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Residual symptoms in depression

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Despite successful response to therapy, subsyndromal depressive symptoms appear to be the rule in unipolar depression. Residual symptoms are present in more than 30% of patients who respond to antidepressants, specifically in subjects with more severe initial illness. The most prevalent residual symptoms are affective, somatic, cognitive and sleep disturbance. It has been shown that such persistent symptoms are associated with a higher risk of relapse, chronicity and functional impairment; associated with neuroanatomical changes. It is important to consider the possibility of persistence subthreshold symptoms and look for new therapeutic strategies for improving the level of remission in the treatment of major depressive disorder.

Key words:
Depression. Residual symptoms. Prognosis. Antidepressants.

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Síntomas residuales en la depresión

A pesar de la efectividad de la respuesta a los antidepresivos, la persistencia de síntomas subsindrómicos tras el tratamiento de los episodios depresivos es un fenómeno frecuente. Más del 30% de los pacientes que responden a un tratamiento antidepresivo presentan síntomas residuales, sobre todo los que sufren episodios depresivos más graves al inicio. Los síntomas residuales más frecuentes son los síntomas subsindrómicos de las esferas afectiva, somática y cognitiva, y las alteraciones del sueño. La presencia de síntomas residuales empeora el pronóstico del trastorno depresivo, con recaídas más frecuentes y más rápidas y déficits en la funcionalidad que se asocian con alteraciones neuroanatómicas. A la vista de los datos a la hora de enfocar el tratamiento de un trastorno depresivo es necesario tener en cuenta la posibilidad de persistencia de síntomas residuales y buscar, con todos los medios al alcance, la recuperación del paciente.

Palabras clave:
Depresión. Síntomas residuales. Pronóstico. Antidepresivos.

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INTRODUCTION

At the end of the 1980's, a work group from the MacArthur Foundation reviewed terminology regarding the evolutive course of Major Depressive Disorder (MDD) and established different stages defined with operational criteria (episode, remission and recovery). In addition, they contemplated the possibility that some patients would have symptoms after the treatment that would not have the sufficient entity to meet MDD diagnostic criteria, a situation that they called «partial remission»[1]. Since that time, the DSM-IV classification[2] has continued to contemplate the concept of partial remission, defining it as: the presence of some symptoms of a major depressive episode, that are not sufficient to meet all the criteria, or the absence of significant symptoms after a major depressive episode for a period of less than 2 months.

Subsequent investigations have provided more clarification on discovering that the patients who reach remission (defined as a score < 8 on the Hamilton depression rating scale - [Ham-D][1]), during the course of an antidepressant treatment have one or more residual symptoms associated to psychosocial functioning deficits in 80 % of the cases[3]. Thus, they propose more restrictive criteria, considering: partial remission as the presence of mild residual symptoms (score on Ham-D scale between 3 and 7); complete remission as complete absence of symptoms (scone on Ham-D scale < 3); and recovery when the complete remission is maintained for at least 4 months[4]. The data that support the

proposal coincide with those obtained in previous antidepressante efficacy studies that have shown that symptoms called «residual» or «subsyndromal» persist in spite of improvement in many patients with MDD treated with these drugs[5,6].

The subjective perception of the patients is an especially valuable element in an area such as that of residual symptoms in which the sensitivity of the detection instruments used is limited. Depressive patients differentiate between symptomatic reduction and remission, granting special importance to functionality and understanding that the resolution of the symptoms is only one element of the remission. The presence of positive mental health characteristics such as optimism, energy and self-confidence associated to «finding oneself that same as before» and return to normal functioning level are more reliable indicators of remission than absence of the depressive symptoms for the patients[7].

Frequency of residual sympton

Up to 30 % of the patients who respond to an antidepressive treatment have residual symptoms[6]. Although the data are not totally comparable between studies, similar values have been obtained by different research groups, these being even higher (up to 40 %) when stricter partial remission criteria are used[8-13]. Similar results to the above obtained in patients treated in specialized settings have been observed in samples of depressed patients treated in primary care or samples extracted from the general population. This has made it possible to propose the hypothesis that this is a phenomenon that occurs independently of the severity of the depression[14,15].

The investigation on residual symptoms has limitations due to, above all, the fact that the studies have not been specifically designed for their detection and they use instruments whose primary objective is to evaluate the efficacy of antidepressive treatments. This generally limits the characterization of the residual symptoms to clusters on the Hamilton depression scale, overlooking such important aspects as persistence of cognitive symptoms (the so-called cognitive residual syndrome) or social deterioration[16, 17], that are only detected when they are included in specific instrument studies for their evaluation[18-20]. Assuming the limitations, the depressive symptoms that have been described as being the most frequent are: affective symptoms (depressed mood, loss of interest and pleasure, apathy, psychic and somatic anxiety); somatic symptoms (fatigue, somatic symptoms without clear organic cause, gastrointestinal symptoms and sexual sphere symptoms); cognitive symptoms and sleep alterations[3, 21-23]. Elderly patients deserve to be mentioned separately. Persistent anxiety, sleep alterations and executive dysfunction take on special importance in them[22, 24-26].

There are signs of the association between certain clinical characteristics and greater frequency of residual depressive symptoms. The following are among the factors that have a strong association: greater severity of the depressive disease at the onset[11]; longer duration of the disease also has an association, although this is weaker. Regarding premorbid personality, the data varied among those who support a weak association, above all dependent personality disorder[27] or psychoticism[12] and those who do not find any association[3]. However, it seems that the existence of a personality disorder would act as a cofactor that amplifies or worsens the impact of the residual depressive symptoms in long-term functioning and quality of life[28,29]. The little data existing on this have not found any association between residual symptoms and other elements such as: diagnosis of previous dysthymia or the use of lower doses of the antidepressive drug during the episode[11]. However, an association has been found with lower plasma concentrations of antidepressants during maintenance therapy[30]. Less methodologically rigorous studies have found an association with other factors such as: the presence of somatic symptoms[31], poor premorbid social function, and social support[3]. In elderly patients, some physical rheumatic and dermatological diseases could play a role in the persistence of residual depressive symptoms[32]. In any case, the data on clinical markers of risk of residual depressive symptoms are not very conclusive.

Associations have been demonstrated between residual symptoms and some neurobiological correlates that basically involve the floor architecture and hypothalamic-pituitary-adrenal axis[18]. The studies performed with functional neuroimaging have shown that patients with residual symptoms have a serious and generalized hypoperfusion in the prefrontal cortex and the anterior cingulate[33]. In spite of its potential value, its current utility in the psychiatric practice is practically null[34].

The possible differential impact of antidepressants having different pharmacodynamic profile in the persistence of residual depressive symptoms has been studied little. However, it is possible that using molecules with optimum profiles of effectivity and tolerability would make it possible to reach «high quality remissions»[35,36].

Clinical and etiopathogenic prognostic implications

Research data confirm that the subsyndromal symptoms that persist after treatment of a MDD are elements of poor prognosis that affect the number and speed of the relapses, social functioning and adoption of abnormal illness behavior norms.

Presence of residual symptoms is associated to an increase in the risk of developing new episodes (relapses or recurrences) and greater speed of their appearance[5, 11, 37-39]. It has been demonstrated that relapses occur three times

faster in the patients who have residual symptoms[40]. Although some data partially question the phenomenon, showing that the effect on the increase of relapses of the residual symptoms disappear at 5 years of the depressive episode[12], the presence of residual symptoms is one of the strongest predictors of MDD[40].

Social dysfunction and incapacity are important consequences of a depressive episode that tend to persist even after this has remitted[16,41]. The presence of residual symptoms would have an amplifying effect on the functional deficit, this being associated to deterioration in the social and work sphere[3,4,14,16,42,43]. Although there is significant unanimity on the association between residual symptoms and incapacity, the data on out-patients do not all coincide with those of samples of patients seen in the specialized setting. The latter show an asynchronic situation in which the incapacity is present during the depressive episode and sometime after it, but is resolved in the subsequent months on the contrary to the residual symptoms that persist[14].

The presence of residual depressive symptoms, above all somatic symptoms without organic cause[44, 45], is also associated with the appearance of abnormal illness behavior[46] since the greater the number of visits to the doctor, the greater the demand for attention in the emergency services, more psychiatric hospitalizations and greater frequency of suicidal thoughts and attempts[47].

In recent decades, data have appeared that relate chronic depression with neuroanatomical alterations. These are fundamentally decrease of hippocampal volume[48], whose size decreases in direct relationship with the time of untreated depression[49]. Although the findings are less clear, chronicity of depression has also been associated with increase in amygdala volume and with reduction in frontal cortex volume, especially in some subregions such as the orbitofrontal cortex[50]. Modification in the hippocampal volume is also related with persistence of residual symptoms. The data suggest that a greater volume of the hippocampus in patients with MDD may be directly related with capacity to reach remission[51]. A significantly lower proportion of residual symptoms has also been found in depressive patients whose volume of gray matter is above the mean in the system made up of the anterior cingulate cortex, insula and right temporoparietal cortex[52].

From the etiopathogenic point of view, residual symptoms pose unresolved theoretical problems. As they are considered an active state of the depressive condition[40], there could be two alternative explanatory hypotheses. One of them is the theory of «vulnerability». According to this, the residual symptoms would be preexisting personality traits that would act as a risk factor for the development of depression and that would persist after the episode[5, 27, 53]. This hypothesis would be supported by the fact that many of the residual symptoms are already present in the prodromic phase of the disease[18]. The other one is the theory of «depressive scar»[54]. This considers the residual symptoms as sequels in the affects produced by the depressive episodes that cannot be attributed to previous personality problems or to adverse drug effects. Recent electroencephalographic studies have contradicted this theory. They find that a background of depressive episodes is not associated with definitive alteration of the neuronal network dynamics[55]. Another weakness of both models is that the role of comorbid anxiety, neuroticism or other personal traits whose possible importance could be justified by the favorable therapeutic response of the residual symptoms to the psychotherapy is not clear in any of them[56-59]. However, the fact that psychotherapy is the most effective on the relapses rates than on the intensity of the residual symptoms leads us to think that the psychotherapy techniques would act more on the disease adaption processes than on their depressive symptoms[60,61].

CONCLUSION

In recent years, awareness has been increasing on the growing impact of depression on the disease burden[62]. Parallelly, there has been some questioning of the efficacy of the antidepressants[63], and acknowledgement that although depressive disorders generally improve when treated with antidepressants, the persistence of residual symptoms seems to still be the rule[64]. It seems as if these drugs would have abandoned the action mode «focused on the disease», where the drug resolves a hypothetical abnormality that is the cause of the problem in order to act by «focusing on them», causing abnormal mental conditions which accidentally could improve some of the symptoms presented by the depressed patients[65]. In developed countries, the increase of the importance of depression does not seem to be due to the increase in the prevalence of severe conditions but rather to the inclusion of conditions of malaise that, although they meet diagnostic criteria, suppose milder or non-specific mood alterations, within the concept of depression. This extension of the spectrum used to current approach the antidepressants could explain the reduction in their effectiveness, with inversely proportional therapeutic benefits to the severity of the clinical pictures. In some cases, these are moderate when compared with the placebo[63, 66].

In view of the data, it is clear that a cross-sectional and simplistic view of the depressive disorder must be avoided. This means abandoning the usual therapeutic optimism, establishing the treatment with a longitudinal view and resolutely fighting with all the therapeutic means available until reaching the recovery of the patient[67]. The therapeutic results should be evaluated in the long term, using a multicategorial measurement that contemplates partial remission, residual symptoms and incapacity[68]. The complexity of the subject raises the doubt about whether all the psychopharmacological strategies used at present in the treatment of depression have the same efficacy for all the types and phases of the depressive disease. The future

will probably require us to establish specific therapeutic strategies oriented towards the disease phase and to evaluate the efficacy of the treatments not only by their capacity to produce response or remission but also by the amount of residual symptoms that remain after the response[18].

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