Depression Associated Disorders: Comorbidity, Neurobiological and Neurobehavioural Link

Radhakrishnan Mahesh, Dilip K. Pandey, Shvetank Bhatt, Baldev Gautam

Pharmacy Group, FD-III Birla Institute of Technology and Science, Vidya Vihar

Campus Pilani, Rajasthan, India-333031

Summary

Comorbidity commonly refers to the co-occurrence (or dual diagnosis) of two disorders or syndromes in the same patient, regardless of whether the disorders are coincidentally or causally linked. Indeed, illnesses have been classified in discrete diagnostic categories although no sharp discontinuities in symptom distributions are observed across most mental disorders. Depression is a relatively common psychiatric comorbididy of most neurological disorders, with prevalence rates ranging between 20 and 50% among patients with stroke, multiple sclerosis, epilepsy, Parkinson's disease and dementia. Furthermore, depression is an independent predictor of poor quality of life in these patients and has a negative impact on the response to treatment, course and recovery of neurological deficits. Comorbid depressive disorders in neurologic patients can be indistinguishable to the primary mood disorders and may mimic major depression, dysthymic, minor depressive, and bipolar disorders described in the DSM-IV classification of mood disorders. In addition, the great overlap of medical and psychiatric symptoms in depression and neurologic disorders may lead to both false-positive and false-negative diagnoses of depression. Patient with comorbid condition have lower response rate and /or a longer time to response, greater reports of side effect early in treatment and greater likely hood of dropping out. In this review, we focus on comorbid disorder associated with depression.

Keywords: Comorbidity, Depression, Neurobehavioural

Corresponding author: Dilip Kumar Pandey

Pharmacy Group, FD-III

BITS, Pilani-333031, India

pandeysdl1408@gmail.com

Contact: +919571553001

Introduction

The term "comorbidity" has many—and often puzzling. It generally refers to the co-occurrence (or dual diagnosis) of two disorders or syndromes in the same patient, regardless of whether the disorders are coincidentally or causally linked [1-3]. Comorbidity" is also known for the epidemiologic linkage between two disorders in which one share pathologic mechanisms with or is a risk factor for the other over time [4-6]. Two disorders may be "clinically comorbid" if the presence of one alters the normal course of the other [1,7]. The phenomenon of comorbidity is relevant because it has in general a negative impact on health outcomes, quality of life, and health care use [8]. Several studies have reported a high prevalence of comorbidity with psychiatric disorders as well as with general medical conditions, both of which lead to a complex clinical presentation. Comorbid mental disorders occur with chronic medical conditions n many patients, causing significant role impairment, work loss and work cut-back [9, 10]. Affecting 10.3% of the U.S. adult population in any year [11], depression has become the leading cause of disability in adults (15–44 years old) within Western Europe and North America [12]. Depression increases symptom burden and functional impairment and worsens prognosis for heart disease, stroke, diabetes mellitus and other psychiatric disorders (Fig. 1) [13,14]. Affective disorder can influence the physical disorder through biological, bahavioural, cognitive and social pathways as shown Fig.2.
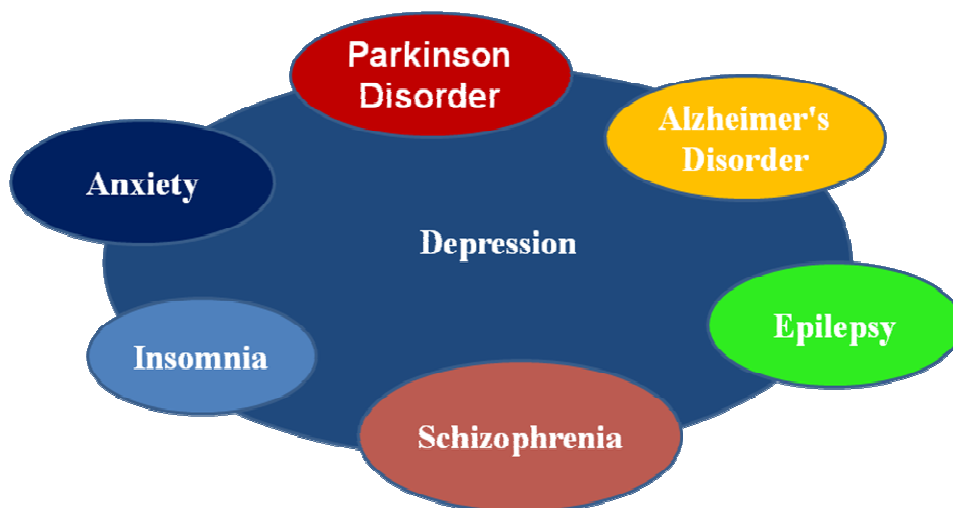

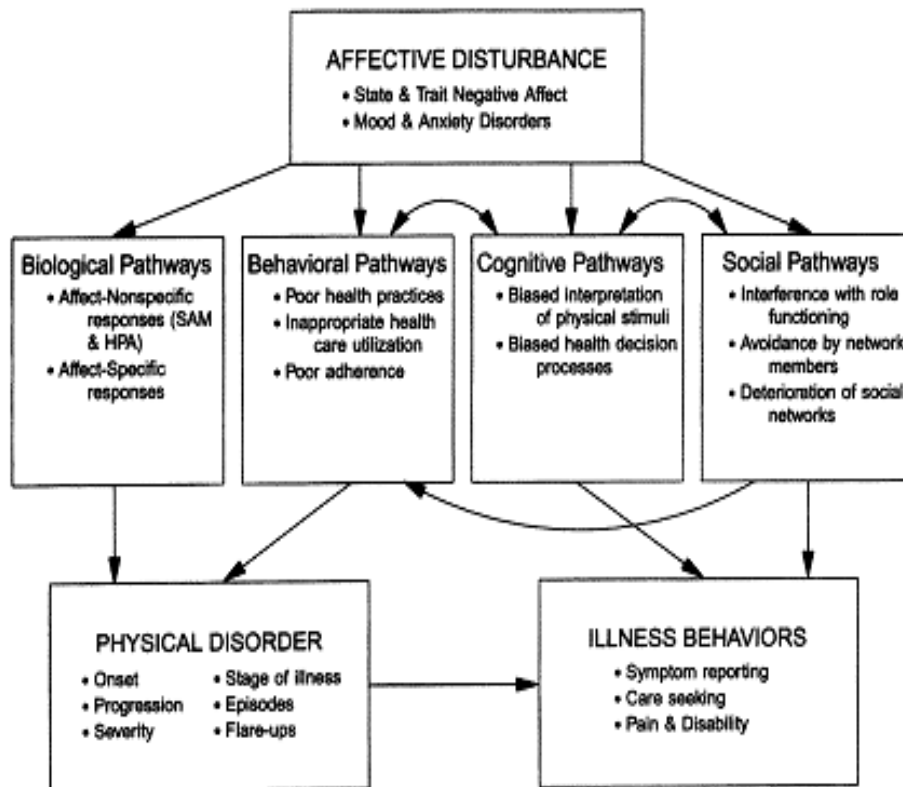Fig. 1. Comorbid disorders with Depression.

Fig.2. Pathways linking affective disorder influencing physical disorder [15].

Comorbidity is common among patients with major depression, but in most instances it may be of little relevance. Nonetheless, it is a complex issue because of its relation to treatment response, and few studies have attempted to address this. Most have examined comorbidity after the fact in secondary analyses. In this review, we focus on comorbid disorder associated with depression.

Comorbid Depression and Anxiety

Previous research indicates that depressed patients with comorbid anxiety disorders have a poorer prognosis, are less responsive to treatment, and may experience greater deficits in psychosocial functioning, when compared with depressed patients without comorbid anxiety disorders. In the National Comorbidity Survey, 58% of major depressive disorder (MDD) patients were found to have an anxiety disorder; among these patients, the rate of comorbidity with generalized anxiety disorder (GAD) was 17.2%, and with panic disorder, 9.9% [16]. Depression is frequently associated with anxiety and anxiety is a common symptom of depression. The inter-relationship between these two disorders is still being established and will undoubtedly receive further attention in the future, but the overlap is significant. The International Classification of Disease (ICD-10; World Health Organization, 1991) includes a category of mixed anxiety and depressive disorder, which is the association of sub threshold depressive symptoms and sub-threshold anxiety when neither symptoms of anxiety nor symptoms of depression (when considered separately) are severe enough for the diagnosis of a

disorder to be justified (Fig. 2). Nearly half of depressed patients have anxiety symptoms and half of anxiety patients have depressive symptoms. Anxiety is not a requirement for the diagnosis of major depression, bipolar disorder or dysthymia, as presented in either DSM-IV [17] or ICD-10 (World Health Organisation, 1992), in which mood and anxiety disorders are recognised as separate and distinct diseases as shown in Fig. 3. However, the idea that they may lie on a continuum has never been completely abandoned and the concept is supported by the fact that a group of 'in-between' patients with symptoms of both anxiety and depression has repeatedly been described. There are indications that anxiety is one of the most prevalent symptoms in clinical depression and that both the assessment and treatment of severe anxiety are of vital importance in the successful treatment of depression. The DSM-IV criteria for mixed anxiety-depressive disorder (Table 1) may be helpful in establishing whether the patient has subsyndromal features.

DSM-IV Diagnostic Criteria for Mixed Anxiety-Depressive Disorder

Presence of persistent or recurrent dysphoric mood lasting 4 weeks and accompanied by 4 of the following symptoms:

  –Concentration or memory difficulties
  –Sleep disturbances
  –Fatigue or low energy
  –Irritability
  –Worry
  –Being easily moved to tears
  –Hypervigilance
  –Anticipating the worst
  –Hopelessness or pessimism about the future
  –Low self-esteem or feelings of worthlessness

Symptoms are not due to a medication, drug abuse, or a medical condition and cause significant distress or impairment in social, occupational, or other important areas of functioning

Symptoms do not meet criteria of any other mental disorder

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.
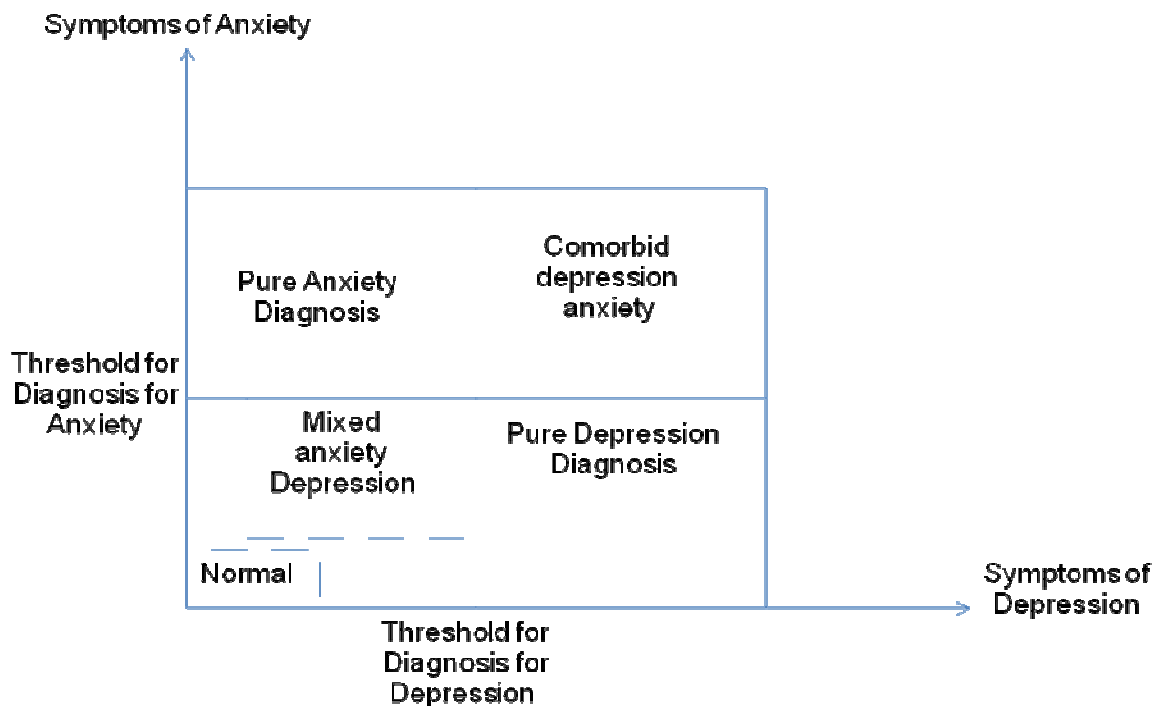Adapted from the American Psychiatric Association.

Fig.3A. ICD-10 concept of mixed anxiety–depression: the presence of anxiety and depressive symptoms below the threshold for diagnosis of an anxiety disorder or depression (ICD-10; World Health Organization, 1991).

The consequences of anxiety and depression on their own are serious, however when they occur together there are additional socioeconomic consequences. For example, there is an increased utilization of mental health service resources in patients with comorbid anxiety and depression compared with patients with either pure anxiety disorder or pure depression [18]. Patients who have depression and anxiety comorbidity have higher severity of illness, higher chronicity, and significantly greater impairment in work functioning, psychosocial functioning, and quality of life than patients not suffering from comorbidity. One of the most important clinical reasons to screen for comorbidity is that unrecognized depression/anxiety comorbidity is associated with an increased rate of psychiatric hospitalization and increased rate of suicide attempt.

Genetic studies suggest a biologic link between depression and anxiety. Family members of patients with comorbid depression and panic disorder have higher incidences of mood and anxiety disorders and alcohol abuse than the relatives of patients with depression alone [19]. Patients with depression and GAD have more relatives with depression than patients with either disorder alone. Neurobiochemical evidence also suggests that both conditions are related to disturbances in serotonergic and noradrenergic transmission and regulation. The involvement of these neurotransmitter systems in both normal and pathologic mood states suggests a continuum from normal arousal to anxious and depressive states. One hypothesis is that sustained hyperarousal may deplete these neurotransmitters in critical areas of the forebrain, which may in turn make a patient more vulnerable to developing the emotional and somatic manifestations of depression [20].

Comorbid anxiety and depression often complicate the treatment of psychiatric disorders. Previous studies have examined psychopharmacologic treatment approaches for depressed patients with anxiety symptoms, which include the use of antidepressants, anxiolytics, and other novel compounds [21]. Psychotherapeutic approaches have also been tested and include the use of traditional cognitive behaviorally based approaches [22] as well as interpersonally oriented psychotherapies [23]. While some outcome studies suggest that standard evidence-based treatments are effective in reducing both depressive and anxiety symptoms, other studies recommend modifications to traditional treatment approaches in order to optimally manage depression with comorbid anxiety [21]. For example, Bakish [24] supports the use of the novel serotonin–norepinephrine reuptake inhibitor, venlafaxine, for depression with concomitant anxiety, and work by Kuzel [21] finds nefazodone to also aid in treating depression with comorbid anxiety features. Significant advances have been made in the understanding of comorbid depression and anxiety disorders. More refined diagnostic criteria have provided more precise distinctions between the discrete depressive disorders, anxiety disorders, and mixed anxiety-depression seen in clinical practice. Studies of antidepressants and anxiolytic drugs are providing additional information about the underlying neurobiological derangements responsible for these psychiatric illnesses. Recent evidence suggest that serotonergic and noradrenergic mechanisms underlie anxiety and depression is providing support for the use of newer antidepressants; their use may enable clinicians to help patients achieve wellness or full remission instead of simply experiencing improvement with treatment.

Comorbid Depression and Parkinson Disease

Mood disturbance and especially MDD, is a common condition in Parkinson's disease (PD), with an average prevalence of 25–40% in outpatient settings [25]. Its prevalence varies, depending on the study methodology, but an approximate 40% were generally accepted, with half of these patients meeting criteria for major depression and half for dysthemia [26,27]. The cause of depression in PD remains controversial [28]. Depression is one of the most common non motor symptoms of Parkinson disease (PD) occurring in approximately half of patients [29]. Rates of depression have also been shown to vary widely between different countries. Whereas the Global Parkinson's Disease Survey, in five countries including the US, found that approximately half of PD patients had depressive symptoms that significantly impacted their daily functioning. Depression can impair both fine motor skills [30] and cognitive function [31,32] and is a primary factor negatively affecting quality of life in PD [33]. The diagnosis of depression in PD is particularly difficult because, perhaps more than any other medical disorder, the symptoms of PD overlap with the symptoms of depression. Its symptoms, such as bradykinesia, lack of concentration, weakness and sleep disturbances, are similar to the PD symptoms. The recognition of signs and symptoms of depression comorbid with PD is crucial for the clinician in a view of the fact that it influences the functional disability and quality of life. Patients with advanced PD often have significant sleep disturbance, fatigue, psychomotor slowing, difficulty concentrating, and diminished sexual function. PD patients can appear withdrawn from social activities, because they are unable to participate due to disabling dyskinesia and are socially uncomfortable with their appearance [34]. Depression is associated with a reduced quality of life, increased functional disability, more severe cognitive symptoms, and enhanced caregiver's stress. Although there is some knowledge about risk factors associated with depression in PD, little is known about its pathophysiology [33].

Depression in PD is the consequences of the neurodegenerative process of brainstem monoamine and indolamine afferents and variable involvement of a number of sub-cortical nuclei [35]. Parkinson disease is characterized by degeneration of the sub-cortical nuclei, some of which have been implicated in depression, such as the ventral tegmental area (VTA), hypothalamus, dorsal raphe, and locus ceruleus. The relationship between the neurodegenerative process and comorbid depression is demonstrated in the correlation of depressive symptoms with specific clinical features of PD [27,26]. The serotonergic hypothesis is one of the few hypotheses that have tried to link the pathophysiology of PD with an increased risk of depression [28]. This hypothesis is based on three observations. The first is that serotonergic activity is reduced in PD. Moreover, in vivo studies have consistently demonstrated reduced levels of 5-hydroxyindoleacetic acid (5-HIAA), a breakdown product of serotonin, in the cerebrospinal fluid (CSF) of PD patients [36,30], with some studies reporting an additional reduction of 5-HIAA in depressed PD patients [37]. These findings shows the involvement of serotonin in comorbid depression associated PD. Based on these observations Mayeux et al. [28] have framed the serotonergic hypothesis of depression in PD. This hypothesis considers the reduced serotonergic tone, a physiological adaptation to the reduced dopamine activity, while at the same constituting a risk factor for depression [37, 28]. The presence of this biological risk factor for depression may explain the high prevalence of this condition in patients with [24]. It may also explain the increased incidence of depression preceding the diagnosis of PD, because of the fact that pathophysiological compensatory mechanisms are already in action long before clinical symptoms become apparent [38]. Moreover, other neurotransmitters may be more directly related to mood symptoms in PD, such as dopamine. The 'dopaminergic hypothesis for depression in PD,' was formulated by Fibiger in the same year as the serotonergic hypothesis was formulated [39]. This hypothesis would also provide an explanation for the high prevalence of depression in PD and the fact that depression may precede PD. Although this hypothesis too is still in need of experimental verification.

Comorbid depression and Alzheimer's Disease

Major depression (MD) is the most common psychiatric disorder, with almost 1 in 5 people experiencing a depressive episode during their lifetime [9]. Apart from the well-known affective changes in patients with MD, many also exhibit a large range of cognitive deficits. Common cognitive dysfunctions consist of impairments memory recollection, list learning, recall, verbal and visual memory, executive function, attention and verbal fluency [40, 41, 42]. It has been demonstrated that there is a link between depressive complaints and the risk of cognitive decline during aging. More specifically, it appears that higher levels of depressive symptoms lead to a more rapid decline of global cognition [43, 44]. Recently it has been postulated that MD could also serve as an independent risk factor for developing AD [45,46], possibly by reducing the brains 'reserve capacity' . In fact, according to a meta-analysis, having a lifetime of depressive episodes increases the chance of developing AD by at least twofold [47]. Some Studies reported that this effect was due to early onset of depressive complaints [48], a history of depressive episodes [49], or education, with only those with higher levels of education having an increased risk of developing AD. Both Alzheimer's disease (AD) and depression (D) are prevalent disorders in old age and may co-occur in the same individual.
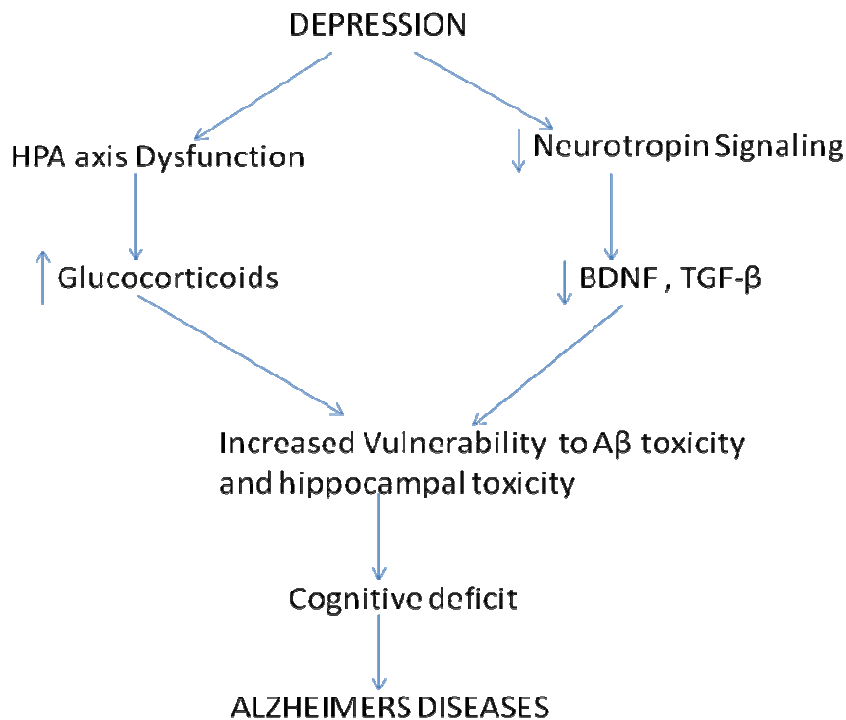
Fig.3B. From depression to Alzheimer's disease: neurobiological links and hypothetical pathophysiological mechanisms. Dysfunction of hypothalamic–pituitary–adrenal (HPA) axis, chronic inflammation and deficit of neurotrophin signaling exert a central role both in the pathophysiology of depression and Alzheimer's disease by increasing levels of glucocorticoids and pro-inflammatory cytokines and also reducing brain-derived neurotrophic factor (BDNF), and transforming-growth-factor-$\beta 1$ (TGF-$\beta 1$) levels. These alterations might lead to an increased vulnerability to β-amyloid toxicity and hippocampal atrophy, thus favouring the onset of cognitive deficit and finally the progression from depression to Alzheimer's disease [50].

Recent evidence, from epidemiology to neurobiology, suggests a strong relationship between depression and dementia. For different years depression and dementia have been considered completely distinct clinical entities. The term"pseudodementia" is used to define a clinical picture characterized by depression associated with cognitive impairment and responsiveness to anti-depressant treatment, as opposed to depression as an early symptom of dementia, which is instead unresponsive to antidepressants [51]. Recent evidence suggests that depression can act as a risk factor for dementia, in particular Alzheimer's disease, and, most importantly, common pathophysiological mechanisms between these two diseases have been identified, which might explain the progression from depression to Alzheimer's disease (Fig. 3and 4).
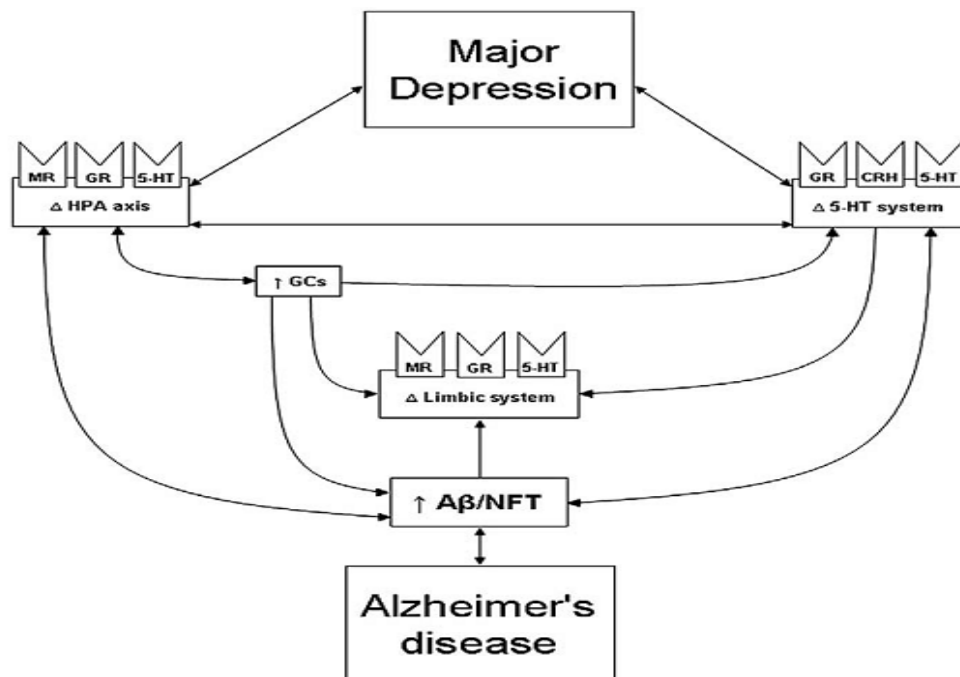
Fig.4. Schematic and simplified overview of the interactions between the HPA-axis and the serotonergic system. Major depression leads to alterations (Δ) in both systems, which are highly interconnected. (Abbreviations: 5-HT: serotonin; Aβ: Amyloid-β; CRH: corticotrophin-releasing hormone; GCs: glucocorticoids; GR: glucocorticoid receptor; HPA: hypothalamus-pituitary-adrenal; MR: mineralocorticoid receptor; NFT: neurofibrillary tangles). [52].

Epidemiological evidence supports a role for stress as a risk factor both for depression [53] and Alzheimer's disease [54]. Several studies clearly show that chronic exposure to stress and stressful life events may lead to the development of major depression [55,56] and that elderly individuals prone to psychological distress are more likely to develop dementia than age-matched non-stressed individuals [53].

Stress and HPA axis abnormalities have been demonstrated both in depression and Alzheimer's disease, with an impaired negative feed-back of glucocorticoids on the activity of the HPA axis,which results in elevated cortisol levels [57]. High basal cortisol levels are associated with more rapid cognitive decline in Alzheimer's disease patients [58,59]. Excess glucocorticoids may have a central role in the pathophysiology of both depression [60] and Alzheimer's disease via multiple mechanisms. High levels of glucocorticoids, through the activation of glucocorticoid receptors, can reduce neurogenesis in the hippocampal dentate gyrus [60], induce the retraction of hippocampal apical dendrites [61] and cause neuronal death in hippocampal neurons [62]. All these events can contribute to the reduction in hippocampal volume found both in depression and early Alzheimer's disease. All these data demonstrate a central role of HPA dysfunction and high levels of glucocorticoids both in depression and Alzheimer's disease pathogenesis and suggest the possibility that glucocorticoid receptors might be a suitable target both for anti-depressant and anti-dementia drugs.

Neurotrophins are essential for the maintenance of neuronal homeostasis and modulation of synaptic plasticity [63] . Changes in the levels and activities of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), and TGF-β1 have been described both in depression and Alzheimer's disease [64,65]. Significant decreases in BDNF have been detected in stress-induced animal models of depression (for review see [60]) as well as in depressed patients [66]. An impairment of BDNF signalling has been demonstrated also in Alzheimer's disease [65,67]. The levels of BDNF and its receptor, tropomyosin receptor kinase B (TrkB), are reduced in Alzheimer's disease brain, and a deficiency of BDNF signalling has been related to synaptic dysfunction, neurodegeneration and finally cognitive deficits [65,67]. Based on these observation it could hypothesized that hyperactivation of HPA axis, chronic inflammation and deficit of neurotrophin signaling can be considered as common pathophysiological mechanisms between depression and Alzheimer's disease.

Comorbid Depression and Schizophrenia

The recognition of depression as a distinct syndrome within schizophrenia is a relatively recent development. The International Survey of Depression in Schizophrenia was designed to evaluate current clinical practice and prescribing trends in the management of the depressive component of schizophrenia. Descriptive and epidemiologic studies have documented a 25% modal occurrence rate of depressive-like syndromes during the longitudinal course of schizophrenia [68], and depressive symptoms have been noted in up to 81% of this population [69]. Despite the high prevalence of depressive symptoms in schizophrenia, however, relatively little is known about their precise nature and course. Emergence of depressive symptoms in individuals with schizophrenia has been associated with poor outcome, increased medication usage, greater morbidity at discharge, increased hospital readmission rates, and early relapse [71-74]. In addition, comorbid depression may contribute to the disturbingly high rates of suicide among patients with schizophrenia: a 10% incidence of suicide in the first 10 years of illness and a 15% lifetime incidence have been reported [75,74], and suicide is considered as the main cause of premature death in this population [76, 77]. Depression, and especially the associated symptom of self-reported or perceived hopelessness, is an important comorbidity factor in the assessment of suicide risk [77]. It has been estimated that up to 20–50% of patients with schizophrenia will attempt suicide, a rate comparable to patients with mood disorders, and over 20 times higher than that in the general population [78,79]. Patients with major depression also have a significantly higher risk of attempting suicide than the general population, with a lifetime risk of around 15% [80,81]. Indeed, correlations are found between depressive symptoms and positive symptoms (mainly hallucinations and delusions) and with negative symptoms [82]. The question of common or distinct physiopathological mechanisms of the two clinical dimensions is under debate.

Comorbid Depression and Epilepsy

Depression is considered as more prevalent among the people with epilepsy as compared with the general population [83,84], with people with poorly controlled epilepsy especially reporting higher rates of depression [85]. The nature of the association is, however, complex. There is some evidence that the relationship between seizure onset and depression onset is bidirectional [86], with diagnosis of epilepsy acting as a risk factor for the onset of depression and depression acting as a risk factor for the onset of epilepsy [87]. There is emerging evidence that this bidirectional relationship between depression and seizures is also evident for those with current

epilepsy [88].   The relationship between epilepsy and depression has been recognized since antiquity, and today it is well established that depressive disorder (DDs) constitute one of the most common psychiatric comorbidities in patients with epilepsy. In epilepsy, however, DDs can

frequently also present with clinical characteristics that differ from those of idiopathic depression

and fail to meet the criteria included in the Diagnostic and Statistical Manual of Psychiatric Disorders-IV. Patients with epilepsy have a higher risk of suicide compared with the general population [89], and those with epilepsy who commit suicide have higher rates of comorbid psychiatric illness [90]. Depression in patients with epilepsy is associated with a lower quality of life [91], with one study finding depression to be the only predictor of quality of life [92]. Patients with epilepsy and depression also use more health resources compared with patients with epilepsy alone [93], and most patients with epilepsy and depression do not have depression diagnosed or adequately treated [94].

The hippocampus plays a critical role in both seizure activity and mood disorders, which suggest that pathology in this area of the brain, might provide a link between epilepsy and depression [95]. Paradoxical features of epilepsy, i.e., seizure-induced increases in hippocampal neurotrophin expression and neurogenesis, suggest that the most important factor in the neurobiology of depression might be the extent to which the hippocampus can adapt appropriately to changes in the environment through alterations in hippocampal synaptic connectivity. Although further research in this area is needed, neuroimaging studies are revealing an underlying brain network of depression in psychiatric patients without a neurological disorder, in keeping with the findings in patients with epilepsy [96]. There are studies linking frontal lobe dysfunction to depression in epilepsy. The latter have emerged from investigations using brain imaging (positron emission tomography (PET) or single-photon emission computed tomography (SPECT)) and neuropsychological batteries. Hermann et al. [97] noted that patients with temporal lobe epilepsy and depression were more likely to perform poorly on frontal lobe neuropsychological tasks, especially with a left-sided seizure focus. Schmitz et al.[98] noted similar frontal changes and localisations using SPECT, and, using PET, Bromfield et al. [99] reported that patients with temporal lobe epilepsy and associated depression revealed bilateral reductions of frontal lobe metabolism, a phenomenon also called 'hypo-frontality'. Although these studies were on a limited number of patients, concordance between the findings supports an anatomical association between temporal lobe epilepsy, depression and frontal lobe dysfunction.

Depression in epilepsy represents a frequently encountered psychiatric complication. It is likely to be related to a number of variables that are both biological and psychosocial. At one time, arguments for the majority of the clinical presentations being explained by psychosocial factors were prominent. However, the literature suggests that the link between depression and epilepsy may not be unidirectional, further supporting the hypothesis of common underlying biological reasons. Depression in epilepsy can be phenomenologically different from the usual forms of depression and it is essential that treating physicians assess for these varied forms as well.

Comorbid Depression and Insomnia

Chronic insomnia is a common complaint and a risk factor for the development of depression. Depression was once classically viewed as a cause of insomnia, but a growing body of epidemiological studies has suggested that insomnia may itself be a risk factor for depression [96,100]. As the relationship between sleep and depression has been explored over the years it has become apparent that each affects the other in a bi-directional manner; yet the question remains as to whether insomnia is a precursor to depression, a premorbid trait, or an independent risk factor [101]. Sleep disturbances (both insomnia and hypersomnolence) are so frequently observed in patients experiencing acute episodes of mood disorders that they form part of the diagnostic and statistical manual (DSM) criteria for these disorders. In particular, patients with depression often complain of difficulty getting to sleep, frequent awakenings during the night, early morning awakening, or non restorative sleep [102,103]. Epidemiological studies have shown that patients with mood disorders exhibit higher rates of sleep disturbance than the general population, and sleep disturbance can continue even during periods of remission [103]. On the other hand, patients with insomnia are up to 10 times more likely to have depression than normal sleepers [104], and individuals with persistent insomnia have a significantly higher risk of developing new-onset depression than those who have no sleep complaints [105].

Occasional studies have reported non-significant or trend changes in cortisol measures [106,107] in insomniac patients. However, the facts that experimental sleep loss in healthy subjects stimulates the HPA axis [108] that insomniac patients normalize their cortisol secretion after successful treatment [109] or that a glucocorticoid receptor antagonist seems effective in treating chronic insomnia [110] strongly suggest a positive relationship between arousal level and HPA function. A similar pathophysiological mechanism has been proposed in major depression: due to maladaptive cognitive functioning, an arousal reaction is maintained despite the removal of the stressful situation [111]. Indeed, stress-induced arousal responses that implicate the HPA axis [112] the locus coeruleus, [113] and the autonomous nervous system, have also been clearly demonstrated in depressed patients.

Low Serotonin levels are believed to be linked with depression, insomnia; when levels of serotonin are brought up to normal, sleep falls into place. Sleep disturbances feature strongly in depression, with insomnia reported by more than 90 percent of depressed patients.3 Altered sleep patterns in depression occur in the phase of sleep associated with memory known as random eye movement (REM) sleep and are considered a marker for major depression [114]. People with low serotonin have been found to spend less time in non-REM sleep, the longest part of the normal sleep cycle. Restless leg syndrome, the annoying muscle twitches and restlessness that interfere with sleep, has also been related to low serotonin functioning [[15]. Sleep disturbance is common in patients with depression, and patients with insomnia are at increased risk for developing depression. The mechanisms for these sleep changes are uncertain but may involve neurological or neuroendocrine systems, altered activity in specific brain regions, and involvement of neural plasticity-related cascades. Before this association can be fully defined, there is still much to learn about the shared neurobiology of sleep and mood.

Conclusion

The high rate of comorbid mental illness need for a comprehensive approach that identifies, evaluates, and simultaneously treats both disorders. Patients with co-occurring disorders often exhibit more severe symptoms than those caused by either disorder alone, underscoring the need for integrated treatment. Careful diagnosis and monitoring will help ensure that symptoms

related to comorbid condition are not mistaken for a discrete mental disorder. Even in people whose comorbidities do not occur simultaneously, research shows that one mental disorders can increase vulnerability to subsequent disorder or constitutes a risk factor for subsequent mental disorders. Therefore, diagnosis and treatment of one disorder will likely reduce risk for the other, or at least improve its prognosis.

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