorder, always considering that the indicated first-line treatment would be cognitive behavioral therapy[6].

METHODOLOGY

A search was initially conducted through the Pubmed database using the following keywords: “BIPOLAR DISORDER”, “COMORBIDITY” and “ANXIETY DISORDER”, in order to identify articles that specifically dealt with the topic of comorbidity between bipolar disorder and anxiety disorders, limiting the search by adding the word “TREATMENT”. This search was filtered to articles in English published in the last 5 years, including systematic reviews, meta-analyses, randomized clinical trials, and reviews. Initially, 22 articles that met the characteristics described were found. Subsequently, their summaries were reviewed to choose the most pertinent, leaving 14 articles. When performing the complete reading of these articles, some of the references cited in them were searched, finding 4 more articles that were related to the subject under review (1 of them found through a digital medium and another obtained as a chapter in a book).

RESULTS

In the search performed, some antidepressants (SSRIs), benzodiazepines, pregabalin, gabapentin, quetiapine, and valproate appear as pharmacological alternatives, which will be reviewed in greater depth below.

The treatment indicated in case of comorbidity needs a pharmacological adjustment with a different approach to the treatment of each anxiety disorder separately.

As described in the introduction, the impact that comorbid anxiety disorders have on mood disorders is widely reported in the literature, negatively affecting the course and results obtained in the indicated treatments in patients diagnosed with both disorders.

Among the most notorious characteristics that impact the course of the disease are increased irritability with deterioration in interpersonal relationships, greater severity in mood episodes with more severe symptoms in both manic and depressive episodes.[9]

In individuals with comorbid anxiety disor-

ders, greater severity of the episodes is described, which is reflected in a longer duration of the episode itself; especially in those oriented towards the depressive pole with higher rates of chronicity in patients who are diagnosed with an anxiety disorder associated with the diagnosis of bipolar affective disorder.

Patients with these characteristics present particularly high numbers of subsyndromic symptoms, a shorter duration of remission of mood episodes, higher risks of early recurrence or relapse [9] and, consequently, a greater tendency to hospitalizations associated with the severity of the clinical symptoms.

This has a negative impact on global functioning and impoverishes the quality of life of individuals who have presented both diagnoses, mainly related to poor responses to indicated treatments due to delayed diagnoses, greater adverse effects to indicated medications, less adherence to treatment, and greater use of health services, which implies higher costs in terms of the care required by each individual whose comorbidity has not been diagnosed and treated in a timely manner[9].

High suicidal risk.

The presence of a comorbid anxiety disorder presented a statistically significant association with higher rates of suicide attempts through different studies that reflect this association, with special importance given the severity and impact on the population diagnosed with both comorbid pathologies.[7]

The majority of individuals with bipolar affective disorder experience symptoms consistent with an anxiety disorder throughout their lives, so these high rates of associated suicide attempts make them clinically relevant and expose the need for appropriate treatment[4].

There is evidence that partially associates the greater tendency of suicide attempts in bipolar patients to an increase in anxious rumination[4, 10].

The findings indicate that having a comorbid anxiety disorder is associated with greater co-occurring suicidal ideation and lifetime suicidal ideation in patients with bipolar affective disorder.

The diagnosis of an anxiety disorder throughout the life cycle in these patients was associated with more than twice the risk of presenting active or passive suicidal ideation[7] with the consequent impact on the results of insufficient treatment or in the event of presenting an undiagnosed comorbid anxiety disorder in high suicidal risk patients.

Treatment of comorbid anxiety disorders in bipolar affective disorder.

Although there are consistent data regarding the rates, correlation, and impact of anxiety disorders as a comorbidity of affective disorders, the search regarding the efficacy of different treatment modalities for this comorbidity tends to be less productive, with less evidence than support specific treatments.

Treatment is a challenge for clinicians, mainly due to the difficulties of comorbid diagnosis and the high frequency of inadequate response to suggested treatments[9].

It is necessary to remember that the “easiest” and potentially riskiest treatment for most of the anxiety disorders described is the use of antidepressants[12], considering that the evidence advises against their use due to the increased risk of mania in bipolar patients, or, in the case of continued use, can cause worsening of the course of the disease in people diagnosed with bipolar affective disorder.

The extensive use of benzodiazepines in anxiety disorders can be effective (except in comorbidity with OCD, which although separated from anxiety disorders in the DSM 5, has anxiety as an important symptom[6], and substance use disorder where

its use is discouraged) (12), without worsening the course of bipolar affective disorder as described with antidepressants.

However, its long-term use is discouraged due to the development of tolerance, dependence and withdrawal risks when discontinuing its use. Further, it is not an effective solution for disorders that usually require medium- and long-term treatment on a consistent basis.

In some patients with anxiety disorders in which benzodiazepines are not well tolerated or are ineffective, the use of antidepressants may be necessary despite the previously described risks, which implies their use for limited times and at lower doses than those usually described for anxiety disorder without presenting comorbidity with bipolar affective disorder.

In this regard, the antidepressants Paroxetine and Bupropion could eventually be used because they are the only ones that have shown a lower risk of causing acute mania compared to tricyclic antidepressants in randomized studies, but always considering that there is a sub-group of patients for whom long term use seems to worsen the results of the treatment and the course of bipolar disease if use is maintained[12].

If required, although it is ideally suggested to avoid the use of antidepressants, there are cases in which their use may be unavoidable once the risk/benefit assessment has been conducted[6], especially in individuals who are more difficult to manage, as occurs in patients diagnosed with an obsessive-compulsive disorder comorbid with a bipolar affective disorder. There is evidence about the combined use of mood stabilizers (Lithium, Divalproex or Carbamazepine) associated with atypical antipsychotics (Olanzapine) and subsequently associated with an SSRI antidepressant (Paroxetine, Fluoxetine) if the symptoms of obsessive-compulsive disorder persist, establishing that there would be no increased risk of mania if the drugs are used in combination, protecting the development of mania if the antidepressant is added sequentially after the indication of the drug mood stabilizer associated with atypical antipsychotic.[13, 14]

The approach described by S.N. Ghaemi regarding the hierarchical diagnosis[12,13] in psychiatry can provide an answer to this complex dilemma regarding the type of treatment indicated in the case of establishing a possible comorbidity between both disorders.

Mood disorders would be hierarchically above psychotic disorders, which in turn are above anxiety disorders[12,13], which would explain why anxious symptoms underlie the diagnosis of a mood disorder, considering then that an effective treatment aimed at achieving and maintaining euthymia with the use of mood stabilizers, preventing the appearance of anxiety symptoms, and not necessitating additional new psychopharmaceuticals in all cases in which the presence of comorbidity between both disorders is suspected.

Mood stabilizers have anxiolytic effects, some greater than others based on their mechanism of action, Divalproex being a mood stabilizer that has the most biologically specific anxiolytic mechanism due to its direct stimulation of GABA receptors, having relative advantages over other agents[12,13, 14].

In relation to Olanzapine and Lamotrigine, there are two randomized controlled trials conducted in patients with comorbidity between bipolar affective disorder and anxiety disorders, showing in one case greater efficacy with the use of Lamotrigine and Olanzapine added to the use of Lithium for the treatment of anxious symptoms in euthymic patients[6].

In addition, greater effectiveness has been observed in the use of Olanzapine compared to lamotrigine in a follow-up of 6 and 12 weeks[11]. Favorable results have also been seen with the Olanzapine-Fluoxetine

combination in the management of anxiety symptoms in patients with bipolar depression[6].

Regarding the use of drugs called atypical antipsychotics, in a double-blind, placebo-controlled study highlighting anxious symptoms as a primary target for patients with bipolar affective disorder and co-occurring anxiety disorder (panic disorder or generalized anxiety disorder), the study fails to show that risperidone is superior to placebo in reducing anxiety symptoms in eight weeks of treatment with doses between 0.5 – 4 mg daily, despite its good tolerance[7].

There is evidence regarding the use of Quetiapine in anxiety disorders with demonstrated efficacy both in monotherapy and in adjunctive therapy, with actions at the level of the serotonergic, noradrenergic, and dopaminergic systems being a potential explanation for this effect in terms of anxious symptoms. Both Quetiapine and its active metabolite norquetiapine show high affinity for the serotonin 5HT2A receptor and dopaminergic D2 receptor. It is also noteworthy that norquetiapine inhibits the norepinephrine transporter with high potency, a property that it shares with some antidepressants, which may contribute to its theoretical therapeutic effect in anxiety disorders[18].

Considering the above, Quetiapine XR has been named with putative effect in anxiety disorders co-occurring with bipolar disorder. In a randomized, double-blind, placebo-controlled study by Gao et al. 2014, in their primary analysis, did not show a reduction in anxious symptoms with the use of Quetiapine XR compared to placebo in this group of patients. A post hoc analysis conducted by the same team, showed that patients with generalized anxiety disorder, bipolar disorder, and recent consumption of alcohol or cannabis were able to observe a reduction in anxious and depressive symptoms measured through the Hamilton Anxiety Scale, but due to the complex relationship between substance abuse disorders, bipolarity, and anxiety, it is not clear why they respond better compared to patients without substance use. Another study by Kinrys et. al. (2019), with a sample of 482 patients, did not show improvement in anxiety symptoms comorbid with bipolar disorder in patients who used Quetiapine with personalized adjunctive therapy versus Lithium+ personalized adjunctive therapy. This finding contrasts with what has been previously described in the literature regarding Quetiapine being effective against anxiety symptoms in the presence of bipolar disorder[16]. More studies are recommended, although the theoretical potential is recognized, the evidence is not conclusive regarding its use in the case of individuals with anxiety disorders in comorbidity with bipolar affective disorder.

Another possible strategy for dealing with anxiety disorders in this context is the use of gabapentinoids such as Gabapentin and Pregabalin, approved in Europe for Generalized Anxiety Disorder but not by the FDA in the United States.

It should be considered that both pregabalin and gabapentin have essentially identical pharmacodynamic properties, being chemically very similar to the neurotransmitter GABA, with the corresponding affinity for GABA receptors[15]. Both are known to inhibit neuronal signals by binding to the alpha 2 delta subunit of voltage-gated calcium channels in the central nervous system, which would explain their anticonvulsant, antinociceptive, and anxiolytic properties[15]. Due to this potent binding to the alpha 2 delta subunit, it reduces calcium influx to nerve terminals by reducing the release of glutamate, norepinephrine, and substance P[16].

It should be considered that pregabalin is absorbed more rapidly, with linear absorption kinetics and a bioavailability of 90%, in contrast to Gabapentin, which has a non-linear absorption, with saturable absorption

kinetics, with decreased absorption as its dose is increased. The bioavailability of 100 mg in a single dose is 80% and in the case of 1600 mg it is 27%[15].
Both are renally excreted, so they must be adjusted in the case of renal failure, especially in older patients[16].
Pregabalin is considered effective in the treatment of Generalized Anxiety Disorder, showing in 7 of 8 randomized controlled trials a statistically significant effect in a range of 150 to 600 mg, being at least as effective as Lorazepam and Venlafaxine 8 weeks of follow-up, with lower rates of recurrence and lower risk of withdrawal[17].
Regarding Gabapentin, the evidence is less clear, obtaining benefits in OCD as it is an adjunct treatment to Fluoxetine and in women surviving breast cancer, but it fails in a placebo-controlled trial regarding responses in the context of panic disorder.
Due to its pharmacokinetics, pregabalin presents a higher abuse potential than gabapentin (IV in the classification of drugs with abuse risk according to the law of controlled substances used in the USA), possibly because of its absorption rate. This could be a future risk to consider, specially in patients with history of problems with drug use. Although global risk seems low, it must be kept in mind.
Regarding the risk of discontinuation symptoms when stopping its use in patients with long-term use (for example, use greater than six months), there is a low incidence of discontinuation symptoms and also a low incidence of "rebound" in anxious symptoms. and it seems not to be related to the dose or the duration of treatment in the case of patients diagnosed with generalized anxiety disorder[17]. Given this evidence, we support the suggestion of gradually tapering Pregabalin over a week given the existing (but low) potential for discontinuation symptoms in patients with generalized anxiety disorder[17].
It is presented as an alternative associated with other drugs in the absence of an effective response or as an option without greater risk of worsening the course of the disease in the case of individuals diagnosed with bipolar affective disorder, considering that they do not have a beneficial effect as mood stabilizer per se, unlike other anticonvulsants such as Valproate[12].

CONCLUSIONS

Comorbid diagnoses are a highly frequent situation in clinical practice, being a constant challenge for the approach of different psychiatric disorders. The approach to individuals diagnosed with bipolar affective disorder and comorbid anxiety disorder is no exception, with considerable scope that can define the course of the underlying disease, notably affecting the quality of life of individuals suffering from both disorders.
The main strategy will continue to be to maintain longer euthymia times, considering that anxiety symptoms are frequently secondary to mood episodes, in which case the use of mood stabilizers with an anxiolytic profile is a reasonably useful choice.
Atypical antipsychotics seem to play an important role as coadjuvant agents in mood disorders and, considering their mechanism of action, they can have a positive impact in the management of anxiety disorders as a specific target of action.
The use of gabapentinoids (Pregabalin and Gabapentin) seems to be another useful strategy for the approach aimed at managing anxiety symptoms, considering that in addition to their anxiolytic properties, they show a reasonably safe use profile and do not alter the course of the mood illness as If it occurs with continued use of antidepressants.
Better pharmacological strategies should be the target of new research considering the high prevalence of specific and

non-specific anxiety symptoms and the impact they have on the quality of life of individuals suffering from these disorders.

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Lebenswelt's concept in the melancholic according to Tellenbach.

Derderián B. María Francisca

Abstract
In the following text, the concept of lebenswelt introduced by Husserl is approached from a phenomenological perspective, to describe the way of being in the world of Typus Melancholicus, described by Hubertus Tellenbach. Doing an analysis in the different dimensions of experiencing; temporality, spatiality, relationship with others, and self-awareness. In each of them, this way of being-in-the world of the melancholic is expressed. However, it will not only described, but it is intended to refer to the theory proposed by Tellenbach for the pathogenesis of melancholy, in which the active role of the environment in the genesis of mood disorder with the concept of Situation and the incorporation of the Endon. This last concept refers to a certain biological arrangement that is in line with the rhythm of nature, with the natural world, and biological cycles. Identifying the typical pre-depressive situations, the active role that the subject has in the genesis of them is understood.

Key words: *Phenomenology, depression, Typus Melancholicus, endon, world of life, situation.*

INTRODUCTION

The concept of mental disorder from the phenomenological paradigm is far from the notion of nosological diagnosis centered on symptoms. A major depressive disorder, included as such in the third edition of the Diagnosis and Statistical Manual of Mental Disorders (DSM III), is characterized by a heterogeneous symptomatology that alters affectivity, the cognitive area, the sensory-motor area, and social interaction. Those people who are depressed can feel sad, anxious, exhausted, worried, irritable, guilty, hopeless, or empty. They also lose interest in activities that caused them pleasure in the past, and can show alteration in appetite, concentration or memory problems, difficulty in making decisions, and death-related thoughts or desires, as well as suicidal actions. However, clinical presentations are diverse. Since low mood as the main symptom is conceptually neither clear nor defined, we usually find that descriptions center on sadness, but mood can vary from dysphoria to apathy(1). The concept of melancholic depression has been generally considered as a clinical condition featuring physiological changes, such as loss of appetite, energy and sleep, as well as depressive mood with circadian variations (29). Some authors mention that psychomotor retardation and pathological guilt are the most distinctive symptoms of melancholia (3), adding that these alterations are considered endogenous, to refer to a phenomenon that appears spontaneously and not as

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a reaction to adverse life events. When talking about melancholic depression in psychopathological terms, we refer to a depression that is characterized by a painful experience of loss of emotional resonance (1). It is described as type of depersonalization characterized by the sensation of loss of feelings. One characteristic of this indifference is that it is experienced with deep suffering characterized by self-reproach and feelings of guilt. Tellenbach described and analyzed 119 patients admitted to the Heidelberg University Clinic who presented psychotic depression. His study used an empirical approach when detailing and recording the patients' experiences and behaviors, as well as a phenomenological analysis when considering these phenomena as manifestations of the way of relating to himself and to the world (4). In this sense, Tellenbach argues that the symptoms always refer to some delimited fields of alterations and are, therefore, expressions of particular changes. He affirms that, in the description of the phenomena of melancholia, the wholeness is revealed "in every phenomenon of melancholia the wholeness is contained". This is a turn from the symptomatic to the whole existence of the person (5). Tellenbach coined the concept of Typus Melancholicus to describe the structure of premorbid and intermorbid personality of the subjects that suffer endogenous depression (6). With personality structure he refers to certain fundamental and distinctive traits that determine a certain way of being, and that, in certain life situations, predispose to the development of endogenous depression. From another perspective, mental pathology shows in a more global and ample way a relation between not only the biological and psychical realms, but also with the surrounding world, that which surrounds the connection, such as the conception of rhythm linked to the natural cycles. The attempt of Tellenbach of proposing a theory to explain the pathogenesis of melancholia introduces a new link, leaving aside the classical notion of endogenous/ exogenous, or the separation between the psychogenetic and the biological realms. Therefore, it incorporates the concept of Endon, which, in melancholy, it is manifested in the change of the rhythmical. This refers to biological cycles, the phasic and the periodical, and also to the expression of the whole, because every aspect of melancholy is contained in the whole (7). It can also be seen in the melancholia present in maturity cycles (pregnancy, postpartum, climaterium, etc., as well as its reversibility) (8). His work Melancholia (1974) describes characteristics of the way of being of depressive patients (monopolar melancholy), contributing not only the concept of premorbid personality, which promotes the onset and development of the disorder, but also highlighting how the close interaction with the surrounding environment constitutes the cornerstone of the pathogenesis of melancholia. This is how it describes the following: "But now it is necessary to emphasize the fact that the elements that constitute endogeneity can only be thought as a context that includes the reference to the world" (7). This is where we find the concept of lebenswelt, which tries to account for this environment or world that surrounds each person, in this case to the typus melancholicus, and the active role that the latter has in its constitution. Thus, the patient's experience in terms of feeling, of meaning, of assessing through the analysis of the lebenswelt or world of the life of the melancholic person, and the active role that this lebenswelt has in the genesis of melancholia, will be developed.

Concept of Lebenswelt

The concept of lebenswelt was introduced by Edmund Husserl in "The Crisis of European Sciences and Transcendental

Phenomenology" (1936). Although three fundamental stages are recognized in Husserlian phenomenology (descriptive, transcendental and constitutive), it is precisely in this third stage when the concept of Lebenswelt is formally developed, which, translated from German, is understood as the world of life. (9). Here, the word life does not have a physiological sense, nor does it relate to natural sciences, but refers to the life that we live daily, the reality that is given, that exists, but without entering into categories or explanations from science. It is the world of life lessons, of experience, of the subjective environment that accounts for the vital relations established by the subject with the world, with its immediate environment. Husserl warns that, for each person, their lebenswelt is their objective world —a world built in a process that each of person lives as pure ego through transcendental moments. With this term, Husserl distinguishes between the immanent (that which is inside the conscience of pure ego, that is the I), and the transcendent (that which is outside pure ego, of the conscience) (10). By using this distinction, he wants to highlight that, even though the lebenswelt, or the world of life, accounts for the subjective environment, it does not refer to the subjective world "inside the conscience", but to the surrounding world that is not any world, but that which has a spatial, temporal, and corporeal organization. And that the very I builds, incorporating in it facts, other egos or alter egos, things, etc. (11). The concept of the world of life is a tool that allows us to access the description of the patient's subjective experience, being the scene of all shared human experiences, but not understood as an immutable background but rather as a "dynamic horizon" in which we live and which "lives with us in the sense that nothing can appear in our world of life but is as something lived"(1).

In this way, we understand that the world of life corresponds to this basic, subjective structure of the patient with its own meaning and a way of experiencing time, space, body, itself, and others (12).

Tellenbach incorporates the concept of situation as a vision of the subject and his world in a cross-section, at a given time. With this, he does not try to enhance the static but quite the opposite, mentioning the kinetic aspect of the concept. Highlighting that this conception corresponds to a global definition, "in which the individual and what surrounds them within the world are still united" (5), he adds that they are always in a situation and that they cannot get out of it, without entering into a new one. It is important to differentiate it from the concept of action-reaction situation, as the person does not respond to an environmental stimulus, nor can the situation be purely created by the person, that is, there is no causalist logic. Rather, he tries to recognize how in a situation it is not only about the action of the circumstances of the environment on the subject, but also in the action of the subject on the environment. It is different from the notion of situation of Jasper, as it recognizes that the constitution of that environment has also been created by the subject (13). Tellenbach emphasizes the experience lived by the person, evidencing, on the one hand, that it has active role in the constitution of the situation and, on the other hand, it has a passive role in the sense that there is no intention or will to create the situation in itself by the person, or for not being able to do it otherwise. Regardless of how it is handled, the relationship of the subject and the world will be modified.

Tellenbach, with his analysis, describes how, from specific and determined characteristics that he calls premorbid melancholic personality, the subject in question builds a way of being in the world, a way of being with others, and of being with himself. Thus, this way of

living the relationship with the world in a reciprocal exchange, in a relationship of interdependence with the environment, especially with the social context, the way of understanding life and the way of relating to others, the hierarchy of their priorities and values, make these people have a typical type of relationship (14). One could say that each type of person tends to constitute a given type of situation; in this sense, it involves an active role of the person in constituting it, but also an inactive role, since it is not performed voluntarily.

The phenomenological exploration of the lebenswelt of the patients allows us a qualitative description of the experiences lived by them. These lived experiences are always situated in the body, in time, in the self, in space and in others. Each person can account for these dimensions in self-descriptions, but also in behaviors and their experiences (1). That's how Tellenbach agreed to the self-description of his patients to explore their lebenswelt. (5)

The development of phenomenology has taken the concept of the world of life or lebenswelt, and has tried a systematic description of different ways of existence in psychopathology, focusing on the understanding and description of these modes of being and of constituting the surrounding world (12). In broad terms and as a way of defining these dimensions, they will be described below, considering that each of them has deep connections with psychopathology. We understand then that those constituent elements of lebenswelt, or world of life, each acquires the adjective of lived, that is, of "being" perceived by the subject. This is how chronological time does not agree with the time lived; the distance between the present and the future is experienced in a different way, it can be shortened and expanded according to the stage of life, or to the affective state. Usually the passage of time is experienced as a continuous flow, which can be faster or slower (15). In turn, the space lived is the way in which we experience the distance that unites us to the things that are ours and that binds us to our surroundings. It is not a distance in terms of geometric or physical unit, but as that lived space that connects the person with their environment. In relation to corporality, or the body, we are referring to the lived body. Husserl distinguishes between Körper and Leib; one, the object body, the physical, anatomical, measurable body, and on the other, the body of primary experience, of perceiving, the body-subject. Leib or the body lived, is the body that I am, but also the place from where my perception of the world springs, is my point of reference (16). The lived body is understood as the body from which I place myself in the world, as the center of my experience, in the first person. Another component of lebenswelt or world of life is self-awareness. This dimension refers to the basic sense of self as the center and core of one's own experience, perceptions, emotions, actions and thoughts. This experiencing is a pre-reflective, tacit, and implicit phenomenon, it is immediate. The French phenomenologist Michel Henry coined the term "ipseity" to refer to this basic form of self-awareness (17). Intersubjectivity is another dimension of lebenswelt, which emerges from the lived body. It refers to this pre-reflective way of connecting with the other and recognizing the other body as another human being as an alter ego. This encounter with the other has the characteristic of being embodied, incarnated, and not just a relationship between separate people. Intersubjectivity and intracorporeality allow me to recognize in the body scheme of another a human being similar to myself. Along the same lines, "otherness" or the experience of others is a component of the world of life that refers to how I experience the Other, considering that every time I experience myself as an I it is before another.

The World of the Life of the Melancholic Person.

Now attempting a systematic analysis of the lebenswelt or vital world of the melancholic person, we find that time is a nuclear element in the theory of the pathogenesis of depression, and of affective disorders in general. The rhythm aspect was described as a fundamental element by Tellenbach, considering it as a form of the flow of life that manifests itself in a natural harmonic synchronization of the person with the world (15). Fuchs (2001) describes melancholy as a desynchronization between the person's time and the world in which time passes too quickly for the person to catch up (1). Desynchronization is the slowing down or acceleration of subjective time in relation to the social sphere. The melancholic aspect is terrified by this threat of slowing down, falling behind the demands of others, their commitments, and social obligations. In the lebenswelt of the melancholic aspect, desynchronization is always incipient. That is why they always go ahead, make an effort, trying to meet their demands on time, becoming hyperactive and over engaged. They are always anticipating the requirements of others. Tellenbach describes this way of being-active as one of excessive thoroughness and high self-demand in one's own performance (5).

We find the same tendency in the experience of spatiality or the space of the lebenswelt of the melancholic person; this way of being hyperactive and overcommitted is a way of preserving harmony in the social space. The first thing that stands out in this way of remaining is to remain in an order. And as long as this being-in-an-order is threatened, a threat of existence is experienced in its entirety, being evidenced how it is not-adapting is a characteristic of the usual situation of the melancholic type. When we talk about an attachment to order, we refer, to differentiate it from a normal range to a feature of rigidity, to be fixed by an order, with a lack of elasticity and free disposition without being able to distinguish the important from the less important. López Ibor coined a neologism of the translation of the German term Ordentlichkeit as ordanelity (5) Here, everything has its place assigned according to a pre-established order. Space is not a geographical element, but it is a position in the hierarchical social relationship. Things are not mere objects. The melancholic person takes refuge in this typical organization of space, in which he or she assigns a social role around him to things and people. The melancholic person feels safe attached to this controllable and predictable order, showing an intolerance to ambiguity and a repulsion towards improvisation (1) (12).

The identity of the melancholic self is also rigid and inflexible. When internalizing its identity of social role, it is identified with it, and simplifies its identity in a partial and superficial way. For him there is no possibility of being different or otherwise; this is seen as a source of alienation. The melancholic person cannot be perceived in another way other than in their social role.

In this same way, the melancholic person sees others partially; the union with the other is the union with the social role of the other, not as an individual person. The others, for the melancholic person, are like a generalized other; they are the incarnation of impersonal social norms. This generates a pseudo intersubjectivity, despite the fact that the melancholic ensures that they are there for the other. This being there is "to take care of", not to simply be and enjoy the company of the other (1). Tellenbach describes how the restrictive mode of order also interferes in interhuman relations, thus being-for-another has the way to render-for-the-another. In the eyes of the melancholic type, their importance to the other is only in performance, never in simply loving existence. Conversely,

the melancholic type has a way of being so close to being-one-with-the-other that it becomes a symbiosis, so that when family members move away, whether due to marriage, death, separation, there is an intolerable emptiness.

Despite this way of being for the other, this other must also meet certain requirements to relate and establish social encounters; mainly, he or she must be respected and with high morals. Likewise, free exchanges without the obligation to return something are not contemplated. The melancholic cannot owe anything, so they need physical and financial self-sufficiency to avoid any dependence on others. Also, in the relationship with himself, Tellenbach describes this specific mode of scrupulosity in a high and sensitive moral conscience expressed in an intolerance to fall into guilt.

The Pathogenic Situation

So far, the melancholic type does not meet the criteria of melancholy or depression, however, this narrow mode of functioning in the world can be threatened by different vital circumstances that can intensify the fixations and turn the situation into a pathogenic situation (6). In these situations, internal movements are necessarily imposed on the melancholic type that, due to their idiosyncrasy, are simply not allowed. What we call vital circumstances or fatal events are events that, together with the habitual situation of the melancholic type, can constellate a pathogenic situation, which, like any situation, implies modification, in such a way that the melancholic type, due to its narrow range of movement, has no more to do than to give way to the pre-depressive situation.

Tellenbach defines some fundamental situations, which account for an increase in demands and tasks that overloads the melancholic person's ability to maintain a certain predetermined order (5). The melancholic type is not capable of establishing a certain order and prioritizing, nor can he discriminate in order to temporarily postpone some demands.

It should be noted that the melancholic person has created his or her life world towards in the direction of pathogenicity (8).

In the following paragraphs we will see how the constitution of a vital world with the distinctive characteristics described can easily fall into crisis, threatening not only the constitution of the vital world but, as has already been understood, its own existence.

Includence is a self-contradiction that puts the melancholic type, on the one hand, engaged in an extreme attempt to maintain and re-establish order, exceeding his own limits. This is how the orderly and meticulous way of being is destabilized (5). While in remanence, it falls behind in staying behind in its commitments, and not paying its debts or social obligations. The melancholic type lives in the contradiction of paying their debts in advance. Tellenbach describes him in his extra-depressive period, with an inclination to lag behind, behind himself, where the essential thing is to lag behind self-demand, that is, "to be in debt" to the demands of one's performance, or a "to be in debt" in the face of the demands of love for one's neighbor or in the face of the demands of ethics and religion. This "being-in-debt" manifests itself in working life in being permanently busy, in a continuous activity and never being able to finish. The day is seen as a closed temporary figure that structures life and what the day brings must be concluded, because if unfinished things are left behind, they will feel behind in relation to the demands of the objective of the day. The scruples play against achieving these objectives. Being in debt in the melancholic type acquires the form of guilt, which may arise from both the surrender, occupation,

or being indebted to someone, or feeling guilty in the ethical-religious sense. The melancholic type in the situation of pre-depressive remanence self-realization becomes impossible, because a structured being in a certain way must live a situation in which it is not able to exist: it is then in front of a contradiction with itself, causing then the depressive transformation.

To understand what is understood by includence, a typical situation can be used to which this aspect of spatiality is involved: in moving or changes of address(8). If we recognize the mode of the order in which the melancholic lives in their home, this way is interwoven by a network of references relations based on the proximity of both objects and the human. Everything then has its constant place. Here the past is preserved in objects and memories, existence is installed firmly and remains accommodated in this home form where the usual careful care becomes easy, transforming the home into a kind of cocoon in which the melancholic type can hide and take refuge. The change of domicile, although initially lived with joy, gives way to a growing depression in an incomprehensible way. This change in spatiality is equivalent to a kidnapping of all protective wraps; in this helplessness, new orders must be established, new relations for which elasticity and freedom are needed; too high demands for the melancholic.

Other vital events that can lead to includence are the diseases that affect their corporality (6), preventing the melancholic from trying to order and thoroughness that is their form of self-realization. This same phenomenon is observed in depressions after a professional promotion, moving from a subordinate status, dependent to another freer, with greater responsibilities and risks. In all these events the melancholic type is not able to transcend its usual way of performing, even when it has a willingness to perform well, thus facing a contradiction that its existence cannot resolve. Later, it gives way to the transit from a pre-depressive situation to melancholy. Here appears the despair, from the translation of the German Verzweiflung and despair in English that refers to the emotional and cognitive state characterized by the inability to establish priorities in which decisions cannot be made (1). In this state, the person experiences feelings of ambivalence feeling moved towards two opposite directions, realizing this contradiction but unable to solve it. The nucleus of Despair is indecision, and the opposite mental state is not hope but decision. Giving way to melancholy, in which the experience of temporality, corporality, spatiality, is altered again, but this is out of the scope of this essay.

CONCLUSION

We have reviewed from Tellenbach's proposal and the phenomenological empirical description that he made detailing not only those known characteristics of Typus Melancolicus, but expanding the conception of the genesis of melancholy to the concept of lebenswelt and the elements of the endon as the rhythmic, the periodical, the global, elements that bring us closer to the current conception of the evolution of mood disorders and chronobiology (18). The analysis of lebenswelt opens a new look, not only in being able to know in a systematic way the elements of the subject's experience, but that recognizing in this concept that the pathogen or those circumstances experienced as dramatic and destabilizing or that directly cause depression, they are partly conscious by the same melancholic in this narrow and rigid mode that they have to live. Knowing this way of being-in-world allows us to recognize in melancholic patients what pathogenic situations, which are initially classified as positive events, they can

trigger depression development. It will also allow us to achieve a deep understanding of the subjective experience of those with melancholic characteristics that have the predisposition to the development of depression and allow us to orient ourselves psychotherapeutically. Finally, recognizing as cultural elements aimed towards success and the production or, in Tellebach's terms, the performance, is fundamental to structuring the premorbid personality. In the same way, it is meaningful to ask ourselves what "typus" is the subject that gets depressed more frequently, what their values and priorities are, what constitution of their vital world is, what their influence in society is, what their culture is, etc., thus incorporating an integral and broad perspective on modern psychiatry.

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Depression in the elderly: clinical and etiological aspects.

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ABSTRACT
Introduction: Geriatric depression is a heterogeneous entity that includes early-onset mood symptoms that reach old age and others, beginning after 60 years of age, with confusion in their nomenclature. It has neurobiological, epidemiological and clinical peculiarities that deserve consideration. Methodology: Literature review is performed in PubMed, Google Scholar and in specialty books, which included the following main concepts: geriatric depression, late life depression, and 3d psychogeriatrics. 16 relevant articles are selected in relation to the objectives, which were reviewed for the epidemiological, neurobiological and clinical aspects of this entity, in addition to a book chapter. Results: The nomenclature is reviewed first, stating that late-onset depression (LOD) corresponds to the most suitable definition to differentiate this age group. Second, risk factors, prevalence and other relevant characteristics are analyzed. Subsequently, clinical characteristics to be considered are described, particularly the differences between symptoms at a young and late age, as well as some clinical keys focused on phenomenological differences and the "3Ds in psychogeriatrics" mnemonics. Finally, the relevance of weighing these epidemiological, neurobiological and clinical symptom differences for the correct approach to depression in older people is discussed.

Keywords: Geriatric depression, 3D geriatrics, Late life depression.

DEFINITIONS

When talking about mood disorders associated with old age, different authors agree that these clinical pictures have become highly relevant in recent decades. The progressive increase in life expectancy, with an older population that often has other comorbidities and, in turn, with various socioeconomic determinants of health, makes it imperative to update the understanding of these conditions and try to show an approach more in line with what is known as Comprehensive Geriatric Assessment (CGA), an interdisciplinary work model that attempts to encompass the different illness variables in elderly patients.
With regard to depressive disorders, they have both etiological and treatment peculiarities that differentiate them from depressive symptoms in adult life—a distinction that many times is not given the proper differentiation in commonly used diagnostic criteria and epidemiological studies.
In the literature, depressive disorders have been called many names: depression in

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the elderly person, geriatric depression (GE), depression in old age, end-stage or terminal depression (Late Life Depression, LLD), and late-onset depression (LOD), among others. These last two have been defined as depression that occurs after the age of 60. Special emphasis is placed on the fact that the focus of this definition is on unipolar depressive disorders1. For the purposes of this work, we will talk about this condition, using its abbreviation (LOD) and accepting that the concept "late-onset depression" seems to be the most suitable to do justice to the different neurobiological, epidemiological, and risk factors of this condition, unlike other mood disorders.

LOD is the most important cause of emotional suffering in older adults and aggravates the prognosis of many other conditions in this stage of life. It can contribute to the morbidity of different medical conditions. Very often, in turn, it determines a deterioration in the quality of life, an increase in mortality due to both suicide and decompensated medical illnesses, in addition to the fact that it tends to be more chronic than depression at younger ages.2

It is important to distinguish between early onset depression (EOD, Early Onset Depression) with recurrent episodes extending into old age, from late onset depression (LOD, or Depression of late onset, DIT in Spanish) in which the onset occurs late in life or old age. They have differences in neurobiology, forms of presentation, and disease course. In many adults with LOD, symptoms appear in the context of underlying medical and/or neurological conditions, such as cardiovascular diseases, dementia, or other1,2.

EPIDEMIOLOGY

North American literature states that geriatric major depressive disorder affects 2 to 4% of patients; this prevalence being lower than that found in young subjects2,5. This data can be interpreted in various ways, including: older people tend to report fewer depressive symptoms, present both medical and psychiatric comorbidities, which is why they are usually excluded from clinical studies and others. On the other hand, many of the usual diagnostic criteria (DSM or famous scales such as the HAMD or MADRS) do not consider the symptomatic differences in older patients. Other studies suggest that there would be no significant differences in the prevalence of depression at this age3.

There are other factors responsible for the decrease in the detection of these conditions. Many times, they can come from the patient themselves due to their fear of the stigma of being diagnosed with a mental illness, or on the other hand, from the medical teams that may consider some of the depressive symptoms typical of this age as normal 4.

In a narrative review published in Psychogeriatric, Agüera-Ortiz et. al. described a prevalence of affective disorders ranging between 0.4% and 35%. Yes, in this review, it was emphasized that the presence of affective disorders increases with greater medical-psychiatric complexity. For example, in the hospital environment, it can reach up to 15%, and in nursing homes, 25% 4, 5. On the other hand, there are studies that show higher prevalence when evaluating specific groups, reaching up to 50% prevalence. They correspond to cancer patients, hospitalized, sequelae of cerebrovascular accidents, or heart attacks, among others. The prevalence at discharge from hospitalization after illnesses that require critical care are very high in various series, covering up to 50% of patients5,6.

A review performed in our country described that geriatric depression (global, not differentiating if it is LOD) is more frequent

in women, widows, chronically ill, patients with insomnia, motor disability, and social isolation. It also mentions underdiagnosis, revealing that access to treatment in men is lower. It indistinctly refers to “masked depression”, “minor depression”, and other definitions that, as mentioned in this work, are not so widespread today 7.

Recent epidemiological data from our country, for example the recent National Health Survey (NHS) published in 2018, describe a 12-month prevalence of 8.5% between 45 and 55 years old and 6.2% between 55 and 75 years old--quite high figures in relation to other stages of the life cycle. It should be mentioned that the instrument (CIDI) used in said research does not rule out some possible false positives that are very probable at that age (physical pain, grief, among others)1.

Neurobiology and risk factors

Similar to what happens at younger ages, in late-onset depressions, neurobiological factors converge with other environmental ones. Within this same “nature/nurture” duality, we could also add that human beings are immersed in an evolutionary process in which the passage of time generates modifications in our entire organism, including the nervous system, putting all the capacities to mold themselves at stake and overcome the challenges that these constant changes imply. One of the key aspects to consider in adaptive capacity is neuroplasticity (the ability of neurons to adapt to changes). It should be noted that during aging there is a reduction in brain weight and volume that has been calculated at 5-7% with respect to the brain in the average age of life, which would be equivalent to 80-100 g. Brain weight loss can result from a decrease in the number of neurons, neuronal atrophy, or loss of non-neuronal elements, such as blood vessels4. In this context of morphological, functional and neurochemical alterations, it is accepted that the brains of the elderly have much less adaptive capacity and plasticity when facing different stressors or noxae.

However, in relation to genetic factors, studies performed in geriatric depression (late-onset unipolar) suggest that a very modest role of genetic factors in these conditions, compared to early-onset mood disorders. In a study of elderly twins in Sweden, genetic factors account for 16% of the variance in scores on some scales (e.g., CES D: Center of Epidemiologic Studies Depression Scale)8

Some pharmacological studies in depressed older adults have shown an association between polymorphisms of the serotonin transporter promoter and both the rate and incidence of adverse effects due to antidepressants. Some genetic alterations have been associated with geriatric depression, such as: BDNF polymorphisms, methylene-tetrahydrofolate reductase and tryptophan hydroxylase-2, among others. Regarding the receptor changes associated with aging, the functioning of the serotonin 5HT2A receptor particularly decreases markedly in different brain regions. In non-depressed subjects, the number of serotonin receptors decreases dramatically over the years, even reaching percentages of 70%8.

What happens in the brain of the depressed elderly? This is the question asked by Agüera-Ortiz, Losa et. al. when explaining geriatric depression etiologically4. Firstly, it should be noted that in the elderly group of depressive patients, as in the younger patients, a decrease in hippocampal volume is observed in relation to the controls. What is much more noticeable are alterations in the neuronal life cycle, with a decrease in cell number and function, and a decrease in neurotrophic factors, among other anomalies. Depressive illness, in addition to producing a structural alteration, causes (and is at the same time a sign of,

bidirectionally) a functional alteration that contributes to cognitive impairment and neuroendocrine alteration in the depressed elderly4,5.

Testosterone levels decline over the years and have been shown to be more, strikingly, lower in older men with dysthymic symptoms versus other patients with major depression and than in non-depressed individuals9. However, the efficacy of testosterone treatments in men with geriatric depression has not been clearly demonstrated.

On another level, if we consider a second group of disturbances in geriatric depression other than morphological ones, we find pathological changes in the hypothalamic pituitary adrenal (HPA) axis. Hypercortisolemia and the increase in catecholamines have a deleterious effect both on the body and the brain, increasing the risk of somatic and neuropsychiatric diseases. This helps explain in part the high rate of comorbidity between affective and cardiovascular diseases, and between inflammatory and metabolic diseases. But it is not only in relation to cardiovascular diseases where the damage due to hypercortisolemia is noticeable; also, the neuronal tissue itself suffers damage through this pathway, promoting degeneration and neuronal death and decreasing the levels of BDNF, all processes already accelerated by their own change of aging4,5,7.

Studies conducted in healthy individuals between 20 and 60 years of age show a negative correlation between plasma BDNF levels and the age of the subjects. All these modifications undoubtedly affect cognitive performance and, in fact, 15-25% of the geriatric population presents cognitive deficits that influence various functions, especially: memory, attention, language, visuospatial abilities, and executive functions. These deficits interfere with the performance of daily activities, the maintenance of social relationships, and self-care [4,5]. But the impact of changes associated with age is for a cluster of diverse diseases, in which LOD is one more and multiple pathologies are the rule.

Gerontological aspects.

When we perform an analysis of this pathology from a gerontological perspective, a series of considerations must be considered that place us in a different context from that of the depressive patient at other ages. In the first place, especially in Western culture, psychosocial variables related to isolation and loss of productive or social functions, economic impoverishment, for example, related to expenses at this age or to retirement, among others, appear as a group of important social burdens and a deterioration of different aspects of life that directly influence mood symptoms at this age10.

Secondly, the different griefs that people in this age group must deal with are undeniable. Beginning with the deaths of friends, spouses and/or relatives, many people of your generation are slowly getting sick and dying. To the feeling of loneliness and sadness, the fear of being “the next” is added. Now, not only death is a reason for mourning, but also the loss of social functions, changes of address or city, or modifications in the caregivers in charge, add adaptive events that are difficult to cope with to a brain with gradual decrease in their functions and ability to metabolize affects and emotions.

Cognitive deficit is one of the diagnostic criteria for major depression, however, the relevance of severe cognitive impairment in patients with depression, especially in terms of prognosis, is still being studied and discussed. When talking about depression in the elderly, especially if it is an untreated and/or chronic condition, one must think about the prognosis and also consider that this cognitive condition, added to the

emotional one, could be the beginning or the expression of future risk of a degenerative disorder, such as dementia10.

Lastly, a very relevant point from the gerontological point of view has to do with a concept that has been known as "old age". Within this stereotype, it is accepted, in a discriminatory way, that certain conditions that are pathological in a part of the population would be "normal" in this age group. This is the case with chronic pain, dependency, and depression, which is normalized by both the patient and the caregivers, causing a priori delay in access to mental health diagnosis and treatment11.

Clinical Aspects

Patients with LOD present differences in clinical presentation with respect to earlier adult ages. In turn, there may be notorious differences in manifestations among the different elderly patients. Patients with LOD have neurological abnormalities more frequently, including failures in neuropsychological tests and alterations in neuroimaging studies; greater than those expected for their age. These structural changes and the mood and neurocognitive disorder put them at higher risk for dementia12.

Von Mühlenbrock et. al., in a descriptive review of patients hospitalized in a medical service in Chile, reveal certain clinical aspects. It describes that the elderly usually present more psychomotor agitation, cognitive compromise, overvalued and psychotic ideas of poverty, and physical illness in relation to those under 60 years of age, and psychotic symptoms of different kinds7.

The persistence of this disorder is associated with a poor quality of life, difficulty behaving appropriately from a social point of view, poor adherence to treatment, poor evolution of chronic diseases, increased morbidity and mortality, and the suicide rate7,8.

As can be seen, some aspects are quite typical of late-onset depression (LOD), compared to early-onset depression (EOD). To illustrate these differences, they are outlined in the following table.

Table 1.- Comparative differences between EOD and LOD

Phenomenological differences of geriatric depression. An important aspect at the time of the clinical approach, especially for the psychiatrist with an interest in phenomenology and/or psychopathology, is to consider whether there are inter-age differences in the symptoms of patients with mood disorders. In this regard, Hegeman, Kok et. al. published a meta-analysis in 2012, in which studies were systematically reviewed that allowed differentiating forms of clinical presentation between young people and adults. Papers that comparatively compared the different items of the Hamilton Scales (versions of 17, 21 and 24 points) were selected. Finally, the comparative analysis was performed only on the items corresponding to the evaluation of 17 points13.

The most striking thing about the meta-analysis, and different from what is classically mentioned, is that no major differences were found in the type of symptoms according to the age of the depressive picture. The items that showed noticeable differences were in the greater presence of guilt and alterations in sexual behavior in young people versus a higher percentage of general somatic complaints, gastrointestinal complaints, agitation, and hypochondriasis in older adults13.

However, when putting the data on the table, which can reaffirm what many refer to as symptomatologic "differences", it is tremendously challenging to translate them into an unequivocal clinical interpretation. It is very difficult to differentiate whether geriatric depression has a primary predominance of physical symptoms due to its etiological differences or, in this age

group, it overlaps with medical illnesses and the psycho-organic deterioration so frequent in many patients. From a critical and very valid point of view, as stated by the authors of the meta-analysis, it should not be forgotten that the Hamilton test has many items for evaluating somatic symptoms, which can also bias the analysis. On the contrary, it is relevant to mention that the greater number of somatic symptoms in an older patient with depression tilts the balance towards considering the vascular etiology of this13. The following figure reproduces the Forrest Plot of this meta-analysis .

Figure 1. Forest plot of the odds ratios (and their 95% confidence intervals in the extremes of the diamonds) comparing symptoms in young and late ages of the 17-item Hamilton scale (HAM-D-17). Blue diamonds show more frequent symptoms in young people and light blue ones, the most frequent in late-onset depression (LOD).

The 3Ds in psychogeriatrics the two main differential diagnoses of LOD are delirium and dementia (and cognitive impairment). Accompanying the LOD, these three pictures are known mnemotechnically in geriatrics, particularly in North America, as the "3Ds": depression, dementia, and delirium. These "3Ds" explain most of the psychogeriatric conditions to be faced in this age group. Each of these conditions increases the possibility that a patient presents "another" of them and, at the same time, acts as a confounding factor at the time of clinical presentation. To exemplify and try to clarify the above, we will say that dementia cases favor the appearance of delirium and, in turn, when it occurs, they increase the risk of dementia and can be confused with LOD and dementia. A schematic personal adaptation of how these clinical syndromes present is presented below14.

Figure 2: The problem of the 3Ds in psychogeriatrics
Table 2.- clinical comparison of the "3Ds" in psychogeriatrics
Cognitive symptoms and depression. LOD often has negative effects on cognition, especially in the age group this article deals with. It is common for LOD with elements of marked cognitive compromise to be erroneously diagnosed as a dementia condition. Some researchers have suggested that cognitively compromised depression may be a precursor to dementia syndromes, both as a risk factor and as an early indicator, even if it recovers with treatment of the mood disorder. There are several recent works that show that depressive symptoms, particularly recurrent ones, over a period of years, are associated with an increased risk of developing dementia and Alzheimer's disease. The term "depressive pseudodementia" widely used particularly in the past, is not so widely used today. Today, it is interpreted as the presence of both cognitive and affective symptoms that are a mixture of different aspects of the underlying disease and should not be analyzed as one disease being confused with another6,8,16.
Depressive symptoms can often be seen in a person with an established diagnosis of dementia. The term "depression in Alzheimer's disease" has been proposed for patients who meet criteria for AD and who also present 3 significant symptoms of depression (includes depressed mood, anhedonia, appetite and sleep disorders, etc.)16, 17.

DISCUSSION

One of the objectives of this review was to reveal geriatric depression and particularly late-onset depression (LOD) as a different

condition from mood disorders at an early age. They have neurobiology and differentiating risk factors that should lead to preventive interventions that consider these peculiarities. Only by taking these preliminary aspects into account and comparing them with the reality of our country, we could already state that there are no major differences when dealing with mood disorders in this age group in our Health Services. In daily practice, the same diagnostic criteria (ICD 10 or DSM 5) and the same preventive and therapeutic interventions are applied to elderly people who consult, without considering the different gerontological and neurobiological conditions of late-onset mood disorders. Some authors, years ago, have developed and disseminated special diagnostic criteria for these patients. A practical example is the simplification of the Yesavage scale for geriatric depression to only 5 items, based on its predecessor of 30 points, and which presents an appropriate validity and sensitivity, which in only 5 questions allow a screening of good reliability18. Differentiating gerontological factors should also be considered in LOD preventive interventions, seeking to promote, for example, integration with peers, social support and the correct approach, for example, to the different griefs associated with old age.

Finally, especially taking into account the complex neurological and medical differential diagnoses, in addition to the psychiatric ones, approaches such as “3Ds in psychogeriatrics” are very relevant, practical, and schematic when doing clinical work in this group of the population which for demographic reasons has been taking on increasing importance.

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Predominant polarity in bipolar disorder: A comprehensive review.

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Abstract

Introduction: *Bipolar disorder (BD) is a chronic disease with a heterogeneous presentation and complex management. The current classifications are insufficient for the clinical approach of some patients, which is why complementary criteria have been proposed, such as the one based on the predominant polarity (PP), according to the tendency of each patient to present recurrences towards the manic pole or the depressive pole.*

Methods: *Review of all articles on BD in the PubMed database, in which PP was analyzed, updated to July 13, 2020. Additionally, application of an online descriptive survey to measure the degree of knowledge and application of this concept in a group of Chilean psychiatrists.*

Results: *The concept of PP is a current research trend showing consistency in some clinical indicators but also contradictory findings. This indicator has been used in recently published clinical guidelines, including the Chilean one. In the sample of psychiatrists surveyed, a high percentage knows, uses, and considers the application of the PP concept clinically useful.*

Conclusion: *The complementary criterion based on the PP shows a potential utility for clinical decision making, to guide treatment response and prognosis. However, as there is no common definition; some available studies show inconsistent and/or contradictory data. More prospective research with unified methodologies is needed in order to demonstrate its real usefulness.*

Keywords: *Bipolar disorder; Predominant polarity; Mania; Depression; Polarity indexKey Words: Bipolar disorder; Predominant polarity; Mania; Depression; Polarity index*

INTRODUCTION

Bipolar disorder (BD) is a chronic mood disorder that affects 2.4% of the world population and is associated with a significant rate of morbidity and mortality1. It is described with a characteristic course of recurrent and alternating mood episodes, between depression, mania, hypomania, and mixed states2..

Different classifications have been proposed to approach this complex disease; one of the most accepted being that of the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5), which proposes that BD be divided into BD type I (BDI), characterized by the presence of at least one manic episode, and BD type II (BDII), for which diagnosis requires at

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least one depressive and one hypomanic episode.

There is a growing interest in proposing complementary coders that support clinicians in the diagnosis and treatment of BD4. In 1978, Angst proposed a classification based on the predominant polarity (PP), which he called "predominantly depressive polarity" (PPD) if the patient typically decompensated towards the depressive pole, and "predominantly manic polarity" (PPM) if the patient became typically decompensated toward the manic pole5. He also distinguished a third group of "nuclear polarity" when the patients did not show a clear tendency and relapsed both to the manic pole and to the depressive pole.

Recent studies have reported that around 50% of bipolar patients can be classified according to their predominant polarity 6,7, with significant clinical, prognostic, and treatment response differences between the two groups. Furthermore, it has been described that both the polarity of the initial episode and the predominant polarity of subsequent episodes could be a strong predictor of recurrence of a specific episode.

Despite its potential usefulness in clinical practice, the available evidence on this matter is scarce and contradictory since there are no unified criteria for its use in research. Due to this, we have performed a bibliographic review of the most recent findings related to the concept of PP in BD, with the goal of contributing relevant information to the management of this disease. Additionally, and given that it is an emerging concept in psychiatry, with less than 15 years since its operational conceptualization by Colom, we designed the first exploratory experience in a representative sample of Chilean psychiatrists with the objective of evaluating the degree of knowledge and use of PP concept in clinical practice.

METHODOLOGY

For the present work, the PubMed database was used, with a deadline of July 13, 2020 for the inclusion of articles, with the following search parameters («bipolardisorder»[MeSHTerms] OR («bipolar»[AllFields] AND «disorder»[AllFields]) OR «bipolar disorder»[AllFields] OR («bipolar»[AllFields] AND «disorders»[AllFields]) OR «bipolardisorders»[AllFields]) AND «polarity»[AllFields] OR (predominant[AllFields] AND polarity[AllFields]), while on Web of Science, they were bipolar disorder AND polarity OR predominant polarity).

As inclusion criteria, articles in English or Spanish were established on patients diagnosed with BD according to the criteria of the International Classification of Diseases, tenth revision, or the DSM (DSM-III-R to DSM-5) in which PP was analyzed. Articles that did not deal with BD or PP were excluded. Both researchers performed the screening by reading the title and the abstract.

In the first search, a systematic 4review article from the year 2017 that included works until June 2016 was identified, so the analysis of the works published after that date was prioritized, yielding a total of 204 results, of which only 13 articles met the inclusion criteria.

To evaluate the degree of knowledge and use of the PP concept in a group of Chilean psychiatrists, a brief descriptive exploratory survey of three questions was applied: "Do you know the concept of "predominant polarity" applied to Bipolar Disorder?", "Have you used the concept of "predominant polarity" for clinical decision-making?", and "Do you consider the concept of "predominant polarity" useful for clinical practice?"

RESULTS

The classification based on the predominant polarity (PP) was formulated by Angst in 1978, after a 16-year follow-up of a sample of 95 bipolar patients5. In this study, three groups of bipolar patients were identified according to the tendency to relapse with depressive or manic episodes. The former was called “predominantly depressive”, the latter “predominantly manic”, and those who did not show a clear tendency and relapsed to neither the manic nor depressive pole were called “nuclear type”.

From this first definition, different proposals have been published to determine an operational concept that is valid and that allows studies and comparisons to be carried out. In 2006, Colom and his study group of bipolar disorders in Barcelona, proposed that, if at least two thirds of the relapses have been depressive, we would find ourselves before a predominantly depressive polarity (PPD), while if two thirds of the relapses have been manic, it would be a predominantly manic polarity (PPM)6. Another broader definition proposed by González-Pinto8, only requires a majority of the episodes to define this polarity, a criterion that has also been validated.

Different publications suggest that belonging to one or another group would have a significant impact on clinical practice, since each one would present different sociodemographic, clinical, prognostic, or treatment response characteristics.

According to our bibliographic search, there would be only one systematic review that analyzes the concept of PP applied to BD. In this study, García-Jiménez et al. 4 analyzed the content of 16 articles related to this topic and tried to identify and describe the main clinical variables and determinants, which are detailed below, along with the most recent evidence published after the aforementioned review.

EPIDEMIOLOGY

Vieta, in a sample of 788 subjects with a previous diagnosis of BD I, determined that 46.6% could be predominantly categorized with some polarity. Of those, 34% presented depressive PP and 12.4% presented manic PP. 53.4% had uncertain polarity. That is, slightly less than half of the patients with BD type I could be categorized according to the polarity of the predominant episode and PPD was 2.74 times more frequent than PPM, indicating a prominent excess of depression over mania in BD.

In the study by Vidal-Rubio et al.9, a group consisting of 118 outpatients with BD was analyzed, of which 66.1% were BD I and 33.9% BD II. The three types of predominant polarity showed a similar distribution: PPD 39.0%, PPM 32.2% and 28.8% unclassifiable with BD, of which 66.1% were BD I and 33.9% BD II. When separating PP according to BD subtype, it is observed that those with BD type I had a higher rate of PPM (45%) and those with BD type II had a higher rate of PPD (63%).

Popovic et al, in a study applied to a Spanish population of 604 patients diagnosed with BD type I and II, described that 42.55% presented a predominant polarity, of which 55.6% were classified as depressive PP while 44.4% had patients met criteria for manic PP10..

Nivoli, in a sample of 604 BD I and II patients, describes the presence of a

PP in 42.5% of them, with 23.7% of the total sample being depressive PP, and 18.9% manic PP11.

In short, these studies show that the concept of PP can be applied to approximately half of the patients diagnosed with bipolar disorder, but that the proportion of one or another PP varies according to the sample analyzed and according to the type of BD.

Diagnostic manuals and clinical guidelines

The lack of common criteria for its use, both clinically and in research, could

explain the existence of contradictory data in the available literature, such that PP as a concept has not been included in the main classification manuals for psychiatric illnesses, for example, the DSM-5 or the ICD-11

Despite the above, this concept has been incorporated into some clinical guidelines such as the British Clinical Guide for Bipolar Disorder12, the Clinical Guide of the International College of Neuropsychopharmacology for Bipolar Disorder in adults (which suggests standardized management by algorithms 13), and the current version of the GES Clinical Guideline for Bipolar Disorder in people aged 15 years and over14.

Clinical factors associated to PP

According to the review by García-Jiménez et al., the variables of academic level, marital status, or sex would not be associated with a PP. There would also be no concordance between studies that show that depressive PP would be more associated with BD type II and that manic PP with BD type I. The number of hospital admissions, the presence of a seasonal pattern, the installation of psychotic symptoms, the consumption of long-term drugs, and psychosocial functioning would also be contradictory in its association with a specific type of PP.

Another variable studied by Da silva et al. 15 was the degree of awareness of the disease and PP. This clinical variable is usually decisive when establishing adherence and effectiveness of long-term treatments. In this study, those patients with active maniform symptoms presented low disease awareness, regardless of biographical PP, indicating that PP per se does not predict the degree of disease awareness.

Patients with depressive PP would have forms of disease onset with a greater number of depressive episodes or with mixed symptoms, would have a course with a higher prevalence of depressive episodes and would have a notable increase in the number of relapses. Regarding suicidal behavior, the figures for attempted and completed suicides are higher in depressive PP. If patients with mixed symptoms are also added to this group, the figures double with respect to the general prevalence of suicide in patients with BD. This predominant polarity is also associated with a high comorbidity with anxiety disorders, a higher prevalence of melancholic symptoms, and a delay in diagnosis from the onset of the first symptoms, with a more frequent diagnosis of BD type II.

In patients with manic PP, the presence of substance abuse is relevant, especially cannabis, which is related to manic decompensation, more severe acute episodes, and whose consumption prior to the onset of BD is more frequently associated with PPM than with PPD. In addition, this group of patients would have a tendency to present mania and hypomania as forms of disease onset.

A variable evaluated in a single study published by Vidal-Rubio9 shows that there would also be differences in the euthymia time presented by both subgroups. Patients with a predominantly manic polarity had a longer duration of euthymia compared to depressive or indeterminate PPs. In clinical practice, this data is extremely relevant since it would place the focus on the implementation of aggressive, early, and effective interventions aimed at patients with a history of depressive PP, shorter euthymic periods, or more frequent relapses.

Predominant polarity and temperament

Attempts have been made to establish an association between PP and different temperamental variables, specifically between manic PP and hyperthymic

and cyclothymic temperaments, and between depressive PP and depressive temperament. However, the available data is insufficient to establish a conclusive pattern. With respect to this, Azorin et al. 16 in a sample of 278 patients, those with manic PP had higher levels of hyperthymic temperament and those with depressive PP, a negative correlation with hyperthymic temperament.

Neurobiological Studies

A correlated alteration of the hippocampus is already widely accepted in the literature as a neurobiological marker for BD. To date, there is only one study 17 that seeks to evaluate this marker associated with the concept of PP, in a sample of 175 outpatients diagnosed with BD and 150 healthy controls. Hippocampal volume was measured using high-resolution magnetic resonance imaging and it was found that patients with depressed PP and with uncertain PP showed an overall reduction in hippocampal volume compared to controls. This difference was not found when comparing manic PP with controls. So, this first study could indicate the potential usefulness of PP not only applied to the clinic but also as a neurobiological specifier of BD.

In another area, kindling has also been associated with mood illness as a neurobiological factor that could explain the recurrence of episodes. In Subramaniana et al.18, the relationship between biographical stressors, kindling, and maniacal PP is explored in a sample of 149 patients diagnosed with BD type I. In this study, they conclude that in this subpopulation, there is a statistically significant demonstration that the stressors of life are more likely to occur in the initial episodes than in the last mood episodes and that this tendency to recurrence would be explained by the kindling phenomenon.

Pharmotherapeutical indication and PP

We have already described throughout this work the concept of predominant polarity and the existence of some clinical indicators that show that this indicator would probably be useful in distinguishing subgroups of patients with quite different clinical characteristics of mood illness presentation.

If these considerations are effectively met for the diagnosis, it seems natural to establish some relationship with the treatment indicated for these patients. Likewise, in 201310, Popovic et al., explain the need for a differential treatment approach according to the predominant polarity, assuming that until now, treatments for BD maintenance therapy continue to represent a significant clinical challenge. The authors developed an indicator called the Polarity Index to graph the efficacy profile of a drug as a numerical expression. It uses as a base the Number Needed to Treat (NNT), which is an indicator of the treatment effect in terms of the number of patients that a clinician needs to treat with a particular therapy to obtain a response. The Polarity Index is constructed by dividing the NNT of a drug for the prevention of depressive episodes and the NNT for the prevention of manic episodes16.

Drugs with PI greater than 1 have a stronger antimanic effect, while those with a PI less than 1 are more effective in preventing depressive than manic episodes. Drugs with a PI close to the value of 1 would have similar antimanic and antidepressant potential7..

This construct has been published in several studies19; however, it has also been questioned in some publications. Alphs et al.20 present several limitations of this. For example, they point out that this PI is based on several assumptions, including, for example, that there would be a single, accepted definition of relapse, which has been consistently applied to the studies

from which this number is derived, that the risk of relapse is consistent for all patients diagnosed with BD during the course of the disease, and if a PI is being generated from a meta-analysis of different studies, the true means for those studies are similar and are derived from populations similar, so that data collected in separate studies can be validly pooled.

Clearly, given the course and presentation of bipolar disease in different patients, it is very difficult to think that these three precepts are invariably maintained in the samples from which the NNTs were obtained. The authors note that, even assuming a fixed definition of relapse across studies, the baseline risk of relapse varies in different subpopulations and at different times in the course of the disease. For example, one cannot assume that the baseline risk of relapse in adolescents with bipolar disorder is the same as that in older people with a long history of the illness 19, or that it is similar in patients with BD types I and II.

Considering the above, the association between Predominant Polarity and Polarity Index has been studied in some patient samples. Popovic et al. 21in a naturalistic follow-up study of 604 BD I and II patients, managed to differentiate that in those with a depressive PP, Lamotrigine, antidepressants in general, and benzodiazepines are used more frequently. In those with a Manic PP, providers preferentially use antipsychotics of first and second generation, especially Risperidone and Olanzapine. However, the data comes from a single highly specialized center, and, therefore, the data may not reflect practice in other centers.

Carvalho et al. 22, on the contrary, in their review, do not find sufficient literature to clarify this point, so they conclude that the role of PP in predicting responses to acute treatment in BD remains largely an open question.

Use of the concept of predominant polarity in a group of Chilean psychiatrists

In addition to the bibliographic review, we wanted to evaluate the degree of knowledge and use of the PP concept in our local reality. For this, we conducted an online survey of 55 Chilean psychiatrists between 29 and 49 years of age, of which 63.64% were female. In our sample, 90.91% (n=50) claimed to know the concept of PP applied to BD, but only 74.55% (n=41) stated that they had used it for clinical decision-making. Of the total number of respondents, 81.82% (n=45) considered that the PP criterion had clinical utility (Table 1).

DISCUSSION

There are multiple arguments, both for and against the concept of predominant polarity, used to distinguish subgroups of BD patients and suggest a differential therapeutic approach, including the drug polarity index. Critics warn of the risk of falling into an excessive diagnostic and therapeutic simplification of a nosological entity as heterogeneous and complex as bipolar disorder.

Multiple factors, including polarity of index episode, number of previous episodes, number and type of subsyndromal episodes, time since last episode, severity of symptoms in each episode, undiagnosed episodes, self-medication in patients with a long history of treatment for the disease, the rates of abandonment of treatment and the duration of prospective follow-up, can influence the way in which the phases of the disease appear and, therefore, influence the conceptual validity of the concepts presented in this work.

Another important limitation of the concept of PP is related to the non-inclusion of subsyndromal episodes or mixed episodes, despite the fact that the latter have become

Table 1. Use of the concept of predominant polarity in a group of Chilean psychiatrists.

QUESTION	YES	NO	DOES NOT KNOW
Do you know the concept of "predominant polarity" applied to Bipolar Disorder?	90.91%	5.45%	3.64%
Have you used the concept "prevailing polarity" for clinical decision making?	74.55%	21.82%	3.64%
Do you consider the "predominant polarity" concept useful for clinical practice?	81.82%	9.09%	9.09%

increasingly relevant in the current nosology of BD, to the point of being included in the DSM-5 as a specifier in both bipolarity and depression.

In our review, we found statistically significant data that support the complementary use of the PP criterion in BD and that associate it with different clinical, therapeutic, and prognostic variables that are valuable for making effective long-term clinical decisions. However, since there are no unified criteria in the studies analyzed, we also detected some inconsistent and/or contradictory data, which is why we believe that new prospective studies are required that use a common definition and methodology to accurately determine the relationship between PP and BD, as well as the most relevant associated variables for clinical decision-making and follow-up of these patients.

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Mixed depression or why antidepressants are not antidepressants? A nosological review about a case study

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Abstract

Depressive disorders are a highly prevalent group of mental diseases that causes a great amount of personal, family, and economic burdens. They affect approximately 322 million people worldwide, which represents 4.4% of the world population. In Chile, Major Depressive Disorders have a lifetime prevalence of 9.4% in the general population. In the last years, several meta-analysis concluded that, in major depression, antidepressant treatment does not translate into clinically meaningful benefits. Some authors claim that poor treatment outcomes in depression are due to problems of a nosological nature, rather than the absence of effective treatments, and that, Major Depressive Disorder represents an extremely broad spectrum of depressive conditions with different phenomenology, family history, natural course and treatment response. These authors have postulated a different nosology, one that intents to help clinicians to understand, diagnose, and treat these conditions. This narrative review and case report addresses the broad spectrum of depression and the particular case of mixed depression; a kind of depression that does not respond to antidepressants.

Keywords: *Depression, Diagnosis, Nosology, Mood Disorder, Antidepressive Agents*

INTRODUCTION

Depressive disorders are a group of highly prevalent mental illnesses that cause enormous personal, family, and economic costs. According to recent data from the World Health Organization, they affect approximately 322 million people, which represents 4.4% of the world population[(1)]. In prevalence studies conducted in Chile, Major Depressive Disorder (MDD) has a lifetime prevalence of 9.2% in the general population[(2)]. Considering that depression is a chronic disease with frequent recurrences, and that its clinical manifestations involve both affective, psychomotor, cognitive and biological cycle alterations, it is not surprising that it is one of the main causes of disability worldwide[(3)]. To date, antidepressant psychotropic drugs represent the first treatment option in various evidence-based clinical practice

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guidelines, and a meta-analysis has recently been published that seems to confirm the effectiveness of these drugs[4]. However, a growing body of evidence questions the efficacy of antidepressants in the real world[5,6,7]. The main sources of evidence for antidepressant efficacy in MDD come from the regulatory agency database Food and Drug Administration (FDA) of the United States, and the study Sequenced Treatment Alternatives for Resistant Depression (STAR*D) financed by the National Institute of Mental Health of the same country[8]. We must consider that pharmaceutical companies are not required to publish negative studies in scientific journals, but they do have a legal obligation to deliver all the data from their studies to the FDA when a drug is approved for marketing[8]. Most of the published literature shows an overwhelming trend towards the effectiveness of antidepressants in MDD, reaching 94%. But accessing the FDA database and combining the already published literature with many studies that were never made public, the result is that of the total number of studies, 74 randomized clinical trials (RCTs) of antidepressants in MDD with a total sample of 12,564 patients, 51% show positive results and 49% negative. It seems that these drugs are equally effective and ineffective[6,8]. Kirsch's group reanalyzed the same database with 47 RCTs of antidepressants examining the average change in standardized depression scales, finding an average difference between antidepressants vs. placebo of 1.8 points on the Hamilton Scale, below the threshold of clinical significance suggested by the National Institute of Clinical Excellence of the United Kingdom (NICE), of 3 points, but it is interesting that in the group with antidepressants there is a differential response depending on severity, finding clinically significant results in the group of moderate and severe depressive patients treated with antidepressants[5.8]. The well-known STAR*D[9], the largest clinical study conducted by academics without influence from the pharmaceutical industry, was designed to evaluate the effectiveness of commonly used antidepressants and obtain information on their efficacy in resistant depression. The results are concerning: Although 60-70% of acutely depressed patients eventually responded to different treatment combinations or changes, the response decreased significantly after each new trial, and only a third of patients remained in sustained remission for one year[8].

In this clinical case presentation and review, we argue that the problem does not lie in the absence of effective drugs, but at a much deeper level, in the same conceptualization of major depression according to the prevailing classification systems[10], and we propose an alternative that is more consistent with the clinical reality and the psychiatric tradition of the pre-manual classification era.

METHODOLOGY

We present the clinical case of an anonymous patient who receives care in a specialized psychiatric outpatient clinic, who signs a written informed consent in accordance with the Declaration of Helsinki. Subsequently, a discussion of the clinical case and a narrative review are carried out, addressing the clinical heterogeneity of depression and mixed states.

Clinical Case

Female patient, 20 years old, with no personal somatic or psychiatric morbid history, first-degree family history of mood disorder, attends a psychiatric clinic for a clinical picture of approximately one year of evolution characterized by depressed mood, anhedonia, anergy, hypersomnia, hyperoxia with a predominance of nocturnal

carbohydrate intake without objectified weight gain, and recurrent suicidal ideation, of a passive and ego-dystonic nature. She received a diagnosis of major depressive disorder by a psychiatrist and began antidepressant treatment in the first instance with selective serotonin reuptake inhibitors, with no response, and then with progressively increasing doses of Venlafaxine up to 300 mg/day PO, Risperidone 1 mg every 12 hours PO and Clothiazepam 10 mg at night PO. With the aforementioned treatment, she reports not having presented a significant clinical benefit. Her complementary tests, including blood count, biochemical, liver, and lipid and thyroid profile have always been normal. There is no history of manic or hypomanic episodes in the history. On directed examination, very brief episodes (lasting hours) of subjective increase in energy, increased purposeful activity predominantly at night, increased muscle tension, tachypsychia and tachillalia, significant emotional liability, and severe internal tension appear. The Koukopoulos Mixed Depression Scale (KMDRS) was applied with a result of Moderate Mixed Depression (18 points). It is indicated to suspend antidepressant treatment and gradually start an atypical antipsychotic in low doses (aripiprazole, starting with 2.5 mg/day PO and increasing 2.5 mg/day weekly up to 10 mg/day) and prolonged release lithium carbonate in low doses (225 mg /night PO for one week and increase to 450 mg/night).

In control one week later, she reports having presented a partial improvement in symptoms, but still with the presence of depressed mood, internal tension and moderate emotional lability, although without the presence of suicidal ideation. KMDRS with a result of Mild Mixed Depression (12 points). It is indicated to continue progressively increasing aripiprazole and prolonged release lithium carbonate according to the previously indicated scheme.

She returned to control after seven days presenting a clinically significant improvement, with mood tending towards euthymia, without the presence of emotional lability, biological cycles in recovery, gradually recovering normal activities, without the presence of tachypsychia, internal tension or increased muscle tension. No suicidal ideation. KMDRS shows an absence of Mixed Depression (4 points). Continue with prompts are indicated.

In control two weeks later, the patient appears euthymic, does not report significant discomfort, her activity levels are normal, biological cycles recovered, she performs her daily activities normally. KMDRS shows absence of Mixed Depression (2 points). To date, the patient remains in euthymic and functional controls with the aforementioned scheme and psychotherapy. She has not presented adverse effects and lithium levels remain between 0.4-0.6 mEq/L.

Discussion and review of the concept of Mixed Depression

The case presented can be understood in several ways. According to current clinical practice guidelines, we can refer to treatment-resistant depression[3,11]. But it can also be understood as a subtype of depression that has been previously described in the literature, mixed depression. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), defines the depressive episode specifier “with mixed features” as a clinical picture that meets the criteria for a Major Depressive Episode (MDE) along with at least 3 symptoms of a manic episode including elevated or expansive mood, increased self-esteem or feelings of grandeur, pressure to speak, flight of ideas or tachypsychia, increased goal-directed energy, increased involvement

in activities that they have possibilities of painful consequences and reduction of the need to sleep those that must be present almost every day, during most of the day of an MDE[10]. If we consider this definition, the present case does not meet the criteria required by the DSM-5 to refer to an MDE with mixed characteristics. It is known that the North American diagnostic and classification system places great emphasis on specificity, and has been designed to avoid false positives, but in the process generates a high number of false negatives that will not benefit from more specific treatment. In the case of mood disorders, the DSM-5 has divided the Kraepelinian conception of manic-depressive illness into Major Depressive Disorder (MDD) and Bipolar Disorder (BD) based on the polarity of the episodes instead of their recurrence, for which reduces the importance of mixed states, requiring the presence of symptoms that do not overlap between both acute episodes, precisely the least frequent in this context[12,13]. However, already from the work of Emil Kraepelin we can find less strict definitions of mixed states. Kraepelin describes 6 different types of mixed states as the core of the unitary conception of mood disorders, which can present either as transitional forms or forms of single presentation, highlighting in this context agitated depression and depression with escape from ideas[14]. In the same way, Weygandt conceived mixed states as a combination of depressive mood with psychomotor excitement and flight of ideas, occasionally with agitation, and considered them the most frequent manic-depressive illness, showing up in 64% of affective patients in Heidelberg Clinic[12]. Depression with irritability, psychomotor agitation, internal tension and/or acceleration of thought is in clear contrast to what is classically known as melancholia, a type of depression with a high degree of anhedonia and psychomotor inhibition in the absence of any degree of irritability or mood lability[15]. In the modern era, Koukopoulos was the first to suggest that this depression combined with features of psychic or psychomotor arousal should be called Mixed Depression (MD)[15,16]. This position has been endorsed and replicated in part by other authors[15, 17, 18, 19, 20].

The current definition of the DSM-5 is indeed broader than that of its predecessor, but in clinical practice it excludes a vast number of patients without diagnosis or appropriate treatment, which can have severe consequences in the evolution of clinical pictures, specifically receiving antidepressant treatment and therefore worsening agitation, increasing suicidal risk, inducing cycle acceleration, and, perhaps in the best of cases without achieving relief for the patient, prolonging suffering and personal, family and public health costs associated with these disorders[12]. Koukopoulos' perspective is broader, allowing him to capture psychic arousal in general. The core of MD according to Koukopoulos corresponds to psychic agitation, irritability, and marked mood lability, with or without the presence of other excitatory symptoms, proposing operationalized diagnostic criteria[22] that are already validated for clinical practice (Table 1). Other characteristics of this group of patients observed in the validation study are: male sex, younger age, greater possibility of having received psychiatric treatment at an early age, greater number of episodes, higher scores on the Clinical Global Impression (CGI) scale associated with greater severity, lower assessment of global functioning, greater presence of mixed symptoms in the index episode, a greater history of substance abuse, a lower educational level, a lower probability of having been hospitalized, and a higher prevalence of rapid cycling[15]. This strongly suggests that we are dealing with a subgroup of depressed patients

Table 1. Koukopoulos criteria of for diagnosis of Mixed Depression (MD) Koukopoulos et al, 2007[22]

Major Depressive Episode (MSD) + ≥ 3/8 of the following symptoms
Psychic agitation or internal tension
Racing or tumultuous thoughts
Irritability or unprovoked rage
Absence of psychomotor retardation
More talkative than usual
Dramatic descriptions of suffering or frequent crying spells
Mood lability or marked affective reactivity
Conciliation insomnia

who are clearly differentiated from non-mixed patients, and who are distributed "transdiagnostically" in mood disorders, not being limited to BD but also frequently presenting in MDD, which again challenges the DSM and supports the unitary model of Kraepelin's Manic-Depressive Illness[14].

Considering the severity of these patients, their more severe course of illness with high suicidal risk, greater appearance of psychosis and lack of response (or clear worsening) with antidepressants, a scale based on the Koukopoulos diagnostic criteria has recently been constructed and validated. which aims to facilitate diagnosis and objectively measure the response to treatment in these patients. The validation study of the KMDRS was performed by an international network of mood disorders, with American, Italian, and Chilean outpatients (n=350) with unipolar and bipolar MD and is the only reliable and valid instrument that has as its objective the diagnosis of MD that is validated in our context. The complete version of this scale can be found in Sani et al[23]

To date, only one double-blind randomized controlled clinical trial has been conducted for the treatment of MD[24]. This American multicenter study analyzed 73 male and female patients between 18-65 years of age with acute MDD and the presence of 2-3 symptoms of a manic episode according to DSM-IV, diagnosed with MDD and Bipolar 2 Disorder, who were randomized to ziprasidone or placebo for six weeks. The most frequent clinical presentation was MDE with flight of ideas, distractibility, and reduced need for sleep. Ziprasidone titrated from 40 mg/d PO and was increased by 20-40 mg/d PO based on objective symptoms and tolerability with a target dose of 80-160 mg/d ziprasidone. Baseline drugs were not changed during the study. The primary outcome measured was changes in the Montgomery-Asberg Rating Scale (MADRS) over the course of the study. Secondary outcomes were changes in Clinical Global Impression for Bipolar Disorder (CGI-BP) and Mania Rating Scale from SADS-C (MRS) scales. Treatment response was defined as 50% improvement in MADRS and MRS. Remission was defined as MADRS ≤9 and Young Mania Rating Scale (YMRS) ≤11. A highly significant effect of ziprasidone was

found, with response rates of 52.9% and 28.9% for the active and control groups, respectively. The remission rate was 50% for ziprasidone versus 18.4% for placebo. MRS scores did not vary significantly between groups. The results support both the nosological validity and the practical utility of the MD concept. There are no previous randomized studies evaluating response to atypical antipsychotics in MD, but there are in mixed mania. Considering the results in this literature, it is possible that any type of mixed state, whether predominantly depressive or manic, responds more to atypical antipsychotics than to antidepressants.

The Clinical Heterogeneity of Depression

A review addressing the invalidity of the official classification systems regarding MD would not be complete without briefly reviewing the other ways of experiencing depression. The practice of psychiatric phenomenology is essential even before beginning to discuss diagnoses, and it is a reality that, since its publication, the DSM system has led to a reification of the diagnostic criteria, in such a way that clinicians and researchers do not evaluate the symptoms of patients but whether or not they meet the predefined criteria of an entity that repeatedly does not resist analysis of scientific validity regarding its categorical condition and its clinical utility. In short, it is not enough to simply say "this patient meets the criteria for MDD", since in practice there are thousands of ways to meet it.

Ghaemi et al[25] propose a phenomenological classification of the depressive spectrum included in the broad concept of MDD. Having already referred extensively to MD, we proceed to review the other forms of depression proposed by the authors.

1. Neurotic Depression

It is defined descriptively and unrelated to psychodynamic theory, as a mixture of mild depressive and anxious symptoms that, according to current classifications, could be diagnosed as "MDD comorbid with dysthymia and generalized anxiety disorder." These patients are characterized by a chronic course of mild to moderate depression with prominent anxiety symptoms, as well as high sensitivity to psychosocial stressors that often trigger brief, recurrent unipolar depressive episodes. The main problem of these patients is their baseline anxious-depressive state and their poor response to antidepressants. These patients would mainly benefit from psychotherapy. Ghaemi[26] proposes modified diagnostic criteria originally proposed by Sir Martin Roth (Table 2).

In the view of these authors, this mild depressive base does not reflect a separate clinical condition but rather a temperament that we could call dysthymia, not a disease per se, but, as Kraepelin called it, a "fundamental or constitutional state" inseparable from the disease. of the mood[14].

2. Melancholic Depression

It is the depression that we find in classical psychiatry, masterfully described by Hubertus Tellenbach[27]. It corresponds to a severe and dangerous depression in which the suicidal risk is high, generally not associated with anxiety, phasic, lasting up to one year and characterized by severe psychomotor retardation and marked anhedonia. The central characteristic of melancholia is the complete absence of psychic reactivity: patients are not labile as in mixed depression, nor do they improve transiently with psychosocial events as in neurotic depression. Adverse events do not make them feel worse because they literally "can't feel worse" and positive events

Table 2. Modified Roth criteria for diagnosis of neurotic depression. Translated and modified from Ghaemi S.N., 2008

A. Depressed mood leading to severe subjective distress or marked functional impairment
B. 2-4 of the following criteria:
1. Increased or decreased sleep
2. Reduced interest in usual activities
3. Energy reduction
4. Concentration reduction
5. Increased or decreased appetite
6. Suicidal ideation
Does not meet DSM-5 criteria for an MDE (subsyndromal depressive symptoms)
C. Prolonged or frequent worry, or anxiety nearly every day for most of the day, or sustained or frequently recurring multiple somatic symptomatology (e.g. gastrointestinal discomfort, headache, paresthesia) without secondary somatic cause
D. Criteria A through C present for at least 6 months, for the majority of every day
E. Mood or other symptoms apparently reactive to adverse or favorable changes in the circumstances of daily life
F. No severe psychomotor retardation, guilt, anger, agitation, or psychotic symptoms
G. DSM diagnostic criteria are not met for more than half the duration of symptoms from A to G.

don't cheer them up either. Tellenbach associates this type of depression with a specific type of personality that he calls Typus Melancholicus, characterized by the presence of traits of orderliness, conscientiousness, hyper/heteronomy, and intolerance of ambiguity[28]. This type of depression occurs in both MDD and BD, but is more common in the latter. Due to its severity and potential risk of death, it requires rapid treatment either with electroconvulsive therapy or traditional antidepressants (e.g. tricyclics)

3. Pure Depression

It is a frequent category that basically reflects the absence of the others. Some depressed patients retain emotional reactivity and some interests, they are functional and can even work, they do not have mixed symptoms and little or no anxiety, their illness is frequently phasic with inter-episodic euthymia, but not very recurrent. They are not melancholic, mixed, or neurotic, but clinically depressed. These patients usually see general practitioners, neurologists, gynecologists, or other specialists. Ghaemi et al point out that these patients would be the most responsive to modern antidepressants[25].

4. Vascular depression

It is a relatively new concept that has only recently begun to be explored and understood, but due to the characteristics of our population it is very important. It is defined as symptoms or depressive episodes that begin after the fourth or fifth decade of life, without a previous history of depression, and that are associated with abnormalities of the cerebral white matter that correspond to small microvascular infarcts in the context of cerebral vascular hypertension. in the absence of typical symptoms of cerebrovascular accident due to obstruction of major cerebral arteries. Typical risk factors for developing this type of depression are high blood pressure and/or diabetes mellitus and/or vascular disease. It is important to consider that there may be cerebrovascular hypertension in the absence of systemic arterial hypertension, so most clinicians would not diagnose these patients with hypertension and therefore would not treat them with antihypertensives. Diabetes is specifically associated with small vessel disease , which increases the risk of white matter abnormalities. There is generally a consensus of the worse prognosis associated with this type of depression, since traditional antidepressant treatments seem to be less effective in vascular depression. Considering the pathophysiology of underlying cerebrovascular hypertension, the author hypothesizes that aggressive antihypertensive treatment, with the goal of lowering cerebral blood pressure, could halt the progression of vascular depression and/or potentiate any potential benefits of antidepressant treatment. However, there are no studies on this[8].

CONCLUSIONS

Depression is an extremely common mental illness, which by its nature represents one of the largest causes of disease burden worldwide. For its usual treatment, both at the primary and specialty level, monoamine agonist drugs are used as first line, which have repeatedly failed to demonstrate clinically significant effectiveness. MDD is a diagnostic category created as a form of political consensus in the profession at the end of the 20th century, and which is neither scientifically valid nor clinically useful. Rather, it represents a broad spectrum of distinguishable clinical pictures using the classical diagnostic validators of clinical psychiatry. In routine clinical practice, it is essential to identify and adequately treat these subtypes of depression to improve the prognosis of our patients. It is imperative to generate new sources of randomized evidence that allow us to validate effective treatments for the different forms of depression in routine clinical practice.

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The Role of Thyroid Hormones in Depression.

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Abstract

For decades, the predominant pathophysiological model to explain the etiology of mood disorders has been based on the imbalance of brain neurochemical systems, a concept that ended up being insufficient in accounting for the wide variety of clinical, analytical, and therapeutic aspects of these clinical conditions. Thyroid hormones regulate a number of complex and specific brain processes, so it is highly likely that they have pathophysiological implications in mood disorders. Various authors have shown dysfunctions in the thyroid system in depressive episodes, where, although there is no alteration in hormone production, there is what is known as functional hypothyroidism. These peripheral alterations would eventually be represented along the entire length of the Hypothalamic–pituitary–thyroid axis (HPT). In this article, the authors also review evidence supporting the use of thyroid hormones in the treatment of refractory depression and provide recommendations for their use based on local experience.

Keywords: *depression, refractory depression, thyroid hormone, supraphysiological thyroid hormone administration*

INTRODUCTION

The endocrine alterations observed in Mood Disorders (MDs) are diverse and in many ways constitute an outlook of events that are hard to integrate into sparing hypotheses in order to maintain a coherent perspective. It has not been possible to clarify whether these findings are epiphenomena, the result of pathophysiological processes possibly specific to MDs, etiological, or concurrent factors that determine such disorders, or specific profiles of clinical and evolutionary states of these conditions. It is evident that the predominant model in recent decades, which is based on imbalances of neurochemical systems that supposedly explain the pathophysiology of MDs, is insufficient for understanding multiple clinical, therapeutic and analytical aspects already considered inherent to MDs. It is very likely that the main determinant events of these disorders precede the changes found in the neurochemical systems, and that they actually correspond to the results of previous pathological processes, probably of an endocrinological, inflammatory, chronobiological or trophic nature, among other possibilities. Herein, we specifically review the processes related to the functionality of the HPT axis and

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their possible relevance in relation to the pathophysiology of MDs.

Hypothalamic–pituitary–thyroid axis (HPT)

The influence of the HPT axis on CNS development and functionality is very complex and far from being understood in detail. Thyroid hormones (THs) regulate a number of processes in CNS ontogenetic development, such as the sequencing of neuronal proliferation events and early plasticity and continue to regulate other sensitive aspects of CNS functioning even in the adult brain, such as neuronal and glial differentiation, as well as myelination[1]. THs play a major role in gene regulation, neuromodulation, cotransmission, synaptic activity, and CNS trophic processes[2], among many other critical aspects of brain neurochemical activity. From this standpoint, it seems unlikely for the HPT axis to not have any pathophysiological implications in the group of disorders considered to be Mood Disorders (MDs). Therefore, it is not surprising that a significant percentage of depressed patients report thyroid disorders, among which the most frequent is subclinical hypothyroidism[3]. The following have also been reported[4]: altered TSH response to TRH stimulation (TRH-TSH test), high levels of antithyroid antibodies in depressed patients with thyroid disease, and high rates of TRH in the CSF of depressed patients. Moreover, certain clinical aspects support the complex relationship between alterations of the HPT axis and the evolution of MDs, such as the fact that thyroid alterations are recognized risk factors for evolving to rapid cycling in bipolar patients, as well as the effect of the use of thyroid hormones at supraphysiological doses in refractory depression in euthyroid or subclinical hypothyroid patients[1,5].

Peripheral Thyroid Hormones

Bahls et al.[6] in a detailed analysis of various findings of peripheral thyroid hormones in depressive patients, point out that, during depressive episodes, there is an increase of T4 in peripheral blood and CSF, which normalizes when euthymia is reached. There is also an increase in the conversion of T4 to rT3 (which is inactive in terms of HPT axis functionality) due to an increase in Deiodinase III enzyme activity, and an inhibition of Deiodinase II, most likely secondary to an increase in cortisol. In general terms, this would be a situation of relative central hypothyroidism. Up to 15-20% of depressed patients would present minimal thyroid insufficiency, therefore with a reduced response to antidepressants (AD), and this condition is found in up to 52% of patients with refractory depression. The intensity of the episodes and the time of evolution are likely variables that influence the activity of the HPT axis in depressive episodes, among other factors, in addition to pharmacological interactions. Kamble et al.[7], in a study comparing groups of patients with differing degrees of depression with controls, reported that the greater the severity of depression, the greater the presence of peripheral T4 and the greater the reduction of TSH. Williams et al.[8] describe in a meta-analysis an increase in T4 and a decrease in TSH associated with a longer time of evolution of the depressive disorder.

Thyrostimulatory Hormone (TSH) and Thyrotropin-releasing Hormone (TRH)

Regarding TRH-TSH neuropeptides in MDs, Bahls' analyses[6] summarize the TRH results as inconsistent, meaning there would be an increase in TSH during depressive episodes, an increase in nocturnal TSH secretion, and a flattening of the TSH response to TRH in 25-30% of depressed patients. Likewise, an early relapse has been reported in cases where there is no normalization of the described low TSH response to TRH. On the other hand, there would be an increased TSH

response to TRH in 10-17% of depressive patients. In this area, a Chilean observational study[10] has shown quite clearly that the TSH response to TRH in patients in a first depressive episode of a melancholic nature, without previous treatments, which eliminates the influence of drugs in the analysis, is strongly diminished, with a lower-than-expected T3 increase 2 hours after TRH administration. The implication of this finding could mean that an alteration of the HPT axis may already exist at the onset of the depressive disorder, and it is not possible to rule out an etiological role of the HPT axis in the disorder. These results could suggest that adding thyroid hormones from the beginning of treatment may provide better results. Garlow[9] has compared a group of patients with Sertraline plus placebo in depression versus another with Sertraline plus T3 in doses similar to those used in hypothyroidism. Results at 8 weeks showed no differences. Factors potentially influencing these results could be that thyroid hormones take 2 to 8 weeks to work and that higher doses of T3 are required. A study was carried out in Chile comparing depressed patients with Fluoxetine plus placebo versus Fluoxetine plus T3 in usual doses[10]; brain images were evaluated considering the typical imaging changes of the response to depression and the response to thyroid hormones typical of hypothyroidism treatment. There were also no significant differences between the placebo and T3 groups.

It is possible that thyroid alterations have a greater expression in some aspects of MDs, but they have not merited further study. Gunnarson et al.[11], for example, have shown that memory performances in depression have no correlation with T3 and T4 levels, but there is a positive correlation between memory failure and TSH levels in patients with depression.

Pharmacological treatments

As for the pharmacological influence on thyroid hormone levels, there are a number of data that clarify the influence of various substances on the regulation of the HPT axis. A review on the subject by Gitlin[12] reports that some ADs, including Fluoxetine and MAOIs, decrease T4 and free T4 levels; Fluoxetine, Lithium and Carbamazepine increase Deiodinase I and II activity and reduce Deiodinase III activity; lithium reduces iodine release and distribution; and Carbamazepine increases thyroid hormone metabolism via hepatic enzyme induction. It is likely that several other psychotropic drugs affect the physiology of the HPT axis, and these incidences have not yet been described. Eker[13] has evaluated the response of the HPT axis to noradrenergic, serotonergic and dual ADs in terms of TSH, T4, and free T4. Adrenergic ADs reduce TSH and serotonergic ADs increase it, even though both do not affect free T4 concentration, so such findings are difficult to integrate with what is known about the physiology of the HPT axis.

Supraphysiological administration of thyroid hormones in refractory depression

Since the 1990s, one clinical recommendation in depression refractory to multiple or complex trials with antidepressants and mood stabilizers is the administration of supraphysiological doses of TH. This consists of doses that far exceed those used in conditions like hypothyroidism, such as, according to recommendations from the American Psychiatric Association in the early 2000s, 400-600 µg / day of T4 or doses normally used in T3 hypothyroidism. Current expert recommendations[14] advise the use of T3 or T4 along with antidepressants (except in rapid cyclers), for 4-12 months in the acute period, although they do not have an official stance on thyroid hormones in maintenance schemes. They

suggest being aware of bone density if used for prolonged periods and/or in elderly patients. In general, this hormone trial is underutilized, mainly due to lack of knowledge of the prescription format, which is not being adequately disseminated.

Different evaluations have been carried out to determine whether T3 is more efficient than T4 or vice versa. The results are not unanimous, but generally lean more towards the benefit of T4. There is little literature on this, as well as on the efficacy of THs in specific aspects of MDs. In the best methodologically configured reports[5,15] it is precisely observed that T4 eventually performs better than T3; they also report its efficacy in the different evolutionary and syndromic stages: T4 has better results, mainly in women and in depression, less in men, mixed states, and manic patients.

It is unknown why responders to these procedures do not exhibit the expected side effects at such doses, primarily the life-threatening health condition known as Thyroid storm, i.e. fever, generalized trembling, insomnia, tachycardias and arrhythmias, among other symptoms. In fact, a good early clinical marker for a patient who will respond to supraphysiological doses of TH is no shivering or palpitations with T4 doses above 150-200 µg/day. In our context, we have clinical experience in the Bipolar Disorders Unit of the University Psychiatric Clinic of the Universidad de Chile, with more than 30 responding patients (10), and only some of these patients are discharged due to side effects; in general, the drugs used at the beginning of the trial were withdrawn after installation of the THs, and the patients were left with only T4. The highest dose used was 500 µg/day, and we did not find satisfactory responses below 350 µg/day. Our Unit's recommendations for the use of supraphysiological dose TH are listed in Table 1.

Table 1. Recommendations for supraphysiological administration of T4 in Refractory Depression

• Refractory depression (one or more trials with antidepressants or mood stabilizers) Unipolar or Bipolar
• Use of T4 (Levothyroxine)
• Preferably women
• Dose of 350 *µ*gr / day or more
• The clinical effects of TH occur between 15 and 60 days after reaching the target dose
• In responders there is no thyrotoxicity, which usually appears above 150-200 *µ*gr/day
• Demonstration of hypothyroidism is not essential
• Cautious withdrawal of previously installed therapies may be required
• Drug-induced hypomania can occur

CONCLUSIONS

It is very likely for there to be a wide and unknown interaction that is influential in determining the long-term evolution of MDs, between the functionality of the HPT axis and that of the circuits or regulatory systems of the variable that we refer to today as “Mood.” It is also clear that this unknown interaction is not yet properly considered in the schemes currently represented in models of AT pathophysiology. As long as this is the case, it is likely that a significant number of patients with MD will have a worse therapeutic response than desirable. The scant data on the aforementioned interaction are still contradictory and practically impossible to integrate into one single, sparing hypothesis, so conclusions regarding the pathophysiology of MDs or about clinical explanations on the use of TH in treatment plans are still tentative or stem from the experience of only a few clinicians who have tried them. As this is an area that is probably not very lucrative in general terms, knowledge in this field is likely to depend on the efforts of university or independent groups; thus, it is likely that several decades of work are still needed to reach a definitive model on the subject, which is probably more important than we consider today for many patients who cannot yet be fully identified.

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Vascular depression: a case report and bibliographic review.

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Abstract

Background: *Late life depression (LLD) has become a serious mental health issue in the geriatric population with important repercussions in the quality life of patients and their relatives, as in the public health funds. Implications of diverse systems have been proposed to elucidate the aetiology of the LLD, being the vascular disease the best studied.*

Objective: *To review the clinical picture and some of the systems implicated in the LLD, elaborating on the vascular disease with the contribution of a clinical case.*

Method: We report a 76 years-old woman with a two years history of Major Depressive Disorder subjected to a progressive and vigorous antidepressant and anxiolytic treatment, admitted to the acute geriatric unit due to progressive catatonic symptoms on the last two weeks. We perform a bibliographic review about the LLD and specifically of the Vascular Depression, focusing on the clinic and diagnosis.

Conclusions: *The vascular hypothesis proposes that cerebrovascular disease may predispose, precipitate or perpetuate some LLD. Vascular Depression definition is composed by both clinical features as MRI findings, i.e. the presence of vascular risk factors with Depression-executive dysfunction (DED) and White matter hyperintensities (WMHs). DED is characterised by psychomotor retardation, apathy, impaired insight and behavioural disability, being the latter a main feature for pharmacological response to antidepressants, which is usually slower, poorer or abnormal in comparison to younger population. Prefrontal processes are supported by multiple neurotransmitters, thus the limited effectiveness of widely used antidepressants, such as SSRIs and TADs. Early evidence supports psychological interventions to reduce depressive symptoms and disability as possibly to increase remission rates.*

Key words: *Depression, Late life depression, Vascular depression, Depression-executive dysfunction, Catatonia*

CASE REPORT

A 76 years-old woman, married, housewife, education received up to year 8, was consulted in the ER after two weeks of psychomotor retardation, decreased mood and autolytic comments, besides the weight loss of approximately 10 kilograms in the last 2 months. She has a history of hypertension and a major depressive disorder in current treatment with Venlafaxine, Bupropion, Risperidone and Etifoxine for the last two years.

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Clinician and neurologist assessments, standard analytics and Brain Computerized Tomography are informed as normal. She is admitted in the Acute Geriatric Unit with the diagnosis of Catatonic syndrome presumably secondary to the underlying depressive disorder, prescribing further studies, i.e. Gadolinium MRI, lumbar puncture (including Oligoclonal bands and IgG/Albumin Ratio), Standard EEG and a solicitude of assessment to the Liaison Psychiatry Service.

At our very first assessment the patient showed psychomotor retardation, perplexity and mood restriction, mutism with brief but logical responses and conserved orientation. Hypomimia, staring and stereotypy of hands are objectivated, upper trunk stiffness and wax flexibility are obtained from the physical examination. By cause of her clinical conditions it's not possible to assess thought and perception, insight nor higher cognitive functions. Due to clinical features and history a Lorazepam trial is performed with 2 mg IM. Reassessment is performed after 30 minutes, noticing an increased facial expression, decreased upper trunk stiffness and absence of wax flexibility, stereotypies and staring. Brain MRI and Electroencephalographic studies are performed.

- Gadolinium MRI of the Brain: mild decreased parenchymal brain volume, some higher than expected for age. Subcortical White Matter foci of gliotic hyperintensities of the frontal lobes.
- Standard Electroencephalogram: Digital Video EEG in patient alternating between waking and sleeping cycles shows an irregular trace without slow focality nor epileptiform activity. Register within normal ranges for age.

Neurological clinical assessment is not compatible with neurological focality, besides further studies are informed as normal for the patient, therefore the assessment can rule out an organic aetiology. In sum, the patient can be transferred to the Psychiatry Unit.

In order to deepen the clinical history, an interview is scheduled with the daughter of the patient. It is referred a clinical picture of approximately two years of depressive symptoms, described as low mood, lack of pleasure in activities once enjoyed, insomnia and anorexia with weight loss of roughly 15 kilograms, subsequently erratic behaviour and delusional ideas are added. The patient interprets environmental stimuli as threats, arguing she's been looked for to pay family's old debts. In this context she's assessed by a Neurologist, proposing Alzheimer Disease as aetiology of the symptomatology. Afterwards a Geriatrician proposed a Major Depressive Disorder, prescribing Escitalopram and referring to the Psychiatrist, circa one year before of the current episode.

The family describes a proper clinical response to the first antidepressant (AD) trial, resolving psychotic and behavioural symptoms, anyway low mood and anhedonia persisted, consequently psychiatrist switched AD to Venlafaxine XR up to 225 mgs per day, adding Risperidone up to 3 mgs and Etifoxine up to 200 mgs per day. After this trial depressive symptoms are reduced, reaching a good performance in daily activities, maintaining like this up to two months prior to consultation. Anyway, the family points that even when resolving the most disruptive symptoms, mild psychomotor retardation remains, besides a reduction in the volume and speed of the speech.

As described, after one year of clinical response to the antidepressant trial, the patient undergoes psychological stress by being victim of theft. Approximately two weeks after the traumatic event the depressive symptoms reemerge, being

described by the family as low mood, pervasive retardation, including mutism and anorexia with objective weight loss. The patient now turns suspicious about the neighbours, arguing they're planning to make her pay for his father's faults. Besides she expressed in a couple of times autolytical ideas, as jumping off a moving car or throwing herself to the traffic when had to leave the house. After the assessment of the attending psychiatrist, current medication is modified, adding Bupropion up to 150 mgs per day and reducing Venlafaxine to 150 mgs per day. A torpid response is obtained, worsening the psychomotor symptoms: reduction of the already reduced speech and physical activities, refusal to eat and disturb of the sleeping cycle (conciliation and sleep-maintenance insomnia). After the failure of the pharmacological attempt the patient is referred to the ER for further studies and management.

DISCUSSION

Late life depression (LLD), common term to refer to the depression in the elderly, is defined as any depressive episode taking place after the age of 65 or later1. In contrast to depressive disorders in younger population, LLD is commonly associated to cerebrovascular disease and microvascular lesions, particulary represented as white matter hyperintensities (WMHs) on MRI, subcortical lacunes, microinfarcts and microbleeds, frontal and temporal grey matter changes/atrophy, neurodegenerative pathologies and related biochemical changes2.

Alexopoulos et al., back in 1997, proposed that small vascular lesions are able to critically affect frontal and subcortical regions leading to a progressive disfunction of the monoaminergic pathways, thus the pathogenesis of depression3. It has also been proposed the homocysteine depression hypothesis, in which increased levels of homocysteine leads to cerebrovascular disease and neurotransmitters deficiency, again a linkage with depression pathogenesis4. Another mechanism proposed for LLD is the endothelial dysfunction, since the impairment of endothelial function is thought as the final stage of inflammatory phenomena currently present in the elderly depression5. It has changed the former view of LLD from a lesional to a multifactorial one, including such as homocysteine, immunological mechanisms, endothelial dysfunction, etc., which interact in complex ways leading to depression, albeit further research is required to explore these interactions6. Due to its "organic basis", those etiological factors used to identify the disorder through the old concept of "atherosclerotic depression"7 to the concept of "vascular depression" (VaDep). In this way the VaDep hypothesis proposed by Alexopoulos et al. argues that Cerebrovascular Disease (CVD) may predispose, precipitate or perpetuate some geriatric depressive symptoms as consequence of structural damage to frontal-subcortical circuits8.

According to MRI based studies, VaDep accounts for up to 50% of LLD. Krishnan et al., boosted by modern neuroimaging techniques, coined the entity of "MRI-defined VaDep", including, by definition, the CVD findings on MRI9. Patients with VaDep were suggested to have a distinct profile and a positive association with hypertension, backing the concept of VaDep as a unique and valid subtype of LLD10. The MRI literature that supports the VaDep hypothesis shows that the loss of the brain volume and white matter integrity are associated with the poorer clinical response12,13, relating in this way a greater link to cognitive impairment14. Our patient has a clinical history of hypertension and 2 years depressive disorder hard to manage,

being necessary the use of a vigorous antidepressant trial to reach clinical improvement, despite a good adherence to medication after a mild stressful event the patient undergoes a worsening of her base mood with a progressive psychomotor retardation, ending in catatonia. It calls the attention the presence of white matter hyperintensities on the MRI, besides the pervasive neurodegenerative changes.

The clinical manifestations of VaDep are distinct to other presentations of LLD15. The difference can be secondary to the age of the depression onset, due to VaDep tend to have later age of onset16. The patient had no psychiatric history up to age 74, when depressive symptoms take place, in absence of stressful events.

The clinical presentation of VaDep is characterised by psychomotor retardation, abulia and apathy. The medical history of hypertension is present, and family history of depression is absent. The impairment of cognition is commonly present, executive dysfunction and impaired processing speed. Sometimes the functional disability can be disproportional to the severity of the cognitive impairment. In sum, patients undergoing VaDep have a greater cognitive impairment and disability in comparison to non-vascular depressive patients17,18,19.

Back in our patient, the current episode is characterised by psychomotor retardation, abulia and apathy, which led to psychotic and catatonic clinic. Even when the first assessment is compatible with catatonia, if we look for the characteristics described above, we could find psychomotor retardation, executive disfunction and impaired processing speed. When the former episode is asked to the family, it is described a clinical pictured characterised by depressive mood, adynamia and anhedonia, core traits to identify any MDD, special traits in our patient are the psychomotor compromise besides, again, of abulia and apathy. Other important trait is the resistance to the antidepressant trial, even when it's known that up to 30% of patients undergoing an AD trial can be resistant to treatment, in this case it's striking the vigour needed to reach a clinical improvement. After the remission of the disruptive symptoms, the family remarks the remaining of a mild psychomotor retardation and a reduction in the volume and speed of the speech.

Even when MDD is diagnosed, treated and studied by psychiatrists, the diagnostic manuals do not acknowledge the diagnosis of VaDep nor address its treatment-resistant course. In addition, MRI is commonly used to rule out organic causes for psychiatric symptoms rather than to validate a psychiatric diagnosis. In such a way, it is clear the elusiveness remained on the definition of this entity and its diagnostic criteria, thus complicating the studies in this area and the introduction of therapeutic options20.

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I. Journals

a. Standard article

Format: Author(s), title of the paper, name of the journal according to the abbreviation in the Index Medicus, followed by the year; volume: first and last page with complete numbers. (we have decided to omit the number within the volume). Only the first six authors are listed. If there are more than six authors, the first six must be listed followed by the expression et al. in italics.

Angst J. Bipolarity from ancient to modern times: conception, birth and rebirth. J Affect Disord 2001; 67: 3-19

Akiskal HS, Hantouche EG, Allilaire JF, Sechter D, Bourgeois ML, Azorin JM, et al. Validating antidepressant-associated hypomania (bipolar III): a systematic comparison with spontaneous hypomania (bipolar II). J Affect Disord 2003; 73: 65-74.

b. Organization as author

The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 164: 282-284

c. Volume with supplement

Diekstra REW. Suicide and the attempted suicide: An international perspective. Acta Psychiatr Scand 1989;40 Supl 354: 1-24

d. Number of pages with Roman numerals

Fisher GA, Sikic BI. Drug resistance in clinical oncology and hematology. Introduction. Hematol Oncol Clin North Am 1995; 9:xi-xii.

II. Books And Monographs

Format: authors, title of the book, city in which it was published, publishing house and year. Punctuation must be limited to the use of commas to separate authors among themselves.

a. Author(s) of the complete paper

Kraepelin E. manic-Depressive Insanity and Paranoia. Edinburgh: Thoemmes Press, 2002

b. Editor(s) as authors.

Yatham N, Kusumakar V, Kutcher S, editors. Bipolar Disorder. A Clinician's Guide to Biological Treatments. New York: Brunner-Routledge, 2002

Gasto C. Historia. In: Vieta E, Gasto C, editores. Trastornos bipolares. Barcelona: Springer-Verlag Ibérica, 1997

c. Book Chapter
Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press, 1995

III. Other Sources
a. Audiovisual material
HIV+/AIDS: the facts and the future [videocassette]. St. Louis (MO): Mosby-Year Book; 1995

b. Electronic material
Online Journal
Tsui PT, Kwok ML, Yuen H, Lai ST. Severe acute respiratory syndrome: clinical outcome and prognostic correlates. Emerg Infect Dis [serial online] 2003 Sept [date cited]. Available at: http://www.cdc.gov/ncidod/EID/vol9no9/03-0362.htm

Document at the website of an organization

International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Updated October 2001. Available at: http://www.icmje.org/ Access verified on February 12, 2005

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