

DEPRESSIVE DISORDERS AND COMORBIDITY: SOMATIC ILLNESS VS. SIDE EFFECT

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SUMMARY

Background: The rate of comorbid depression and medical illness varies from 10 to 40%. Patients with depressive disorder compared to general population more often have cardiovascular and cerebrovascular disorders, diabetes, irritable bowel syndrome, and some types of tumor. Side effects of mental health medications may appear in a form that is very similar to clinical presentation of somatic illness. Side effects that appear during treatment of depressive disorder, e. g. cardiovascular, gastrointestinal, movement disorders, etc., may provoke certain diagnostic issues regarding origin of such symptoms (somatic illness vs. side effect). The aim of this article is to review literature regarding comorbidity of depressive disorder and somatic illness and to point at possible diagnostic problems in differentiating comorbid somatic illness and side effects of antidepressants.

Content analysis of literature: Literature research included structured searches of Medline and other publications on the subject of comorbidity of depressive disorder and somatic disorders and possible diagnostic problems in differentiating comorbid somatic illnesses from side effects of antidepressants.

Conclusion: Comorbidity between depressive disorder and various somatic disorders appears often. Investigations suggest that depressive disorder is underdiagnosed in such cases. Side effects of antidepressants are sometimes very hard to differentiate from symptoms of somatic illness, which may lead to diagnostic issues. Bearing in mind frequent comorbidity between of depressive and somatic disorders, early recognition of such comorbidity is important, as well as the selection of antidepressant. It is important to recognize depressive disorder in patients with somatic illnesses, as well as somatic illness in patients primarily treated because of depressive disorder.

Key words: depressive disorder - somatic illness - side effects - antidepressants

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INTRODUCTION

Side effects of mental health medications may appear in a form that is very similar to clinical presentation of somatic illness. Side effects that appear during treatment of depressive disorder, e. g. cardiovascular, gastrointestinal, movement disorders, etc., may provoke certain diagnostic issues regarding origin of such symptoms (somatic illness vs. side effect). In the same time, it is a well known fact that comorbidity of depressive disorder and somatic disorders (e.g. cardiovascular) appears often. In the cases of somatic symptoms that appear during therapy with antidepressants psychiatrists have to decide upon the origin of such symptoms and adjust treatment accordingly.

Monitoring of side effects should be undertaken during treatment with antidepressants. Patients who are prescribed antidepressants should be informed of potential side effects. Potential side effects should be considered when selecting an antidepressant (Uzun & Kozumplik 2009). The rate of comorbid depression and medical illness varies from 10 to 40% (Goodnick & Hernandez 2000). Somatic symptoms are the leading cause of outpatient medical visits and also the predominant reason why patients with common mental disorders such as depression and anxiety initially present in primary care. At least 33% of somatic symptoms are medically unexplained, and these symptoms are chronic or recurrent in 20% to 25% of patients (Kroenke 2003). Patients with depressive disorder

compared to general population more often have cardiovascular and cerebrovascular disorders, diabetes, irritable bowel syndrome, and some types of tumor (Jakovljević 2004). The results of the study that examined self-reported physical disorders in people with recurrent depression compared with a psychiatrically healthy control group showed that those in the cases group had significantly higher rates of gastric ulcer, rhinitis/hay fever, osteoarthritis, thyroid disease, hypertension and asthma. The authors concluded that people with recurrent depression show high rates of many common physical disorders, and that, although this can be partly explained by body mass index BMI, shared aetiological pathways such as dysfunction of the hypothalamic-pituitary axis may have a role (Farmer et al. 2008). Unexplained or multiple somatic symptoms are strongly associated with coexisting depressive and anxiety disorders. Antidepressants and cognitive-behavioural therapy are both effective for treatment of somatic symptoms, as well as for functional somatic syndromes such as irritable bowel syndrome, fibromyalgia, pain disorders, and chronic headache (Kroenke 2003). The results of a cross-sectional nationwide epidemiological study on patients with major depression that evaluated the prevalence of somatic symptoms and physicians' attribution of their origin showed that ninety-three percent of patients had at least one somatic symptom fully or partially attributed to depression, and 45% of patients had four to nine symptoms. Painful symptoms, despite being the most frequent, were the least often attributed to depression (fewer than 25% of patients with pain) and significantly more often attributed to a combined origin (Caballero et al. 2008).

The aim of this article is to review literature regarding comorbidity of depressive disorder and somatic illness and to point at possible diagnostic problems in differentiating comorbid somatic illness and side effects of antidepressants.

CONTENT ANALYSIS OF LITERATURE

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CONTENT ANALYSIS OF LITERATURE

Cardiovascular disorders

Cardiovascular diseases appear approximately ten years after appearance of the first depressive episode. Mortality over cardiovascular disorders is 50% higher in patients with depressive disorder than in the general population. It is estimated that depressive disorder is present in over 25% of the patients with cardiovascular disorder and 15-33% of patients with myocardial infarction (Jakovljević 2004). In the study that reviewed data examining the relationships between depression, antidepressants and cardiovascular disease, the results showed that depression and cardiovascular disease are closely associated clinical entities. Depression appears both to cause and worsen cardiovascular disease, and cardiovascular disease is in turn associated with a high incidence of depression. Depression is associated with increased mortality in cardiovascular disease, and after myocardial infarction and stroke (Taylor 2008). In the study that evaluated whether depression is a risk factor for incident myocardial infarction (MI) in Department of Veterans Affairs (VA) patients with rheumatoid arthritis (RA), it was concluded that depressed RA patients, without a history of cardiovascular disease, were 40% more likely to have a heart attack as compared to those without depression. These data demonstrated a rapid (within 6 years) transition to MI following onset of depression in RA patients (Scherrer et al. 2009). In another study that investigated whether incident and non-incident depression after MI are differentially associated with prospective fatal and non-fatal cardiovascular events (post-MI depression was defined as the presence of depression after MI; however, only about one-half of post-MI depressions represent an incident episode, whereas the other half are ongoing or recurrent depressions) the results showed that compared with non-depressed patients, those with an incident depression had an increased risk of cardiovascular events, but not those with a non-incident depression. It was concluded that only patients with incident post-MI depression have an impaired cardiovascular prognosis (De Jonge et al. 2006). Investigations show that post-MI depression is significantly associated with all-cause mortality, that depressive MI patients are at risk for new cardiovascular events and that post-MI depression

was associated with a 2- to 2.5-fold increased risk of impaired cardiovascular outcome (van Melle et al. 2004). One of the important questions from this area of clinical research is the association between therapy of depressive disorder and appearance of cardiac events. A study that assessed whether nonresponse to treatment of post-MI depression is associated with new cardiac events provided preliminary evidence that nonresponse to treatment of post-MI depression may be associated with cardiac events (de Jonge et al. 2007). The choice of antidepressant is very important, especially bearing in mind frequent comorbidity between depressive disorder and cardiovascular disorders. According to previously published data, tricyclic drugs are highly cardiotoxic in overdose and may induce cardiovascular disease and worsen outcome in established cardiovascular disease. Reboxetine, duloxetine and venlafaxine are known to increase blood pressure, while other antidepressants have neutral or beneficial effects in various cardiovascular disorders. Sertraline, fluoxetine, citalopram, bupropion and mirtazapine appear to be safe to use after MI; the use of sertraline, and response to citalopram and mirtazapine may improve mortality. Paroxetine and citalopram appear to be safe to use in patients with established coronary artery disease (Taylor 2008). Cardiovascular disease complications can be related in many cases to platelet clumping produced by medications; reductions in morbidity can be achieved by reducing platelet adhesiveness. Specific results have shown sertraline administration to be safe in the post-MI state. This is a time of depression-induced increases of 200-300% in mortality. Evidence for safe administration of bupropion, as well as the selective serotonin re-uptake inhibitors (SSRIs) fluoxetine and paroxetine, is also available (Goodnick & Hernandez 2000).

Cardiovascular side effects appear during treatment with antidepressants. Palpitations, tachycardia, hypotension, chest pain, extrasystolia, as well as changes in ECG are well known side effects of treatment with antidepressants (Uzun et al. 2005). Cardiovascular side effects may appear during treatment with different classes of antidepressants – e.g. SSRIs, selective norepinephrine reuptake inhibitor (NRIs), tricyclic and tetracyclic antidepressants (TCAs), etc. (Uzun et al. 2005). These cardiovascular side effects may be misinterpreted as comorbid somatic illness, not as a result of therapy with antidepressants, and be treated, accordingly.

Diabetes mellitus

Depression is frequent among diabetic patients and impairs diabetic management (Goodnick & Henry 1995). Cross-sectional research shows a consistent positive association of diabetes and depression (Eaton 2002). According to results of research, the prevalence of anxiety and depression symptoms in patients with diabetes is considerably higher than in general population samples (Collins et al. 2009). According to results of an earlier investigation, the prevalence of depression in diabetics varies from 8.5% to 27.3%, and severity of depression correlates strongly with many symptoms of diabetes mellitus (Goodnick & Henry 1995). In the investigation that aimed to estimate the prevalence of depression among people with diabetes and to examine the association of comorbid depression with lost productivity and health resource utilization in persons with and without diabetes, the results showed that the prevalence of diabetes in the sample was 6.2%, and 13.4% were classified as depressed. Adults with diabetes were two times more likely to have depression versus individuals without diabetes. Those with diabetes and comorbid depression were older, less educated, more likely to be female and physically inactive, less likely to be employed, and married and had more comorbidities. Also, people with diabetes and depression had significantly greater odds of prolonged bed days due to illness, prolonged length of hospital stay (≥ 18 days), and multiple hospital admissions compared with nondepressed diabetic patients (Vamos et al. 2009). Recent research has shown that depression may predict incident diabetes. In the study that aimed to investigate if symptoms of depression and anxiety precede the onset of diabetes or vice versa and to examine if mediating factors may explain such associations, the results showed that diabetes did not predict symptoms of depression or anxiety. Symptoms of depression and anxiety emerged as significant risk factors for onset of type 2 diabetes independent of established risk factors for diabetes, such as socioeconomic factors, lifestyle factors, and markers of the metabolic syndrome. The comorbidity between depression and anxiety may be the most important factor (Engum 2007). In the study that examined the association of depression, anxiety, and stress with Type 2 diabetes (T2DM) in Bahrain, higher proportion of T2DM patients were found in the mild-moderate and severe-extremely severe depression, anxiety, and stress

groups. Anxiety, depression, and stress were associated with T2DM. The results suggested a positive contribution of T2DM to increased depressive and/or anxiety and/or stress disorders among the patients examined, thereby recommending counseling for T2DM patients (Almawi et al. 2008). The results of another study that aimed to determine whether type 2 diabetes contributes to the presence of depressive and anxiety disorder diagnoses in low-income adults with hypertension, asthma, and/or arthritis suggested a positive contribution of type 2 diabetes to increased rates of depressive and/or anxiety disorders in patients with hypertension, asthma, and/or arthritis and support prior research that type 2 diabetes may serve as an indicator of depression and anxiety in low-income adults treated in primary care clinics (Thomas et al. 2003). Again, bearing in mind these data, the choice of antidepressants is very important. An increase of catecholamines appears to increase glucose while both reducing insulin release and reducing sensitivity to insulin that is available. In contrast, increases in serotonergic function by increased precursor, increased release, or blocked metabolism and blocked reuptake in contrast seem to increase sensitivity to insulin and reduce plasma glucose (Goodnick 2001). The appearance of major depression and diabetes mellitus has been successfully treated with fluoxetine, sertraline and nortriptyline (NTI), however, NTI may lead to a worsening of glucose indices due to its noradrenergic specificity (Goodnick & Hernandez 2000). Clinically, MAOI use is limited by the possible severity of the induced hypoglycemia, induced weight gain, and required diets. The tricyclic antidepressants may lead to hyperglycemia, to an increase in carbohydrate craving, and impaired memory. Serotonin selective reuptake inhibitors may be hypoglycemic (causing as much as a 30% decrease in fasting plasma glucose) and anorectic (causing an approximately 2-lb decrease), while possibly improving alertness. To maximize response of both depression and diabetic disorder, one should consider the SSRIs in preference over the TCAs (Goodnick & Henry 1995). In diabetic neuropathy, perhaps due to the fact that catecholamines and serotonin may both be implicated in pain pathways, dual-action antidepressants appear more effective at lower doses than do specific serotonergic agents. In diabetic neuropathy without depression, the best choices among non-TCAs may include sertraline,

citalopram, and perhaps, venlafaxine (Goodnick 2001). Diabetes appears to increase the risk of developing depression; therefore early detection and treatment intervention provide the best protective mechanisms available against the effects of depression on diabetes outcomes, and a psychological service provision for people with diabetes is needed (Khamseh et al. 2007).

Asthma

There is evidence that asthma is associated with increased frequency of psychiatric symptoms and mental disorders (Valença et al. 2006). In the study that aimed to assess the frequency of anxiety and depressive disorders in a sample of asthmatic outpatients and observe if there is any relationship between this comorbidity and the severity of asthma the results showed that 43.5% patients met criteria for at least one psychiatric diagnosis. The most frequent diagnoses were major depression (24%), generalized anxiety disorder (20.9%) and panic disorder/agoraphobia spectrum disorders (17.7%). It was concluded that the results support the high morbidity of anxiety and depressive disorders in asthmatic patients, independent of the severity of asthma (Valença et al. 2006). The results of another investigation that aimed to examine the relationship between youth-reported asthma symptoms, presence of anxiety or depressive disorders, and objective measures of asthma severity among a population-based sample of youth with asthma showed that the presence of an anxiety or depressive disorder is highly associated with increased asthma symptom burden for youth with asthma (Richardson et al. 2006).

Cancer

Comorbidity of depressive disorder and cancer was investigated in the previous studies, also.

In the study conducted between 2001 and 2003, that compared the rates of major depressive disorder between long-term cancer survivors (LCSs) and people without cancer histories in a nationally representative cross-sectional multistage cluster survey sample, the National Comorbidity Survey-Replication (participants with cancer diagnoses at least 5 years before the interview were considered LCSs) the results showed that LCSs do not appear to have elevated rates of major depressive disorder. However, they may experience greater impairment from major depressive disorder compared to those without cancer (Pirl et al. 2009).

The results of the investigation that aimed to review the available literature on depression in women with metastatic breast cancer in terms of prevalence, potential risk factors, and consequences, as well as pharmacological and psychological interventions, showed that the prevalence of depression appears to be especially elevated in patients with advanced cancer. Despite the fact that depression appears to be associated with numerous negative consequences, this disorder remains underdiagnosed and undertreated. Both pharmacotherapy and psychotherapy have been found to treat effectively depressive symptoms in this population, but cognitive-behavioral therapy appears to be the most cost-effective approach (Caplette-Gingras & Savard 2008). Head and neck cancer patients experience among the highest rates of major depressive disorder of all oncology patients with an incidence of 15-50%. Correct diagnosis is critical to expeditious management. Oncologists are not always adept at making the diagnosis as medical and treatment side effects can mimic the signs and symptoms of depression (Lydiatt et al. 2009). Another investigation aimed to present a comprehensive summary of the existing research literature related to prevalence and correlates of depression in adult patients with head and neck cancer to establish a knowledge base for future research. The results showed that prevalence rates of depression are high at diagnosis, during treatment, and in the first six months following treatment, and mild to moderate depression may continue for three to six years after diagnosis. Certain patient demographic characteristics (e.g., marital status, education), symptoms, and specific time points in the illness trajectory (e.g., time of treatment) were correlated with depression (Haisfield-Wolfe et al. 2009). A Swedish/Norwegian head and neck cancer study was designed to assess prospectively the levels of mental distress and psychiatric morbidity in a heterogeneous sample of newly diagnosed head and neck cancer patients. Approximately one-third of the patients scored as a possible or probable case of a major mood disorder at each measurement point during the study year, with new cases of anxiety or depression at each time point. The anxiety level was highest at diagnosis, while depression was most common during treatment. Patients with lower performance status and more advanced disease reported higher levels of mental distress and more often scored as a probable or possible cases of psychiatric disorder. The prevalence of psychiatric morbidity found in this study empha-

sizes the importance of improved diagnosis and treatment (Hammerlid et al. 1999).

Dermatological disorders

The physical symptoms of psoriasis include itching, irritation, burning/stinging, sensitivity, and pain. Patients also suffer psychological distress, especially as a result of stigmatization, self-consciousness, and embarrassment, which can in turn affect employment and social activities. Relatively high rates of depression are reported in patients with psoriasis (Van Voorhees & Fried 2009). A number of previous investigations have confirmed association between various dermatological diseases and depressive disorder. The results of the study conducted in Turkey, that investigated the frequency of depressive symptoms in psoriasis vulgaris and lichen planus and to evaluate the relationship between the Beck depression scores and the Psoriasis Area and Severity Index (PASI) scores of subjects with psoriasis vulgaris showed that subjects with psoriasis vulgaris, lichen planus and healthy controls had depression scores of 58%, 53% and 20%, respectively. The study confirmed the importance of depressive symptoms in two common dermatological diseases (Akay et al. 2002). The results of the cross-sectional study that investigated the frequency of anxiety and depression in patients with psoriasis showed that there was an association of psoriasis vulgaris with anxiety and depression (Nasreen et al. 2008). Vitiligo affects one to four percent of the population, regardless of age, race or sex. People with this disorder may experience emotional stress, particularly if vitiligo develops on visible areas of the body, such as face, hands, arms, feet, or on the genitals. The cross sectional study conducted in Karachi, that investigated the frequency and pattern of psychiatric disorders amongst patients with vitiligo showed that major depressive illness, was the most frequent psychiatric illness followed by generalized anxiety, mixed anxiety and depression, social phobia, agoraphobia and sexual dysfunction (Ahmed et al. 2007). It has been proposed that depression plays a role in how psoriasis affects quality of life. In the study that investigated the role depression plays in how patients experience psoriasis (cross-sectional study was conducted in 2005, 265 adults with prevalent psoriasis were included), 32% of all participants screened positive for depression. Only 16.5% of those with high depression scores were currently treated for

depression. Both dissatisfaction with antipsoriatic treatment and illness-related stress were highly associated with depression. It was concluded that patients with high subjective distress and low objective measures of psoriasis should be evaluated for depression (Schmitt & Ford 2007). Some psoriasis treatments have demonstrated improvements in symptoms of psoriasis as well as in measures of depression and health-related quality of life. Physicians managing patients with psoriasis must be aware of the psychological effects of psoriasis and need to use a multifaceted approach to managing this disease, focusing on both the physical and psychological aspects (Van Voorhees & Fried 2009).

Different dermatological side effects may appear during therapy with different classes of antidepressants. Skin rash, itching, acne and urticaria are side effects that appear during treatment with SSRIs. Skin rash and photosensitivity may appear during therapy with TCAs (maprotiline, klomipramine). Skin rash may also appear during therapy with moclobemide. (Uzun et al. 2005).

Neurological disorders

Depressive disorder appears frequently in patients with some neurological disorders. For instance, it was estimated that 26-34% of patients with cerebrovascular diseases and about 40% of patients with Parkinson's disease have depressive disorder (Jakovljević 2004).

The investigation conducted in China, in 2004, that investigated the prevalence of depressive and/or anxiety symptoms in patients with some neurological diseases (face-to-face interview was used in data collection together with the self-completed Hospital Anxiety and Depression (HAD) scale for depressive and/or anxiety symptom, were screened) showed that the prevalence rates of "self-scaled" depressive and/or anxiety symptoms were 19.5%, 24.1% and 21.9% respectively in patients with stroke, Parkinson's disease and epilepsy. Among cases with "self-scaled" depressive and/or anxiety symptoms, the prevalence rates of depressive and/or anxiety symptoms were 50.8%, 73.1% and 38.6% respectively; less than 17% of subjects had obtained a diagnosis of depressive disorders and had been treated but only 4% of the subjects having obtained a diagnosis of anxiety disorders and been treated prior to the study (Fu et al. 2006). An association between depression and headache is well established, but the specificity to migraine is

unclear. The results of a study that investigated the specificity of the association of depression and migraine (people with recurrent depression were compared with psychiatrically healthy controls) suggested that not only is there a general relationship between headache and depression but also that among people with recurrent headache there is a specific association between depression and migraine with aura (Samaan et al. 2009). An investigation of the association between psychiatric disorders and headache syndromes conducted in Switzerland showed that migraine with aura was associated with hypomania, recurrent brief depression, and all of the anxiety disorders, whereas only the phobic disorders and panic were elevated among subjects with migraine without aura. Similar findings emerged for the longitudinal data, with the exception that major depression was associated with both subtypes of migraine. Prospective study data indicated that the age of onset of anxiety disorders generally preceded that of migraine and that the onset of affective disorders in the majority of comorbid subjects followed that of the onset of migraine (Merikangas et al. 1993). Another investigation conducted in Switzerland showed a strong association between migraine and depression. The association between migraine and the anxiety disorders was even stronger than that for the affective disorders. The combination of anxiety disorder and major depression, but not pure anxiety disorders, nor pure depression, were significantly associated with migraine (Merikangas et al. 1990). Regarding neurologic disorders, there is controlled data showing the safety and efficacy of citalopram, sertraline and fluoxetine in post stroke depression. Parkinson's disease has been associated frequently with depression, as might be expected from its characteristic dopamine deficient state. The agents that can block re-uptake of dopamine i.e., TCAs, have been effective in comorbid depression with Parkinson's disease (Goodnick & Hernandez 2000). Beside comorbidity between depressive disorder and neurological disorders, different neurological side effects may appear during therapy with antidepressants. Movement disorders appear during therapy with antidepressants. Extrapyramidal symptoms (EPS) may appear during therapy with SSRIs. Tremor may appear during therapy with different classes of antidepressants. During therapy with amoxapine parkinsonism, akathisia and tardive dyskinesia (TD) may appear (Uzun et al. 2005).

Gastrointestinal disorders

Gastrointestinal disorders appear in comorbidity with depressive disorder, also.

An investigation conducted in China, in 2007, that explored the prevalence and physician's recognition of depression and anxiety disorder in gastrointestinal out-patients showed that gastritis and gastrointestinal dysfunction were the major diagnoses in patients with depression and/or anxiety disorders; the rates were 30.6% and 26.4% respectively. The rate of identification of depression and anxiety disorder by physicians was 2.8%. The authors concluded that gastrointestinal out-patients have a high prevalence of depression and anxiety disorder and the rate of identification by physicians was very low (Jiang et al 2009). Another investigation conducted in China in 2004, that assessed the prevalence of anxiety and depressive symptoms among patients with different somatic diseases showed a high prevalence and low diagnosis and treatment rate of depressive and anxiety symptoms in these patients (Fu et al. 2007). Gastrointestinal side effects are also well known side effects that appear during therapy with different classes of antidepressants (SSRIs, NRIs, TCAs, etc.), such as dry mouth, opstipation, diarrhea, nausea, abdominal pain and vomiting (Uzun et al. 2005).

CONCLUSION

Comorbidity between depressive disorder and various somatic disorders appears often. Investigations suggest that depressive disorder is underdiagnosed in such cases. Side effects of antidepressants are sometimes very hard to differentiate from symptoms of somatic illness, which may lead to diagnostic issues. Bearing in mind frequent comorbidity between of depressive and somatic disorders, early recognition of such comorbidity is important, as well as the selection of antidepressant. It is important to recognize depressive disorder in patients with somatic illnesses, as well as somatic illness in patients primarily treated because of depressive disorder.

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