Review

PSYCHIATRY

The impact of psychiatric comorbidities associated with depression: a literature review

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Abstract

The comorbidity with anxiety disorders has profound adverse implications on the evolution, prognosis and therapeutic responsiveness of depression, it will prolong the time required to achieve remission of the depressive episode, and patients under treatment will tend to drop out of their therapeutic regimens faster than those with depression but without anxious comorbidity. The purpose of this study is to evaluate the importance of the clinical, etiopathogenetic, prognostic and especially therapeutic connotations given by the presence of psychiatric comorbidities in depression. Articles evaluating the presence of psychiatric comorbidities in depression were analyzed using PubMed, Medline, Scopus, Google Academics and WoS databases. To select the articles, we used keywords: psychiatric comorbidity, depression with anxiety disorders, depression with dysthymia, depression with psychoactive substances, depression with personality disorders. From a psychiatric perspective, the comorbidity of mental disorders can be divided into psychiatric comorbidity, when two or more distinct psychiatric conditions are present in the same individual, and medical comorbidity, when a medical-surgical illness is associated with a mental disorder. The presence of major depression is in itself a predictive factor for a later onset of generalized anxiety disorder. The comorbidity of depression in those with substance abuse or addiction has profound implications on their clinical prognosis. The association of personality disorder has a significant impact on the suicidal behavior of patients with major depression.

Keywords: psychiatric comorbidity, depression, anxiety, predictive factors, clinical prognosis

Introduction

The notion of "comorbidity" was introduced for the first time in medicine by Alvin Feinstein to designate those cases in which "an additional distinct clinical entity" appears on another clinical course of another initial disease that started previously [1]. From a psychiatric perspective, the comorbidity of mental disorders can be divided into psychiatric comorbidity, when two or more distinct psychiatric conditions are present in the same individual, and medical comorbidity, when a medical-surgical illness is associated with a mental disorder [2].

In relation to belonging to the diagnostic class, the coexistence of two mental disorders from different diagnostic classes (e.g., major depression and alcohol abuse) is defined as heterotypic comorbidity. Conversely, the coexistence of two mental disorders within the same diagnostic class (e.g., generalized anxiety disorder and social phobia) is labeled as homotypic comorbidity [3].

The coexistence of two or more mental disorders, at the same time and in the same person (e.g., persistent delusional disorder and specific or simple phobia) is defined under the term concurrent comorbidity. When two distinct mental disorders manifest themselves in different periods of a patient's life (irrespective of

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whether there is a causal relationship between them or not), they are in successive comorbidity [4].

Numerous clinical and epidemiological studies have indicated that major depression is a condition with increased psychiatric comorbidity [5]. An important epidemiological study is the Replicated National Comorbidity Study [6,7] which generated interesting data with reference to the level of comorbidity between the various syndromic units. Based on the correlations found, significant comorbidities were highlighted (correlation coefficient > 0.60) between major depressive episode and dysthymia, known as double depression (0.88), between social phobia and agoraphobia (0.68), between anxiety disorder panic and agoraphobia (0.64), between major depressive episode and hypomanic/ manic episode (0.63) within bipolar affective disorder, between major depressive episode and generalized anxiety (0.62) and, as expected, between substance abuse and substance dependence (correlation coefficient 1). The high level of comorbidity of major depression was significantly correlated with the following socio-demographic characteristics: female sex, non-Hispanic white race, unmarried , low level of education, low income and residence outside rural areas. Regarding the distribution of severity, which was strongly correlated with the level of comorbidity, mood disorders had the highest percentage of severe cases (45.0%), while anxiety disorders had the lowest (22.8%) [8,9].

The purpose of this study is to evaluate the importance of the clinical, etiopathogenetic, prognostic and especially therapeutic connotations given by the presence of psychiatric comorbidities in depression.

Methods

To achieve our purpose, articles evaluating the presence of psychiatric comorbidities in depression were analyzed using PubMed, Medline, Scopus, Google Academics and WoS databases. To select the articles, we used the following keywords: psychiatric comorbidity, depression with anxiety disorders, depression with dysthymia, depression with psychoactive substances, depression with personality disorders. Studies assessing depression in children were excluded due to the multitude of factors that would have distorted the information presented. We selected original studies and reviews from international journals. Selected papers included only articles published in English. A final step was further review of the articles to assess the eligibility of studies with relevant statistical data.

Results and discussion

1. Comorbidity of depression with other mood disorders

Comorbidity of depression with anxiety disorders

Depression and anxiety are the most widespread and the most expensive mental disorders for society [10]. The differences regarding comorbidity rates, between depression and anxiety disorders, found in various types of studies are determined by the differences in methodology used within them. Thus, the prevalence of comorbidity of the two types of disorders is constantly higher in clinical studies compared to epidemiological studies, which is attributed to Berkson's tendency or bias. The use of structured interviews resulted in an apparent increase in this comorbidity. However, the prevalence rates of comorbidity between depression and anxiety disorders are higher than those of each of these disorders alone [11,12].

Reference population epidemiological studies have revealed that depression and anxiety are most often comorbid [13]. In patients who have experienced depression at some point in their life, the lifetime prevalence of an anxiety disorder is increased, 47% according to the Epidemiologic Coverage Area study, 58% according to the National Comorbidity Baseline Study and 57% in a meta-analysis by Clark 1989, cited by Stein and Hollander [14]. Although single-occurring anxiety without depression is more common than the reverse situation, i.e., depression without anxiety, the prevalence of depression in those with anxiety disorders is high: 56% in Clark's meta-analysis. Rates of depression vary depending on the particular type of anxiety disorder diagnosed, but in general anxiety disorders are as comorbid with depression (OR = 6.6) as with each other (OR = 6.2) [15].

An intermediate perspective was the recognition of an intermediate diagnostic category called mixed anxious and depressive disorder that was included in both diagnostic manuals, DSM-IV (in the list of additional diagnoses that require further studies) and ICD-10.

The diagnosis of generalized anxiety disorder (GAD) was only introduced starting with the 3rd edition of the DSM and the 10th edition of the ICD, until then not having the status of a distinct nosological entity. The National Comorbidity Survey indicated that 90% of respondents with GAD appearing at some point during their life also reported the existence of another mental disorder during their life, and 66% of those with current GAD had at least one other current psychopathological episode, and depression was among the most comorbid mental disorders [16].

In the National Comorbidity Replication Study (NCS-R), Kessler et al found a significant correlation (correlation coefficient 0.62) between generalized anxiety disorder and major depressive disorder, this being the most comorbid anxiety disorder in depression. In part, the increased comorbidity of depression and generalized anxiety was attributed to the partial overlap of the operational diagnostic criteria of the two distinct mental disorders [17].

The comorbidity between panic and depression was found to be the most significant in a population study [18]. Using data from the Initial Study of National Comorbidity,

Roy-Byrne et al. (2000) found a strong lifetime and current comorbidity between panic and depression [19]. After resorting to the control of the effects that could have been determined by other additional psychiatric diagnoses, this comorbidity was significantly associated with a greater severity of the clinical symptoms, the persistence of the symptoms, with a more important impairment in fulfilling the professional role (in the case of comorbidity current, when it is active, but not during life), with the amplification of suicidality (25% in the situation of comorbidity compared to 16% in depression and 5.2% in panic disorder), and an increase in the use of care services, both psychiatric and medical, as well as those from the social sector. The results did not differ regarding the chronological order of the onset of the two comorbid mental disorders. A more cautious estimate of this comorbidity was 13%, resulting from a large population study conducted by Regier et al [20].

Fava et al. conducted a study of the comorbidity of depression on 369 depressed patients with non-psychotic depression, aged between 18 and 65 years, treated in an outpatient setting, and included in the Depression Research Program of the Department of Psychopharmacology Massachusetts General Hospital Clinic [21]. DSM-IV axis I comorbidity was studied both during life and current. The results showed that, regarding comorbidity during life, while in depressed men the most frequent comorbidity was represented by alcohol abuse and dependence, in women phobic disorders represented the most frequent comorbidities.

Epidemiological studies have indicated an important comorbidity between obsessive-compulsive disorder and depression. The results of the Epidemiologic Catchment Area study indicated comorbidity with major depressive disorder in 31.7% of patients with obsessive-compulsive disorder (OCD), and with dysthymia in 26%. The Cross-National Epidemiological Study revealed a lifetime comorbidity between OCD and major depression that varies from one country to another between 12.4% and 60.3% [22-24].

A study by Perugi et al. demonstrated that 34.8% of OCD patients had an associated diagnosis of major depression which he labeled as "unipolar-obsessive". Depression was the most frequent complication of obsessive-compulsive disorder, whose percentage varies from 13 to 75% [25].

Comorbidity of depression with dysthymia

Keller and Shapiro were among the first to draw attention to the frequent coexistence of the two clinical syndromes, which they labeled "double depression" [26]. According to the Epidemiological Coverage Area (ECA) study, 40% of subjects with dysthymic disorder have a lifetime history of major depressive disorder and only 25-30% of dysthymia cases remain without any psychiatric comorbidity during their lifetime [27].

In the National Comorbidity Replication Study, Kessler et al. (2005) found that the most important comorbidity, during the last 12 months, of major depressive disorder was represented by dysthymia (they presented a correlation coefficient of 0.88) [7].

2. Comorbidity of depression with psychoactive substances and drugs

Studies on the prevalence of depression and alcoholism have highlighted the fact that alcoholism has a higher prevalence among men and depression is more common among women. A large epidemiological study indicated that 24% of men with alcohol dependence had a major depressive episode at some point during their life, which denotes a prevalence of depression 3 times higher compared to that in the general population. Depression among women with ethanol dependence was reported to have a frequency of 48.5%, a rate four times higher than that found in the general population [28, 29].

In psychiatric care units, more than 34% of depressed patients also meet the criteria for ethanol dependence, and between 24 and 59% of patients treated for alcoholism also have depression. The impact of the comorbidity of the two psychopathological conditions is reflected in the following clinical problems: alcoholism can mask the clinical picture of depression, interfere with therapeutic compliance, increase the risk of violent and suicidal behavior, increase the direct costs associated with treatment and constitute a factor in hospitalization. Regarding suicidal behavior, patients with comorbid depression and alcoholism represent the category of psychiatric patients with the highest risk of suicide. Major depression and alcoholism are major determinants of completed suicide with a lifetime prevalence rate of 15% for major depression and an additional suicide risk in alcoholics 60 to 120 times greater than in the general population [30].

A population study demonstrated the fact that the presence of early alcohol consumption, since childhood and adolescence, had a significant predictive value (odds ratio = 1.4; 95%CI = 1.165 – 1.721) for the occurrence of a major depressive disorder later in adulthood, at the end of the third decade of life, even after controlling for demographic factors and diagnoses of major depression occurring in childhood and adolescence [31,32].

Tirado Muñoz et al. reported in an article published in 2018 that the comorbidity of depression with the consumption of psychoactive substances and drugs has a prevalence between 12% and 80%, with negative effects on the treatment and prognosis of the disease. The conclusion of this study was that these two conditions should be treated simultaneously using the integrated treatment model [33].

3. Comorbidity of depression with personality disorders

Classic and contemporary psychiatry has always had in its sphere of concern the identification of specific relationships between the terrain of personality and mental illness [34]. In a reference article, Akiskal states that chronic

depression of subsyndromal intensity can result from four different clinical situations: primary depressions with onset in adulthood and residual chronicity, chronic secondary dysphoria, and characteristic depressions. Characteristic depressions include, in turn, character spectrum disorders with secondary depressive symptoms, non-responsive to any form of treatment and subaffective dysthymic disorders with onset before 25 years of age, with undulating evolution grafted or not by major depressive episodes and which are responsive to treatment (psychotherapy and/or thymostabilizers). This last nosological entity was later renamed by Akiskal as depressive personality [35].

This nosological classification of chronic depressions was supported on the basis of distinct clinical-evolutionary characteristics, therapeutic responsiveness to antidepressant treatment, changes in the physiological characteristics of sleep (REM sleep latency) and their relationship with the character structure [36].

Clinical studies at the specialist outpatient level and primary care showed the high degree of comorbidity of depression with anxiety disorders, the latter being present in over 50% of depression cases. Although psychiatric nosological systems have always differentiated between depression and anxiety disorders, there were authors who advocated the dimensional uniqueness of the two types of disorders, which can be included in a wider spectrum of affective disorders [37].

Sherbourne and Wells conducted an observational study on psychiatric patients with depression treated at primary care and specialty levels. The results of the study indicated that the presence of anxious comorbidity greatly increased the risk of major depression in those with mild subclinical depression, while those with major depression who have comorbidity with panic disorder or simple phobia had a lower remission tendency than those without anxious comorbidity. Those with depression, both clinical and subclinical, and anxious comorbidity reported a greater number of depressive symptoms, while in those with clinical depression, the increased intensity of depressive symptomatology persisted at follow-up assessments compared to those without comorbid anxiety [38].

A clinical study on the cross-sectional prevalence of anxiety disorders related to the bipolar or unipolar character of the depressive episode as well as those with dysthymia indicated a certain heterogeneity. Thus, comorbidity with panic disorder was present in over 30% among bipolar and unipolar depressives and only 13% among those with dysthymia. Comorbidity of social phobia was significantly associated with unipolar depression, while no case was detected in bipolar depressives [39].

Angst (1993) assessed the psychiatric comorbidity of generalized anxiety disorder with depression in a longitudinal epidemiological study conducted in Zurich, Switzerland. He found a highly significant association between generalized anxiety disorder (GAD) and major depression and dysthymia. The presence of GAD comorbidity was significantly associated with the risk of suicide attempt [40].

Brown et al. (1996) found that depressed patients who have panic disorder during their lifetime, show a greater severity of depressive symptoms, a more important impairment of physical and psychosocial functioning. In addition, they were more likely to report a history of alcohol dependence, somatization disorder, and avoidant personality disorder. Another result was that patients with comorbid depression and panic disorder were more likely to drop out prematurely from both pharmacological and psychotherapeutic treatment [41-43].

A population study, published by Katona, which was conducted on the elderly over 65 years of age, revealed that, in the depressed group, there were 2 times more simultaneous criteria for phobic disorder compared to the non-depressed group ($p<0.001$). In France, Cottraux estimated that 50 to 80% of patients diagnosed with OCD have an additional diagnosis of depressive disorder, and Hantouche et al. (2003) demonstrated that OCD is associated with major depression in a percentage of 76% [44-46].

Another study that aimed to determine to what extent single dysthymia, unipolar depression, and dysthymia comorbid with major depression are three distinct nosological entities or three different manifestations of the same unipolar depression unit diagnostic category was conducted by Donaldson et al [46]. For this, the penetrance of the three diagnoses was studied in the first-degree relatives of some study subjects belonging to the three diagnostic clinical situations to which a control group was added. Without ambiguity, the study results indicated the three diagnostic situations (single dysthymic disorder, comorbid dysthymia with major depression, and single major depressive disorder).

A study of the Finnish institutionalized population revealed that alcohol intoxication with a frequency greater than once a week was a predictive factor for the development of depression in the previous 12 months [47].

Corruble et al. conducted a meta-analysis of 25 studies related to the comorbidity between personality disorders and major depression. The authors indicated that the prevalence of personality disorders, from a categorical perspective, was 20 to 50% of international patients with current major depressive disorder and almost double the 50 to 85% of outpatients with the diagnosis [48].

Conclusions

The importance of comorbidity with anxiety disorders has profound adverse implications on the evolution, prognosis and therapeutic responsiveness of depression, it will prolong the time required to achieve remission of the depressive episode, and patients under treatment will tend to drop out of therapy faster than

those with depression but without anxious comorbidity. The presence of major depression is in itself a predictive factor for a later onset of generalized anxiety disorder. The comorbidity of depression in those with substance abuse or addiction has profound implications on their clinical prognosis. The association of personality disorder has a significant impact on the suicidal behavior of patients with major depression.

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