

Depression in the Diabetic Patient

Lucreția ANGHEL¹

Monica BOEV*²

Cristina STĂNESCU*³

Simona MITINCU CARMFIL⁴

Liliana LUCA*⁵

Carmina Liana MUȘAT⁶

Anamaria CIUBARA⁷

¹ Faculty of Medicine and Pharmacy, "Dunărea de Jos" University, 800216, Galați, Romania,

² Faculty of Medicine and Pharmacy, "Dunărea de Jos" University, 800216, Galați, Romania, monica.boev@ugal.ro

³ Faculty of Medicine and Pharmacy, "Dunărea de Jos" University, 800216, Galați, Romania,

dr.cristinastanescu@gmail.com

⁴ Faculty of Medicine and Pharmacy, "Dunărea de Jos" University, 800216, Galați, Romania,

⁵ Faculty of Medicine and Pharmacy, "Dunărea de Jos" University, 800216, Galați, Romania, chiroscaliliana@gmail.com

⁶ Faculty of Medicine and Pharmacy, "Dunărea de Jos" University, 800216, Galați, Romania,

⁷ Faculty of Medicine and Pharmacy, "Dunărea de Jos" University, 800216, Galați, Romania,

Abstract: *Depression is a common emotional state in humans, which is sometimes triggered by stressful events and certain physical and/or mental conditions that may occur and may increase the body's vulnerability to various types of depressive disorders, causing sometimes organic changes difficult to quantify and to treat. Depressive conditions are major clinical problems that occur throughout life and often require a specialized treatment, but the use of the antidepressant compounds is often endangered by the risk of formidable side effects, requiring to stop the treatment or to use medicine doses that cannot determine the desired therapeutic results. These are reasons for the impressive expansion of the research on the depression types, with emphasize on etiological and etiopathogenetical studies, allowing the discovery of compounds with good therapeutic potential and an appropriate pharmacological profile to reduce the side effects. Diabetes (diabetes mellitus) is a major public health problem, with increasing costs and frequency in recent years. Late diagnosis, inadequate treatment, lack of ongoing monitoring or ignorance of the disease can have serious consequences for the health of that individual, his family and his community. The mental state of a patient with diabetes is different from one moment to the next and varies with the stage of the disease and the appearance of various complications. The stress of chronic illness, the pressure to have a lifestyle and a diet according to medical recommendations, sadness, anger and even denial of the disease, are feelings experienced by patients with diabetes at least once in their lives.*

Keywords: *diabetes, depression, cognitive impairment, treatment compliance, hyperglycemia.*

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Introduction

It is known that in the case of diabetes, in any form should be diagnose, there is a close association, obviously quantitative, between the risk factors and the occurrence and/or evolution of the disease. This relationship has allowed the establishment of exact criteria for initiating the prevention of the disease among the population groups considered to be at risk of developing the disease and not only (Ala Hani Izzat et al. 2021). Diabetes is a condition with a large extent and sometimes with an impressive morbidity. The severe negative impact on those affected by the disease, on the patients relatives, but also on the group where they live and work, is ultimately reflected on the whole society. (Pelin et al. 2017)

The risk factors for diabetes have an important social component (lifestyle, behaviors / attitudes, comorbidities), and either eliminating or reducing their intensity leads to proven benefits of specialized interventions. (Balan et al. 2017) Moreover, the existence of a potentially adequate implementation of the benefits of prevention at the Community level, may lead to a more rigorous control of new cases and to the follow-up of those already registered, on population groups with a great diversity of common characteristics (age criteria, socio-economic status, associated diseases, diseases caused by the diabetes evolution). (Anand et al. 2000) It should be noticed that in the case of this exhaustive diseases of the modern world, characterised by a large number of cases and complications, there are many additional benefits when intervening on a large scale then on the individual level. Let's just mention the educational impact on numerically significant groups, the costs reduction of the of materials used and the human force involved in prevention, as well as the social support that interpersonal discussions can determine. (Voicu et al. 2020)

Depression and diabetes coexist in a large percentage of patients, and these two conditions can be initiated and conditioned by each other, regardless of which of them was initially diagnosed. Untreated depression can be triggered at any time, at least by impaired eating habits and/or behavior, changes in glucose tolerance and blood glucose levels. The self-awareness of the patient on its chronic illness, its long-term evolution, burdened by the need for permanent treatment and the danger of formidable complications, some with permanent or even lethal nursing potential, leads in a large number of cases to major depression. (Anghel et al. 2022)

Overview

Clinical depression is a concept that differs symptomatically from the manifestations described quite often as depressive states (sadness, disappointment, dysphoria, demoralization); sometimes considered as normal reactions to some events that occur throughout life.

The clinically manifest depression can be described as a feeling of sadness that occurs for no reason, the person in question finding no reason to perform daily activities. The depressed patient is permanently tired, sad, nervous and irritable, unmotivated and apathetic. The intensity of these symptoms and the prolongation of the periods in which the patient recognizes these symptoms, makes the clinical depression a much more serious condition compared to the depressive reactions encountered in response to certain problems and which are limited in intensity and extent. The result can be the development of negative thinking and the frequent onset of addictions to various substances of abuse. All this can culminate in the subject's suicidal behaviour. (Van Praag et al. 2005)

Some psychiatric conditions can be confused with clinical depression, because many of the signs and symptoms of these conditions can be recognized in depressed patients, but also in patients suffering from dementia or psychosis.

Clinical depression, also called major depression, is an affective disorder that has been known in the past as melancholy (the "black ball" being one of the "four essential moods" described by Galen) (Baldessarini RJ, 2006). Along with the bipolar disorder, more commonly known as manic-depressive psychosis, it falls into the group of major affective disorders. The population frequency of major affective disorders had increased alarmingly in the recent years, which clearly requires the initiation or the continuation of studying to identify and to monitor the evolution of these entities, for a better prevention of their occurrence or for determining the type of the mental disorder, so that the prescribed treatment may have the expected effectiveness. (Tatu et al. 2021)

Major depression is a condition with heterogeneous manifestations, so the classification, definition, characterization and classification of its forms are often difficult to expose in a form that does not give rise to confusion (Gheorghe et al. 2003). Absolutely characteristic clinical manifestations that allow the diagnosis to be established, of overt clinical depression are the significantly depressed mood of the patient and the obvious decrease in the intensity of the body's functions, as well as its ability to react to internal and / or external stimuli. It should be noted that often in a case of major depression, the signs and symptoms overlap with those we

recognize in patients with anxiety disorders. Virtually any form of anxiety should be discussed with a clear differential diagnosis of a depressive syndrome (Baldessarini RJ et al. 2006, VanPraag HM et al. 2005). Moreover, the profound impairment of the mood, the substrate of the onset of the depressive reactions, can be associated not only with the clinical depression but also with psychosis, a situation in which the patient has disorganized thinking and distorted perceptions on the environment to which he belongs.

Classification of depressions

According to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) and APA-IV (American Psychiatric Association), depression can be found as pure syndromes or in combination.

Pure depressive syndromes are major depression (clinical) and minor depression (dysthymia). Bipolar disorder and cyclothymic disorder are associated with depression and mania.

Perhaps the simplest classification is based on a presumed origin of depression. From this point of view, we distinguish (Fauman MA et al. 2002; Potter WZ et al. 2004, Hollister LE et al. 2004):

- reactive depression, also called secondary; is the most common form of depression and occurs as a result of unpleasant impacts (chronic pain, various chronic diseases, among which diabetes occupies a prominent place, trouble)
- endogenous depression, genetically determined; in this form of depression, the biochemical changes that occur cause an inability to feel satisfaction and pleasure or to react appropriately to everyday events.
- depression in association; occurs in the bipolar affective disorder (depressive episode of the manic-depressive syndrome)

According to the International Classification of Diseases (ICD-10) there are several distinct forms of depression:

- depression with melancholy notes
- atypical depression (mood swings or paradoxical anhedonia) and positive thinking
- depression with psychotic notes (eg visual and / or auditory hallucinations)

Melancholy is characterized by anhedonia (lack of pleasure), morning worsening of symptoms, anorexia, and guilt is present.

Etiopathogenesis of the major depression

The importance of the biogenic amines role in the pathogenesis of major depression has been a subject of study for researchers since the middle of the last century, the amino or biological hypothesis of the pathogenesis of major depression (Baldessarini RJ et al. 2006, LE et al. 2004) being argued by pharmacological and / or clinical studies.

There are two neuroanatomical circuits that have a definite implication in the onset of depression: the cortico-thalamo-limbic circuit and the cortico-thalamo-pallido-striato-limbic circuit. The first includes anatomical structures in the prefrontal cortex, thalamic nuclei and amygdala, the second also involves the striatum and globus pallidus. Changes in the interconnective relations between these two circuits and/or the existence of some cerebral structural anomalies may determine a depressive status, due to the occurrence of a deficit of functionality.

In addition to these circuits, it is obvious the intervention of the three monoaminergic systems, noradrenergic, serotonergic and dopaminergic in the pathogenesis of the depression, these systems interacting one with each other, and the activity of the serotonergic structures (5-HT - ergic) determining the reactivity of the noradrenergic neurons. This interaction determines a so-called heterotransmission of the neurotransmission, meaning that dysfunctions of one monoaminergic system determine the consecutive dysfunction of the other two (Gheorghe MD et al. 2003). Among these systems the serotonergic has the primary role, noradrenaline and dopamine being undoubtedly the essential links in the affective disorders occurrence of.

In depression the central level of serotonin, noradrenaline and dopamine decreases, the role of antidepressant drugs being the normalization of these neurotransmitters values. This concept is the basis of pharmacological therapy for different types of depression.

It is known that serotonin deficiency causes a decrease in depression, anxiety, panic and phobia (Gheorghe MD et al. 2003; Stahl SM et al. 1997), while noradrenergic deficiency results in motor inhibition (Anand A et al., 2000). When the two deficits coexist, depression is associated with severe anxiety, suicidal behavior (caused by decreased serotonin levels) and high frequency of relapses (periodic exacerbations of the chronic disease due to changes in the normal amount of norepinephrine). In his article on the neurobiological substrate of depression (Gheorghe et al. 2003) he states that serotonin and norepinephrine can be considered "true markers of depression", a statement justified by the fact that the deficiency of the two amines is maintained during periods of disease remission.

Dopamine has a less obvious role in the onset and development of depression, the psychotic reactions being determined by this neurotransmitter via the mesolimbic and mesocortical pathways (Shireen E, Haleem DJ et al. 2005). Although the amine hypothesis of the pathogenesis of clinical depression seems to be a simplistic explanation of the phenomena that lead to the onset of this condition, many of the studies that aim to discover new compounds with antidepressant properties are based on this idea. In fact, the serotonin and norepinephrine involvement in depression is confirmed by the vast majority of antidepressants used today in therapy, medicines which influence at least one stage of the cascade of the events that result in the synthesis of these amines or in their release from special storage sites. As in anxiety, in depression, hyperactivation of the hypothalamic-pituitary-adrenal axis increases corticotropin-releasing hormone (CRH) levels, stimulates glucocorticoid release, and increases ACTH secretion (Lydiard RB et al. 2003; Serradeil-Le Gal C et al. 2002; Dinan TG et al. 2001). Vasopressin is a neuropeptide localized in the paraventricular nucleus of the hypothalamus and also acts in complementary ways producing effects similar to those of CRF, so that in both anxiety and depression the level of cortisol increases significantly. (Anghel L. et al. 2022, Lydiard RB et al., 2003). These findings not only indicate that the pathogenesis of anxiety and depression are intimately linked, but also open up a new field of research for the discovery of new antidepressants.

Understanding this cascade of events, it is clear that normalizing the functionality of the hypothalamic-pituitary-adrenal axis can be accepted as a method of treating depressive states. Compounds that would cause decreased levels of cortisol, CRH and / or vasopressin may have, at least theoretically, an antidepressant and anxiolytic effect. The hypersecretion of some cytokines (α -interferon, interleukins 1 and 6) causes an increased activity of the hypothalamic-pituitary-adrenal axis (with consequent increase in cortisol secretion) and influences the levels of the biogenic amines (norepinephrine, serotonin and dopamine). Due to these effects, as well as to the induction of a syndrome known as “sick behavior” (in which we recognize symptoms superimposable on those in depression, eg anhedonia, social isolation), it can be stated that cytokine hypersecretion is a mechanism by which the stress (cortisol) induces depression (Gheorghe MD et al. 2003; Miller AH et al. 2000).

In addition to the factors mentioned above, thyroid function also has an obvious relevance in the depression pathogenesis (hypothyroidism accentuates depressive behavior, therefore the normalization of glandular

function can lead to therapeutic benefits in depression) (Jackson M et al. 1998, Stefanopol et al. 2021).

Treatment of depression

Depression in all its forms is considered to be one of the most common psychic conditions which frequency and severity seem to note significant increase lately. In this affective disorder treatment we recognize pharmacological maneuvers, the application of special types of psychotherapy or a combination of the two.

Among the main factors which determine the choice of the therapeutic method it may be mentioned the causes that led to the onset of the condition and the patient's compliance on one or another of the possible treatment strategies.

Before initiating treatment, the diagnostic evaluation should reveal the etiology of the depression type to be treated, meaning that the patient's symptoms are due either to a mental disorder or they are based on a physical condition. Once the etiology has been identified, it is necessary to quantify possible other comorbidities (alcoholism, other mental illnesses, debilitating chronic diseases). Therefore, different types of depression can be treated by psychotherapy and / or pharmacologically. (Baroiu L. et al. 2020)

Psychotherapy in depression

As non-pharmacological treatment options we can mention behavioral therapy, cognitive therapy, cognitive-behavioral therapy, all of which may or may not be associated with relaxation techniques. (Stefanopol I.A. et al. 2022, Stahl SM et al. 1997)

Behavioral therapy is based on the principles of classical Pavlov conditioning and the operant conditioning imagined by Skinner. This type of therapy starts from the idea that a change in behavior will lead to a change in mental state.

Cognitive therapy is a short-term therapy used mainly to treat characteristic symptoms and signs of anxiety and depression. The main feature is the use of the homework.

The combination of the characteristic elements of these two therapy types favors the faster appearance of positive results in the vast majority of patients. And if some relaxation techniques (meditation, deep breathing, a cup of hot tea, self-massage, melotherapy) are added to this combination, the improvement of the clinical situation is obvious.

Antidepressants

Most of the antidepressant compounds act on the metabolism of the monoaminergic neurotransmitters and on their characteristic receptors. Of these neurotransmitters the most common support for antidepressants are serotonin and norepinephrine.

Baldessarini et al., in 2006, classifies antidepressants into: monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (ADTs).

Potter's classification (Antidepressant Agents 2004) is based on the chemical structure of these compounds and indicates that in addition to the above-mentioned categories there are also the heterocyclic antidepressants. These are considered the second and third generation, the first generation of antidepressants being the tricyclic antidepressants, in Potter's opinion.

However, heterocyclic antidepressants are related to SSRIs, not differing in potency, but in their action on other structures (receptors, transport mechanisms).

The main indications for antidepressants are: depression, some anxiety disorders, nocturnal enuresis and chronic pain (Potter et al. 2004, Baroiu et al. 2021). Although there is clear evidence that major depression is the main indication for antidepressants, the depressive episodes of the manic-depressive psychosis also benefits from the therapeutic intake of some of the compounds with antidepressant effect, usually associated with the lithium salts.

Anxiety disorders that require treatment with antidepressants, panic and obsessive-compulsive disorder, generalized anxiety and social phobia respond well to this therapy. Venlafaxine and duloxetine are two of the newest antidepressants and they act on improving the chronic pain, especially of those undiagnosed, but also those encountered in cancer, arteriopathy, insufficiently treated diabetes, or pain detected late or with long-term evolution. There are also other indications of for the antidepressants, including bulimia (fluoxetine) and attention deficit (ADHD), the latter benefiting in addition to imipramine and desipramine of the therapeutic intake of atomoxetine, an atypical antidepressant that selectively inhibits noradrenaline reuptake (Potter et al. 2004, Constantin et al. 2020)

Depression and diabetes

Diabetes is a major public health problem today. Globally, there are currently an estimated 463 million patients with diabetes. The estimate for 2045 is over 700 million patients with diabetes. The most affected age group

is 40-59 years, with 79% of all patients being adults. Most of them live in underdeveloped and developing countries. Approximately 90% of patients have diabetes type 2. It is also estimated that 232 million patients are undiagnosed. (Busila, et al. 2017)

The costs of diagnosing, treating and monitoring patients with diabetes in 2017 are estimated to have exceeded \$ 800 billion. Diabetes is a chronic condition that requires continuous monitoring, daily treatment and proper administration long life. The evolution is marked by the appearance of numerous complications. Diabetes is considered the leading cause of chronic kidney disease, blindness and non-traumatic limb amputations. Type 2 diabetes is a major risk factor for cardiovascular disease: hypertension, dyslipidemia, obesity, renal impairment, endothelial insufficiency, hypercoagulability or proinflammatory status. (Baroiu. et al. 2022)

There are studies that try to etiopathogenetically link two of the most personally but also socio-economically disabling disease of the today's society. Common factors for diabetes and depression have scientifically been identified, patients with a form of diabetes developing an increased prevalence of behavioral and affective disorders. The prevalence was statistically significant in population groups with common characters, the groups being randomized according to a multitude of factors (including age groups, sex, race, living and activity environment, geographical area).

Diagnosis of diabetes

There are specific parameters on the basis of which the positive diagnosis is established. A patient is diagnosed with diabetes if they have:

- specific symptoms (polyuria, polydipsia, weight loss) and a blood glucose level ≥ 200 mg / dl or at least two elevated basal blood glucose levels (≥ 126 mg / dl), or blood glucose ≥ 200 mg / dl 2 hours after 75 g glucose (oral glucose tolerance test) or (since 2011) $HbA1c \geq 6.5\%$ (48 mmol / mol), with glycated hemoglobin (HbA1c) fraction of hemoglobin to which glucose binds non-enzymatically and which is equivalent to the average blood glucose level 2-3 months prior to dosing.

Etiological classification of diabetes mellitus

1. Type 1 diabetes: autoimmune type (1A) and idiopathic type (1B)
2. Type 2 diabetes
3. Specific types of diabetes - genetic defects in β -pancreatic cell function (eg Maturity Onset Diabetes of the Young, MODY 1 - 4)
 - genetic defects in the action of insulin
 - exocrine pancreatic diseases (eg chronic pancreatitis, pancreatic adenocarcinoma)

- endocrine diseases (eg acromegaly, hyperthyroidism, Cushing's disease)
- drugs and chemicals (eg glucocorticoids, nicotinic acid, diazoxide)
- infections (eg congenital rubella)
- rare forms of immune-mediated diabetes (stiff man syndrome)
- genetic syndromes sometimes associated with diabetes (eg Down, Klinefelter, Turner)
- gestational diabetes mellitus - any of the forms of hyperglycaemia found for the first time during pregnancy and which must be explored and reclassified after birth (values that meet the criteria for DM will be considered manifest clinical diabetes)

Risk factors in diabetes

Analyzing as many aspects as possible of this disease that marks the evolution of health status in larger population groups and which is of an impressive diversity, the researchers established that there are significant risk factors that determine the occurrence of the disease, influencing at the same time the symptoms evolution and intensity. These risk factors can be classified from various points of view, the easiest to understand being the following classification:

"Traditional" risk factors for diabetes and intermediate hyperglycaemia

- unchangeable factors - age, sex, family history, history of gestational diabetes, polycystic ovary
- modifiable factors - smoking, dyslipidemia (HDL cholesterol, triglycerides), eating habits, high blood pressure, sedentary lifestyle, obesity (especially abdominal), previous intermediate hyperglycemia, intrauterine environment, inflammation.

We cannot influence the first category, we can only recognize, record and follow them. The intervention on the second category may improve many symptoms, by eliminating some of the risk factors and/or decreasing the intensity of others, consequently improving the patients health and their quality of life. It may also prevent the occurrence of complications due to the chronic evolution of a disease that is making more and more victims. (Dumea et al.2022, Constantin et al. 2020)

In an extended study (Marin et al. 2020) it is specified that two scientifically documented hypotheses can be described regarding the occurrence of the depression signs in patients treated with antihyperglycemic medication, who have developed or not diabetes complications. One of the hypotheses shows the involvement of the biochemical factors in the onset of the depressive reactions in diabetics, which are more intense and longer

lasting compared to those suffering from other conditions. This is an argument for a possible common substratum common to the two diseases (Baroiu et al. 2021) trigger at least depressive reactions.

A group of British researchers recently published in the journal *Diabetes Care* a study whose findings showed that, in addition to changes in micro- and macrocirculation, diabetic patients who developed depression also have a significant exacerbation of characteristic inflammatory markers. Thus, the hypothesis of triggering depression by inflammation was raised, but a direct causal relationship cannot, however, be clearly demonstrated. If an inflammatory reaction clearly occurs in the pancreatic system, the question of whether or not the depressive disorder has occurred before the onset of the affective disorder is evident. What is certain is that in the case of depressed patients, the measurement of biological constants clearly highlights the existence of inflammation in the body. Another conclusion of the above study is that patients with diabetes have a much higher susceptibility to depression, and depressed people may develop over time, probably due to eating disorders altered by affective disorder, at least intermediate hyperglycemia, the very cause of the onset of diabetes.

The incidence of the depression in patients with some form of diabetes has been found to be much higher than in the general population. It should be noted that in many clinical situations, previously diagnosed depression, can trigger diabetes over time, because of the weight gain due to drastic changes in eating behavior. Consequently, although the etiopathogenetic link between the two diseases is far from clear, a possible causal relationship in two ways should be noted (Nemtoi et al. 2019)

Moreover, a number of antidepressant compounds have been found, most with a mechanism of action involving serotonin (fluoxetine, paroxetine, milnacipran, citalopram, escitalopram), which had led to a depression decrease, a reduction in fasting blood glucose and glycosylated hemoglobin. This is an argument in favor of the correctness of the hypothesis that antidepressants, especially by modulating serotonin levels in the body, have some influence on the metabolic control, so successfully treating depression may be reflected in a positive change in the prognosis of diabetes and its complications. (Baroiu et al. 2018)

Also pharmacologically speaking, regarding the antidepressants it has been noted that "duloxetine is the newest antidepressant, being administered for the particularly high specificity in case of pain in patients with diabetes and depression." This is another finding that pleads for the undeniable connection between these two so common and disabling conditions of the present. There are enough reasons why this study was initiated, hoping that

we may answer to some of the questions that arise in almost any discussion that analyzes the possible evolution of patients diagnosed with diabetes and affective disorder, regardless of which one preceded the other (Lydiard et al. 2003, Tatu et al. 2021)

Conclusions

Psychiatric illnesses such as schizophrenia, anxiety, bipolar disorder are among the top 20 causes of disability. Statistical estimates suggest that by 2030, depression will become a major cause of disability worldwide. About 15-30% of patients with cardiovascular disease are diagnosed with depression. (Busila et al. 2017, Anghel et al. 2022) Depression-type mental disorders are still undiagnosed and not properly treated in different categories of people with diabetes. The coexistence of depression and diabetes is obviously due to various factors some of them being the impressive psychosomatic impact of the disease, the cerebral and microvascular damage at different secondary levels of diabetes, a potential genetic susceptibility, and various neuroendocrine abnormalities. We consider that the examination of the mental state is necessary and as important as the examination of the somatic state, at each stage of monitoring the diabetic patient. Given the negative impact of psychiatric impairment on quality of life and adherence to treatment, careful psychiatric examination is necessary, especially when new complications occur or when changes in treatment regimen are required.

The pathogenic link between diabetes and clinically manifest depression is focused on stress, which activates the hypothalamic-pituitary-adrenal axis, with regulation by the autonomic nervous system and the release of proinflammatory cytokines, resulting in increased insulin resistance (Chirita et al, 2012).

Dementia and / or depression clearly influence the clinical course of patients with type 2 diabetes.

Depression, even if mild to moderate, and especially when is clinically manifest, can complicate the progression and the prognosis of any form of diabetes. This development is probably due to the loss of the diabetic patient's self-care. Although there have been demonstrated the obvious benefits of a broad interdisciplinary approach of the diabetic patients, there are still many barriers to integrating all methods of treating depressive disorders. Extensive future studies are needed to identify the full range of emotional problems associated with diabetes and / or chronic complications, as well as the ways to prevent them. In this context, the importance of the psychologist in the diabetes patient care team should be emphasized.

Many patients with diabetes and psychological impairment remain undiagnosed psychiatrically even though patients with diabetes are known to be a vulnerable population for psychological impairment. They should be evaluated at the initial diagnosis of diabetes as well as regularly for psychological and psychiatric conditions such as excessive stress, fear, anxiety, depression, obsession, phobia, hostility and treated as early as possible. Clinical studies have found that anxiety, bipolar disorder, and schizophrenia are the most common causes of mental disorders that require hospitalization for psychiatric treatment. Statistics suggest that mental disorders will become a major cause of disability in the diabetic patient worldwide in the coming years.

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