Sadness as an integral part of depression

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Sadness is considered by numerous authors to be a core symptom of depression. Currently, many arguments exist for its particular importance in depressed patients. Sadness makes up part of the various definitions of the depressive syndrome, even if its presence is not required for diagnosis. Furthermore, it is closely linked to the other depressive symptoms, and has prognostic value, in particular for remission. The recognition and measurement of sadness seem important for therapeutic evaluation, in clinical studies, and in depressed patients at an individual level. This paper presents a selective review of some of the various aspects of sadness as an integral part of depression, and an examination of its links with a disease which is a major health concern.

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Despite their obvious clinical relevance, the terms "sad" or "sadness" are not defined in some major psychiatric dictionaries, such as the *Campbell Psychiatric Dictionary*[1] and the *Lexicon of Psychiatry, Neurology and the Neurosciences*[2] or the French Academy of Medicine's Dictionary.[3] This is even more surprising, given that sadness ("tristis" in classical Latin) was commonly given a psychological meaning in the ancient Latin world. In Latin-based languages, the meaning was linked to melancholia and sorrow later, during the 14th century. The term was used to nickname Don Quixote the "knight of the sad face," in the 17th century.[4]

From a medical historical perspective, sadness was described in patients for a long time before the term depression was introduced. For example, Hippocrates defined melancholia as a state of persistent fear and sadness. In the middle of the 19th century, when the concept of depressive disorder appeared, sadness was closely linked to motor retardation, and sometimes delusions, both included in the depressive syndrome. By the end of the 19th century, Kraepelin had described several types of depression, corresponding to various states of motor and psychic retardation. Beginning with Kraepelin, successive classifications have been developed, so as to better identify depressive disorders, mainly in dimensional ways. Beyond the symptomatic clusters that nowadays define depression, the importance of the core symptoms of depression, and in particular of sadness, could be crucial from a clinical point of view. Its potential value as a diagnostic marker of depression needs to be explored, as well as its usefulness as a criterion for measuring the therapeutic effects of antidepressants. This review aims at critically exploring sadness, as a core symptom—an integral part of depression, and proposes to describe its clinical aspects, its links to neurovegetative symptoms, and the pertinence of its use as a target for therapeutics.

Sadness is an integral part of definitions and classifications of depression

Sadness is considered to be one of the core symptoms of depression by most authors. Its clinical importance for the depressive syndrome has been attested to by various studies. Among the arguments for its clinical value is the fact that sadness is present in an increasing number of patients when depression grows in severity, as Beck described in a study in 486 subjects, ranging from nondepressed controls to severely ill patients *(Table I)*.[5]

As described by Beck, sadness is present in a certain number of healthy controls, who do not reach the criteria for depressive disorders; on the other hand, in severe depression, a low mood is present in only 94% of the subjects, which implies that some severely depressed patients do not experience sadness as part of their depressive syndrome. The clinical reliability of sadness for diagnosing depression could thus be challenged. In developed countries, the medical services available and the decrease in stigmatization should explain the fact that a number of clinical cases of depression are diagnosed before the illness increases in severity. These points should lead to describing and considering each depressive disorder distinctly, using the clinical features of their original description.

In the two main classification systems that are currently used, sadness is one of the main symptoms of depression, but this is not enough for the diagnosis. In the *International Classification of Diseases*, 10th edition, or *ICD-10*,[6] and in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th revision (*DSM-IV*, American Psychiatric Association[7]), whereas sadness is one of the main depressive symptoms, the diagnosis of major depression can be attributed without the presence of sadness. Currently, the diagnosis of major depressive episode is drawn from the presence of five of various symptoms among nine (weight variation, insomnia, psychomotor agitation or retardation, loss of energy, feelings of worthlessness, diminished concentration, recurrent thoughts of death), which must include depressed mood or lost of interest or pleasure in almost all activities.[7] This definition, while including sadness as one of the main symptoms, also raises the possibility that patients suffer from depressive episodes without being sad. Furthermore, elderly patients can suffer from subsyndromal depression, which does not fulfill the complete diagnostic criteria, even when antidepressant therapies are clearly needed.[8] In those patients, sadness can be absent from the clinical presentation.

	Healthy controls	Mild depression	Moderate depression	Severe depression
Low mood (% subjects)	16	72	94	94

Table I. Frequency of low mood acording to the severity of depression. Adapted from ref 5: Beck AT. *Depression: Clinical, Experimental and Theoretical Aspects*. New York, NY: Harper & Row; 1967. Copyright © Harper and Row 1967

Then, the question of the severity of depression is of particular clinical interest, to determine the potential importance of sadness for a patient, as well of the question of its identification. One of the main depression evaluation tools is the Hamilton Rating Scale for Depression (HAM-D[9]). Its various factorial analyses have consistently identified "depressed mood" and "reduced work and interest" to be the main symptoms of depression, which is consistent with international classifications. Scoring instructions have been published in agreement with its author,[10] but not all versions have been approved by him. Other tools have also been constructed, such as the Beck Depression Inventory[11] and the Montgomery and Asberg Depression Rating Scale (MADRS).[12] To determine the clinical value of the various symptoms assessed by these scales, a hierarchical pattern of depressive symptoms has been identified with the use of the Present State Examination (PSE[13]), in a general population study. The authors concluded that the prevalence of the rarer symptoms such as guilty feelings, depression worst in the morning, and suicide, were preceded by a higher prevalence of the most common symptoms, such as depressed mood, lack of energy, and worrying.[14] Such hierarchical patterns have also been described using the HAM-D[15]: for the HAM-D 6-item version, the frequency of depressive symptoms decreases in the following manner: depressed mood, tiredness and pain, psychic anxiety, guilt feelings, and psychomotor retardation. This hierarchical pattern, with a higher prevalence of depressed mood, confirms the clinical importance of sadness in the diagnosis of depression. Furthermore, using a neural network model on the results of the Epidemiological Catchment Area study (ECA), a more recent analysis[16] revealed that sadness was among the symptoms with the greatest impact on the occurrence of depression.

Is sadness synonymous with depression?

As Beck described it,[1] sadness can be present in the general population, without any diagnosis of depression. Some epidemiological studies have reported the prevalence of depression in the general population, but only a few have detailed depressive symptoms. Among them, a relationship has been described between particular life events and depressive symptoms[17] in the general population. Sadness was more frequently associated with deaths of loved ones and romantic breakups to be at the origin of their dysphoric episode in patients reporting an adverse event, whereas subjects for whom no causality could be found reported a low mood less frequently.

Another general population study, conducted in the UK,[14] used the PSE to evaluate depressive symptoms. In this study, depressed mood was found to be one of the most frequent symptoms. Some limitations to this evaluation are that the measurement of depressed mood was based on a categorical scale (present/absent), which is less precise than the HAM-D, where sadness is indicated on a 5-point rating scale. This evaluation could not be precise enough to discriminate between "normal" sadness and depressed mood included in a depressive state. The quality of sadness thus appears to be of importance; this appears in the context of other tools. For example, in the Newcastle Diagnostic Depression Scale,[18] patients are asked whether their sadness is different from "normal" response to stress or life events, so as to discriminate between depressive and reactive states.

Apart from studies in the general healthy population, sadness can be a comorbid symptom of various diseases, which does not imply that it is part of a depressive episode. For example, in Parkinson's disease, 25% of the patients presented with depressed mood,[19] but very few reached the full criteria for depression. However, in this study, the authors concluded that even with a low mood, patients were depressed and required an antidepressant only in a few cases.

Nevertheless, this point is a great matter of debate, and Horwitz and Wakefield argue that, while depressive disorder certainly exists and can be a devastating condition warranting medical attention, the apparent epidemic in fact reflects the way the psychiatric profession has understood and reclassified normal human sadness as largely an abnormal experience. They give strong support to this thesis in a recently published book.[20]

What is the impact of sadness on the clinical features of depression?

Some authors have investigated the clinical importance of the presence or absence of sadness in depression. They focused on the distinction between the presence or absence of anhedonia and sadness, which are the two main symptoms that must be present in international classifications to allow the diagnosis (*DSM-IV*,[8]; *ICD-10*,[11]). In particular, some authors addressed the question of whether depressed individuals who denied low mood would constitute a particular subgroup.[21] In this study in 902 patients fulfilling the *DSM-IV* criteria for depressive episode, 63 did not report low mood. They had briefer, less severe episodes and reported less suicidal ideation than patients with low mood. They also scored higher on four subscales of the SF-36, indicating better health and functioning. These results suggest that patients who deny low mood could constitute a distinct subgroup; furthermore, the clinical importance of sadness for depressed patients is underlined, with a prognostic value. A recent investigation was conducted among 564 patients with major depression, in order to evaluate clinical characteristics of the patients with or without sadness.[22] Sadness was found to be significantly associated with major depressive disorder symptom expression. In particular, sadness was associated with higher rates of reactivity of mood, social impairment, social withdrawal, physical complaints, and terminal insomnia. By contrast, the absence of sadness was associated with higher rates of diurnal mood variations and hypersomnia. A statistical tendency for significance was found for the desire to be dead; the authors suggest that clinicians should carefully monitor patients presenting with sadness for being at higher risk of suicide.

As sadness appears to be a major symptom of depression, it has been postulated that sadness intensity could be used to clinically discriminate subgroups of patients. Recently, some authors used data from outpatients participating in three large American multicenter clinical trials, for the treatment of major depressive episode, in order to evaluate clinical features of bipolar versus major depressive disorder.[23] They report demographic but also clinical differences assessed with the HAM-D and MADRS scales; in particular, fears were more common in patients with bipolar disorders, whereas sadness, but also insomnia, intellectual, somatic, respiratory and genitourinary complaints, and depressed behavior were more frequent in unipolar depression. By using a logistic regression model, 86.9% of

the patients were correctly classified. Such clinical distinctions could be useful to detect bipolar disorders, which could be of importance for the patients' outcome.

Another particular case is that of the elderly. Whereas the prevalence of depression is independent of age,[24] a high rate of depressive symptoms requiring treatments has been reported, among which sadness can be described.[25] In clinical practice, the low prevalence of depression could be due to the inadequacy of evaluation tools in the elderly, with an underdetection of subthreshold depression, of high prevalence in old age.[8] This underreporting of depression could also be due to alternative presentations of depression at older ages, as well as to poorly distinguish sadness as a depressive symptom from "resignation due to age," which in turn is a common misconception.[26]

Is sadness the cause or consequence of neurovegetative symptoms?

Neurovegetative symptoms are important components of the depressive state. They include sleep disorders, appetite modifications, and autonomic anxiety, consisting of cardiovascular, respiratory, and genitourinary symptoms.[27] They differ from the HAM-D "general somatic" symptoms, which include tiredness, muscular tension, and pains, and shares its phenomenology with the core symptoms of depression. In the HAM-D, the neurovegetative symptoms of affective disorders covering autonomic symptoms are combined into a single somatic anxiety item. Some studies have shown that benzodiazepines and β-blockers have a specific effect on autonomic symptoms.[28] Furthermore, in depressed patients, once these symptoms are alleviated, these classes of drugs seem to induce sadness; more than a causal relationship, this effect suggests that autonomic symptoms could mask depressive disorders.

Some epidemiological arguments exist for a close relationship between vegetative symptoms and mood disorders. One of the most studied symptoms, insomnia, has been found to be closely linked to depression. For example, Ford[29] found that subjects with complaints of persistent insomnia were three times more likely to develop depression within a 1-year interval than those without persistent insomnia. In a longitudinal epidemiological study of young adults, the association between sleep disturbance and psychiatric disorders was cross-sectionally and prospectively assessed.[30] The gender-adjusted relative risk for new onset of major depression during the follow-up period was 4 in patients with a baseline history of insomnia and 2.9 for those with hypersomnia. The authors conclude that complaints of 2 weeks or more of insomnia nearly every night might be a useful marker of subsequent onset of major depression. Chang et al,[31] in a longer prospective study of 34 years, reported that the relative risk of clinical depression was double for men who reported insomnia at baseline during medical school, an effect that persisted for 30 years. However, it can not be concluded whether depressive episodes could be "due" to insomnia. It is also of note that depression without sleep disorders or with hypersomnia is common, in particular in seasonal affective disorders.[32]

At the same time, most depressive disorders are characterized by subjective sleep disturbances, and the regulation of sleep is intricately linked to the same mechanisms that are implicated in the pathophysiology of depression.[33] In particular, serotoninergic and cholinergic pathways have been implicated in the pathophysiology of both disorders.[34] Another striking example of the link between sleep and depression is the antidepressant effect of therapeutic sleep deprivation on depressive episodes.[35] However, even if biologically linked, no arguments have been conclusive for the causality of one symptom over the other.

Appetite, another vegetative symptom, is linked to anorexia and weight loss, which are often described in depression. High comorbidity has been described between anorexia nervosa and depression. While some authors have postulated that anorexia nervosa and bulimia may be variant expressions of a primary mood disturbance, and that the striking eating and weight-related symptoms are secondary phenomena,[36] others suggested that the high comorbidity observed could be due to a genetic liability shared by the two diseases.[37] From a biological point of view, some arguments exist for an implication of proinflammatory cytokines in depressed mood, and anhedonic and anorexic responses.[38] In particular, some results suggest that cytokines may contribute to the altered appetite in major depression, through the hypothalamic-pituitary-adrenal axis and leptin. However, the connection between cytokines, appetite, and depression, and in particular of sadness in depression, is at this time not well known. Hyperphagia is another eating disturbance which has been described in depression, and the relationships of hyperphagia, hypersomnia, and emotional dysregulation have been studied in the context of the so-called "atypical depression."[39] For some authors, hypersomnolence might be an adaptive homeostatic response that restores slow-wave sleep during stress, and hyperphagia may be a com-

pensatory response leading to increased dietary intake of L-tryptophan, increasing brain serotonin levels. However, the determinants of hyperphagia should be examined in more detail.

In other studies, a strong association between functional somatic symptoms and depression was reported. In one of them,[40] the association was equally strong for anxiety and depression, and a stronger association was observed for comorbid anxiety and depression. The association between the number of somatic symptoms and the Hospital Anxiety and Depression Scale total score was linear and independent of gender. While reanalyzing the results of the National Comorbidity Survey, Silverstein[41] concluded that the gender difference generally described in depression may result from a difference in a specific subtype of anxious somatic depression including fatigue, appetite, and sleep disturbance.

Is sadness alleviation the appropriate therapeutic target in depression?

In randomized controlled trials of antidepressants, symptom alleviation is evaluated with the use of validated clinical assessments, such as the MADRS and HAM-D scales. As sadness is evaluated with the use of these clinical tools, some randomized antidepressant trials consider it as a global indicator of symptomatic alleviation, and therefore show it separately. However, the manner in which sadness is evaluated in the scale is of great importance: for example, in the PSE, it is scored on a categorical scale (present or absent), in contrast to the HAM-D, where it is measured on a 5-point scale (from 0 to 4).[5] Furthermore, the sensitivity of this evaluation needs to be challenged; this has been done by some studies evaluating treatments with several scales. For example, the results of a study of the antidepressant venlafaxine used against placebo showed depressed mood when assessed with the HAM-D to be more sensitive than when assessed with the HAM-D17 or the MADRS 10: a dose-response effect appeared as soon as the first week, whereas it needed 3 weeks to be assessed with the HAM-D and 4 with the MADRS.[42] One should conclude then, that sadness as evaluated with the HAM-D could be an efficient means of determining antidepressant response, though it should be validated in clinical studies. In fact, sound psychometric properties underlie each construct of distinct questionnaires, and these conclusions should be considered with caution.

Most of the currently prescribed antidepressants have been studied in controlled, designed clinical evaluations, using one of the two main evaluation tools, the HAM-D or MADRS. However, these scales would not be sufficient to assess remission, as pointed out by the ACNP task force on response and remission in major depressive disorders.[43] The authors postulate that remission implies that the signs and symptoms of the illness must be absent or close to it, with return to the day-to-day function that was typical to the patient before the occurrence of depression. The Task Force recommends that remission refer only to the nine criterion domains of the *DSM-IV* diagnosis of depression. Interestingly, they also specify that neither sad mood nor loss of interest or pleasure should be present in the remitted state, because the presence of sadness would be associated with a worse prognosis. Their definition of remission implies that rating scales used to assess remission would assess the nine domains of interest in the *DSM-IV*, but they also recommend not to use total scores with severity thresholds for the assessments, but rather to evaluate the presence or absence of the criteria, in which sadness takes an important part. They emphasize the limitations of the MADRS and HAM-D scales, but at the same time propose that a HAM-D total score ≤5 be used as a criterion for remission, when researchers wish to evaluate this.[43]

Conclusions

Sadness is a clinical main component of the depressive syndrome, though its presence is neither sufficient nor required for the diagnosis of depression. However, it is a frequent clinical feature in the disease, and its clinical correlates, such as suicide and level of daytime functioning, are of importance for the patients. With this perspective, some authors have decided to use it as a criterion for clinical studies of antidepressant efficacy, even if its assessment alone seems insufficient in comparison with standardized evaluations. Though further studies assessing its sensitivity are strongly warranted, its use in clinical practice as a therapeutic target appears to be justified. The prognostic importance of its alleviation for remission has been particularly emphasized.

Given the heterogeneity of the depressive clinical presentation, one should not reduce depression to sadness; at the same time it is justifiable to consider it as a clinical core symptom of depression, and to properly assess and treat it. ❑

La tristeza como parte integral de la depresión

La tristeza es considerada por numerosos autores como un síntoma central de la depresión. Actualmente existen muchos argumentos para este síntoma de especial importancia en los pacientes depresivos. Aunque la tristeza forma parte de las diversas definiciones del síndrome depresivo, no se requiere de su presencia para el diagnóstico. Además, está íntimamente vinculada a los otros síntomas depresivos y tiene valor pronóstico, en especial para la remisión. El reconocimiento y la medición de la tristeza parecen ser importantes para la evaluación terapéutica, tanto en los estudios clínicos como en los pacientes depresivos en forma individual. Este artículo presenta una revisión parcial de algunos aspectos de la tristeza, como una parte integral de la depresión, y examina sus vínculos con una enfermedad que constituye una importante preocupación en salud.

La tristesse : part déterminante de la depression

La tristesse est considérée comme un des symptômes majeurs de la dépression par de nombreux auteurs. Il existe en effet de nombreux arguments cliniques permettant de soutenir son importance très particulière chez les patients déprimés. Elle fait partie des nombreuses définitions du trouble dépressif. Si elle n'est pas une condition obligatoire pour poser le diagnostic, son lien avec les autres symptômes de la dépression et son importance pronostique en font un symptôme clé. En conséquence son évaluation est pertinente sur le plan thérapeutique, tant au niveau individuel que collectif. Dans cette revue, il est proposé de détailler de manière critique certains des aspects cliniques de la tristesse, en tant que part déterminante du syndrome dépressif, et d'examiner ses liens avec la dépression, trouble d'une importance majeure en termes de santé publique.

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