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Antidepressant Drug Use in Patients with Diabetes Mellitus Type 1 – The Effect of Medication on Mental Problems and Glycemic Control

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1. Introduction

1.1 Diabetes and mental health

Diabetes mellitus is a severe chronic life-long disease, which is diagnosed in about 6% of the population. In many aspects it is considered a psycho-somatic disease. Some mental disorders, especially depression, are more common in diabetic patients compared to the rest of the population. Diabetes mellitus affects psyche of the patients, but at the same time mental state of the patients influences the course of diabetes. The causal links are different depending on the type of diabetes and mental disorder. Nonetheless, the association is observed on a level of emotions and mental processes, but also in biochemical and hormonal aspects. In this article we will focus only on diabetes mellitus type 1.

From the moment of diagnosis, diabetes introduces substantial changes in life of a patient. His life-style should be adjusted to them in order to make the course of the disease as favorable as possible. This disease demands maintaining a regular daily regime regarding food and physical activity. The patients must watch their body-weight and measure blood glucose several times a day. Blood pressure and blood lipid level belong to strictly monitored parameters in diabetic patients. Their increase in combination with diabetes significantly influences the cardio-vascular risk of the patients.

Diabetes mellitus type 1 is caused by a selective destruction of beta cells in islets of Langerhans by an immunologic process in genetically predisposed individuals. It is specific by onset in younger age and dependence on insulin since the beginning of the treatment. [Bartoš, 2003]

1.2 Diabetes and depression

The relationship between depression and diabetes is bilateral. Recently, they have been identified as reciprocally interacting risk factors – the presence of diabetes deteriorates the prognosis of depression, while the presence of depression worsens the prognosis of diabetes. [Höschl, 2005]

Prevalence of a more or less severe depression is approximately double in patients with diabetes compared to a general population. On average, it is present in 14% (9 to 27%) of diabetics in the Czech Republic. [Češková, 2004] Depressive reactions in diabetic patients show a higher recurrence tendency in comparison with general population. Depression is more frequent in women. Depression usually follows the diagnosis of the disease in this type of diabetes. Diabetes as a primary disease is typically superimposed by depression as a reactive state. Depression is usually a result of exposure to psycho-social factors that are related to hardship caused by chronic disease. It is necessary to look for associations at the level of emotions and mental processes. For many patients it is difficult to maintain a regular life-rhythm. Their roles in social environment may change as well. Moreover, the patients often lose energy more rapidly. It often takes years until a man accepts and fixates a change in his lifestyle to which he is accustomed. It is even possible that the internal and mental manifestations of diabetes share a common origin. It can be explained through a correlation of insulin resistance and changes in central serotonin system. [Horáček, 1997] Hyperglycemia, hyperinsulinemia and impaired peripheral insulin receptor sensitivity is often found in patients with depression. Decreased insulin sensitivity is associated with lower serotonergic activity. [Höschl, 2004]

Many chronic autoimmune diseases, including the insulin-dependent diabetes mellitus, are accompanied with symptoms of depression. However, a reversed association is also possible. Autoimmune diseases are generally more common in depressed rather than non-depressed population. One of the predisposing factors of onset of an autoimmune disorder is a serious life event that can alter the cell-mediated as well as the humoral immunity.

Furthermore, symptoms of depression often overlap with poorly controlled diabetes symptoms. It is necessary to look for the etiologic connections here as well. The cardinal symptoms include low stamina, fatigue hypomimia, change in body weight, polymorphic somatic complaints, impaired concentration, etc. Even an increase in blood glucose itself can lead to a significant change in mood, including sadness and increased fatigue [Polonsky, 1999]

Several studies concerning comorbidity of type 1 diabetes and depression identified risk factors of depression development; chronic somatic comorbidity and polypharmacy, female gender, higher age, solitary life, lower than secondary education, lower financial status, cigarette smoking, obesity, diabetes complications and a higher glycosylated hemoglobin [Engum, 2005; Bell, 2005; Hermanns, 2005; Katon, 2004]

Studies dealing with consequences of comorbidity of diabetes and depression claim that depression leads to a decrease in metabolic control of diabetes, reduction of treatment response and diet measures effect, deterioration of the quality of life and increase in healthcare costs. [Lustman, 2005] In addition, depressive symptoms have an impact on later somatic problems associated with poor glycemic control, because they affect the patients' ability to care for themselves and follow diet. [McKellar, 2004] Blood glucose regulation is also significantly impaired in depressed patients, compared to individuals without depression. Insufficient regulation of blood glucose can adversely influence patient's state of mind and his response to antidepressant drugs. The incidence of microvascular complications (especially retinopathy, but also neuropathy, nephropathy, and sexual dysfunction) and macrovascular complications is also higher in diabetic patients with depression. This is related to poor metabolic control in depressed compared to the non-depressed diabetic patients.

Furthermore, it was proven that a depression increases mortality in patients with diabetes; the probability of death within 10 years is significantly increased in these patients. [Zhang, 2005]

1.3 Antidepressant drug treatment in type 1 diabetic patients

Psychiatric treatment of diabetic patients is focused on treatment of their mental disorder with respect to diabetes, and on improvement in quality of life with disease. Furthermore, the psychiatrist may try to positively influence the glycemic control. The literature is unequivocal regarding the effect of a psychiatric treatment on glycemic control. Some studies declare its benefit in glycemic control improvement, however, most of them do not confirm it. An important randomized clinical trial demonstrated that extended treatment of patients with diabetes mellitus and severe depression or dysthymia lead an improvement in mental state. However, the improvement in depression itself from the antidepressant therapy did not lead to any improvement in blood glucose, or any significant change in glycemic hemoglobin level. [Katon, 2004 b]

Antidepressant drugs are most commonly administered psychiatric medication. They are used for therapy of mental disorders, as well as e.g. treatment of painful diabetic neuropathy.

Several research efforts regarding the effect of antidepressant drug treatment on glycemic control in depressed diabetics were conducted. According to a study by Lustman et al. the glycosylated hemoglobin decreases during the open treatment phase and remains significantly reduced during depression-free maintenance, regardless of the fact whether the patients are treated by an antidepressant, sertraline in this case, or by placebo. [Lustman, 2006] Another study with sertraline demonstrated that a specific minor population of diabetics with low financial income showed a significant reduction in glycosylated hemoglobin after the initiation of pharmacologic treatment of depression in comparison with placebo. [Echeverry, 2009] Elder diabetic patients with depression, presented in another work, who went through the antidepressant treatment were less likely to die within 5 years compared to depressed diabetics without the treatment. [Bogner, 2007]

The antidepressant drugs are also used as co-analgesics (adjuvant analgesics) in the treatment of painful peripheral diabetic polyneuropathy. They are even more effective than common analgesics. The effect on pain is direct, through the intervention in neurotransmission (serotonin and noradrenaline) and indirect (antalgic) acting through a change in attention distribution, lowering the pain threshold, reducing emotional accompaniment and reducing stress response brought about by the pain. The analgesic effect of antidepressants arises more rapidly than the antidepressant effect, already at lower doses and is independent of the presence of depression in the patient. The antidepressant drugs are the treatment of the first choice in a constant burning pain. [Doležal, 2006]

When treating a diabetic patient with antidepressants, it is important to notice how the medication influences the blood glucose, body weight, blood pressure, and renal functions. If it influences glycemia, it is necessary to advise the patient ahead that a dosage change in insulin or oral antidiabetic drugs may be necessary. The body weight increases the most after tricyclic antidepressants and mirtazapine use and the least after SSRI, MAOI a trazodone. An increase in blood glucose was described in association with TCA, a decrease after SSRI and MAOI.

1.4 Use of individual antidepressant drug groups

The longest used tricyclic antidepressants (TCA) decrease insulin secretion, increase blood glucose, appetite for sweets and body weight. Amitriptyline from this group is used even for diabetic painful peripheral neuropathy treatment.

Selective serotonin reuptake inhibitors (SSRI) decrease blood glucose (even 30% decrease in fasting glycemia has been described), temporarily reduce body weight (most often described in fluoxetine), however, they increase body weight in long-term. They reduce cholesterolemia and serum triglycerides. Citalopram and sertraline have a low potential in creating drug interactions. CYP 3A4 inhibition by fluvoxamine may disrupt metabolism of oral antidiabetic drugs. CYP 2C9 inhibition by fluoxetine, fluvoxamine or sertraline can interfere with the metabolism of sulfonylurea and tolbutamide. [Češková, 2004] In combination they can lead to hypoglycemic states, as these antidepressants cause an increase in the level of the abovementioned antidiabetic drugs.

Trazodone is a postsynaptic 5HT₂ blocker and a weak serotonin reuptake inhibitor (SARI). It has considerable hypnotic effects and does not have a negative influence on metabolism. [Svačina, 2004]

Moclobemide from the Monoamine Oxidase Inhibitors (MAOI) group reduces blood glucose and can thus lead to hypoglycemic states. On the other hand, it usually does not increase body weight.

Norepinephrine dopamine reuptake inhibitor (NDRI) bupropion is neutral regarding the influence on body weight. Higher doses in combination with insulin lower seizure threshold (the risk of epilepsy is increased especially in patients with concomitant mental anorexia). This effect is eliminated in the SR form. Bupropion attenuates sexual dysfunction and facilitates smoking cessation. Both effects are of great importance in diabetic patients, as they suffer from diabetes-associated sexual dysfunction and have elevated cardiovascular risk from smoking.

Noradrenergic and specific serotonergic antagonist (NaSSA) mirtazapine induces sedation and can therefore be used in insomnia. However, it increases appetite and body weight, which is undesirable in diabetic patients. Furthermore, it can lead to an increase in glycosylated hemoglobin and thus deteriorate a long-term glycemic control. [Šabaková, 2008]

From the group of serotonin norepinephrine reuptake inhibitors (SNRI), it is necessary to mention venlafaxine and duloxetine. Venlafaxine does not increase body weight. A small, but statistically significant increase in fasting glycemia was found when using duloxetine in comparison with placebo. [Fava, 2004] Venlafaxine [Kunz, 2000; Rowbotham, 2004] as well as duloxetine [Goldstein, 2005; Raskin, 2005] have a well-established effect on chronic neuropathic pain.

St John's wort extract (hypericin) does not increase body weight, however, there is a high risk of drug interactions.

Summary of antidepressant drug use is presented in table 1.

Antidepressant group (representative)	Important effects in diabetic patients	Use in neuropathy treatment
TCA (amitriptyline)	Increase glycemia, increase body weight	+
SSRI (citalopram, sertraline)	Reduce glycemia, increase body weight	-
MAO (moclobemide)	Reduce glycemia, do not increase body weight	-
NDRI (bupropion)	Do not increase body weight	-
NaSSA (mirtazapine)	Increase body weight and glycosylated hemoglobin	-
SNRI (venlafaxine, duloxetine)	Do not increase body weight, duloxetine increases fasting glycemia	+
St. John's wort (hypericin)	Do not increase body weight, risk of drug interactions	-

Table 1. Antidepressant drug use in diabetic patients

2. Case studies

The following case studies are pointing out patients with depression anxiety problems and diabetes mellitus type 1, where the antidepressant treatment was successful regarding mental state improvement and positive effect on glycemic control.

We chose to convey the information in form of case reports, because in spite of the fact that numerous studies concerning the influence of antidepressant drug treatment on glycemic control in diabetes mellitus have been performed, their conclusions differ or are even contradictory. This work should point out the diabetics, in whom the antidepressant treatment led to an improvement in glycemic control. They are the evidence that the use of specifically selected antidepressant drugs is suitable in diabetic patients, owing to the fact that any, even temporary improvement in glycemic control is desirable.

This article is focused on type 1 diabetic patients, as this type of diabetes is less represented in studies that deal with diabetes comorbidity, mental problems and their treatment using psychiatric medication.

Patients with e.g. a change in insulin dose or insulin delivery mode were excluded in order to clearly demonstrate the effect of the antidepressant drugs. Only the patients who did not undergo any significant change in chronic internal medication, which could have a significant effect on the change in glycemic control, are presented in the case reports.

Mental state of the patients was evaluated by a clinical psychiatric examination and on the basis of patients' complaints regarding their subjective problems. The general mental state of the patients was evaluated using Clinical Global Impression - Severity (CGI-S), which is widely used for global clinical impression assessment of psychiatric patients. The scale ranges from 1 to 7 points, where 1 means "no apparent signs of illness" and 7 denotes extremely expressed symptoms. Data is acquired from information regarding behavior of the patient and a change in his state in the course of the treatment. [Busner, 2009]

Long-term glycaemic control was evaluated according to the glycosylated hemoglobin level. Its values are presented according to DCCT/NGSP calibration. Other somatic and metabolic parameters that are regularly monitored in diabetic patients were also recorded, specifically body weight, blood pressure and blood level of triglycerides and cholesterol. Monitoring of these parameters served for assessment of a potential effect of administered psychiatric drugs on metabolic functions in diabetic patients.

Patient No. 1 was born in 1963. She has been treated with type 1 diabetes since 1987, i.e. when she was 24 years old. She has been treated by intensified insulin regimen since 2008. From chronic diabetic complications, she suffers from lower-extremity polyneuropathy and cardiovascular autonomous neuropathy. Furthermore, she is treated for arterial hypertension, iron deficiency anemia, and dyslipidemia. She is obese. In 2009, she went through a transient ischemic attack and suffers from migraine ever since. Her family history is positive regarding diabetes in grandfather from mother's side, negative regarding mental disorders. The patient works as a staff at a gas station. She is married, has 5 children, her marriage is conflicting.

She was first referred to a psychiatrist in March 2010, i.e. in her 48 years, because of long-term poor glycaemic control and putative influence of mental and family problems.

Already at the first contact, the patient reported long-term deteriorated glycaemic control and put it herself in connection with family problems that distressed her. She felt weak for about half a year, nothing amused her, she did not care about anything, nothing could make her happy, and she resigned to important things. She described her problems in relationship with her partner and acknowledged that she was overburdened by the care of her household with five children. She did not mind working, she was engaged in charity activities. CGI-S – 4 points.

In contact she seemed depressed, in tension, with paradoxically psychomotor agitation and inadequate and excess emotionality. She answered in extensive sentences and often could not adhere to her topic. The accentuation of personal histrionic features was apparent.

A diagnosis of a moderately severe depressive phase based on histrionic features of personality was set and a treatment with antidepressant drug with active substance sertraline was initiated. The daily dose of 100 mg was reached through a gradual titration 50 mg daily for the first week.

Mental state of the patient has completely restituted within the first month of antidepressant use. Mood normalized, the patient started enjoying things she liked or liked doing, tension and irritation disappeared, the psychomotor pace stabilized. Excessive emotionality within personality prevailed, but the patient was satisfied with her state. CGI-S – 2 points. Although the situation in her family did not improve, she had more strength to face the problems. Her mental state is stabilized to date. She attends our psychiatric out-patient department every three months. The antidepressant dose was continued owing to persisting unsatisfactory situation in her family.

Her glycaemic control improved significantly at the beginning of the psychiatric treatment. Glycosylated hemoglobin decreased from 9.4% at the first contact in March 2010 to 8.0% in May. It rose to 8.8% in October, 9.2% in January 2011, and returned to 9.4% in May 2011.

Psychological status (treatment)	time	HbA1c
moderately severe depressive phase (sertraline treatment initiation)	03 / 2010	9.5
without depression	04 / 2010	
full compensation	05 / 2010	8.1
continuation of medication	10 / 2010	8.8
	01 / 2011	9.3
continuation of cooperation	05 / 2011	9.5

Table 2. Timeline of mental state and glycosylated hemoglobin level development - patient No.1

Body weight of the patient was 111kg at the beginning of the treatment (March 2011), it was 115kg in the end (May 2011). There was thus a small increase in the course of the treatment observed.

Blood pressure of the patient was stable, 125/70 torr since the beginning of the treatment. It was not affected by the antidepressant drug treatment.

Her serum triglyceride level was 3.66 mmol/l at the beginning of the treatment, it was 2.33 mmol/l after 6 months, it increased to 3.10 mmol/l 10 months after the beginning of the treatment and 5.98 mmol/l in the end of the treatment. The psychiatric treatment thus led to a gradual increase in serum triglyceride level. Serum cholesterol level was 5.25 mmol/l at the beginning of the treatment and remained unchanged in the course of the treatment.

The depressive disorder completely normalized owing to the antidepressant medication. Her mental state is now long-term stabilized due to the treatment. The long-term glycemic control of the diabetes rapidly improved at the beginning of the psychiatric treatment, however, it returned to its original value within 15 months.

The case of this woman confirms that depressive disorder improvement and stress reduction lead to a decrease in glycemia. The antidepressant drug itself could have played a role in glycemic control improvement. Active substances from the SSRI group may cause a decrease in glycemia, which in turn can lead to a decrease in glycosylated hemoglobin level. The effect is probably only temporary. The initial effect of a new attitude towards her therapy, i.e. psychiatric treatment initiation, can partly participate in the glycemic control improvement.

Patient No. 2 was born in 1964. She was diagnosed with diabetes mellitus type 1 in 1991, i.e. when she was 27 years old. She has been treated by intensified insulin regimen since 2003. She gradually developed chronic complications of diabetes; diabetic peripheral polyneuropathy, non-proliferative diabetic retinopathy, moreover, she was treated with a diabetic foot syndrome of neuropathic etiology in past. Furthermore, she is treated with hyperfunction of the thyroid gland and arterial hypertension since 1996. She also suffers from cervical pain. She underwent appendectomy in 1998. Her family history regarding diabetes is positive; her grandmother had a diabetes type 2. Her family history is positive regarding mental disorders; her brother and father are alcoholics. The patient is married and has two adolescent children. She is a certified shop assistant. She had worked as a ceramic printer, but she retired to a disability pension a few months before the psychiatric treatment commencement, which relieved her from overloading. She is only partly

content with the relationships in her family; she feels that her children do not need her anymore and her husband devotes too little time to her. She is thus forced to look for her own activities.

She was referred to a psychiatric care in May 2005, i.e. when she was 41 years old, by her diabetologist for symptoms of anxiety and depression. At the time of referral, she was already taking an antidepressant for about half a year. She was given 100mg of sertraline by her diabetologist with an insufficient effect leading to an impaired sexual appetite as an adverse effect.

At the first visit at the psychiatrist she complained about a long-term perceived inner tension, tearfulness, inhibitedness, easy fatigability, feelings of uselessness, general dissatisfaction and sexual problems. Moreover, she regarded her diabetes disease as a heavy burden that restricted her at all times and destined her to be monitored by others. She was aware of dependence on her husband and children, which further exhausted her. Her mood was already more positive since she was taking sertraline.

In contact she seemed subdepressed, inhibited, tired, with a psychomotor retardation, slightly blunted affect, hypobulia and apathy. She answered after increased pauses before answering. CGI-S - 4 points.

Diagnosis of a moderately severe depressive phase and accented dependant personality features was made. Her medication was changed to bupropione 15mg daily because of dominant inhibitedness and fatigability. At the following visit after a month, the patient reported an improvement in sexual appetite, but increased nervousness, tension and anxiety, she was tearful and felt that she could not deal with daily life. The antidepressant was therefore changed to trazodon titrated gradually up to a dose of 150 mg a day. CGI-S - 4 points. The patient came for the next visit after 3 months, i.e. in September 2005. She reported a relief from depression, anxiety and fatigue. She also talked about an ambivalent attitude of her husband to the treatment, who perceived his wife as unnaturally sedated. The problems with sexual appetence and tearfulness prevailed. CGI-S - 4 points. Trazodon daily dose was increased to 200mg.

The patient reported a decline of all mental problems at a visit next month (October 2005), her mental state was stabilized. CGI-S - 2 points. The following month (November 2005), she complained of enhanced anxiety, nervousness and distractedness. She had no depressive moods, sleeping disorders or problems in sexual field. She complained of diarrhea and abdominal cramps of unknown etiology for several months and thus a lower appetite and a significant body weight loss. CGI-S - 3 points. The previous daily dose of trazodon 150mg was resumed and the treatment was augmented by sulpiride at a daily dose of 50mg (since November 2005). The digestive problems gradually disappeared, however, increased fatigability prevailed. CGI-S - 2 points. Trazodon was gradually withdrawn and only sulpirid treatment continued (since April 2005). The patient consequently reported a complete amelioration of mental problems and disappearance of digestive problems and was satisfied with her medication. She insisted on its continuation in spite of the fact that it caused a mild menstrual disorder. Stability of her state lasted until a visit in October 2007 despite the fact that her 18 year-old daughter delivered her first granddaughter, which was a significant strain.

At her following visit in December 2007 she complained about depressive moods and worsening of feelings of refusal from her daughter and husband that were producing fear from future and loneliness. CGI-S - 3 points. Sertraline treatment at a dose of 50mg per day was initiated, owing to objective deterioration of the depressive disorder and a concern about further mood depression. Consequently, the mental state improved significantly again, the patient even started to look for own activities more and was generally satisfied with her life. CGI-S - 1 point. This lasted from January until September 2008. Meanwhile, the patient tried to discontinue sertraline, but she felt more even-tempered while using it and therefore decided to use it chronically.

In September 2008, the patient came for a visit complaining about subjectively deteriorated short-term memory and concentration. CGI-S - 2 points. She was educated about cognitive training and was given a preparation with an extract from Ginkgo biloba at a daily dose gradually increased to 160mg. The dose was reduced to 80mg after approximately 6 months and continued until October 2010. All this time she felt psychically stabilized, even though she developed some serious somatic problems associated with diabetes - Charcot osteopathy.

Psychological status (treatment)	time	HbA1c
moderately severe depressive phase (sertraline use)		
depression (bupropione initiation)	05 / 2005	9.2
depression (trazodon initiation)	06 / 2005	
	08 / 2005	8.5
improvement (trazodon dose increase)	09 / 2005	
further improvement	10 / 2005	
anxiety, diarrhea (sulpirid initiation)	11 / 2005	
	03 / 2006	8.1
without problems	04 / 2006	
	05 / 2006	8.7
	12 / 2006	8.2
	06 / 2007	8.7
	09 / 2007	8.2
without problems	10 / 2007	
depression (sulpiride + sertraline)	12 / 2007	
without problems	01 / 2008	8.3
	04 / 2008	7.6
	07 / 2008	8.3
memory deterioration (ginkgo initiation)	09 / 2008	7.8
	04 / 2009	8.6
	06 / 2009	8.5
	09 / 2009	8.9
	03 / 2010	8.5
without problems (sulpiride + sertraline)	05 / 2010	
	07 / 2010	8.1
cooperation continuation	10 / 2010	8.5

Table 3. Timeline of mental state and glycosylated hemoglobin level development - patient No.2

At a visit in October 2010, she agreed on a gradual withdrawal of the nootropic agent. CGI-S - 1 point. She requested chronic use of the other treatment. At present, the patient comes for psychiatric visits every six months and feels mentally stabilized despite lasting somatic problems.

Her glycemic control at the first psychiatric visit (i.e. May 2005) was 9.1% HbA1c. The value decreased to 8.4% in August same year, and 8.0% in March 2006. The value was higher again (8.7%) in May 2006. The glycosylated hemoglobin decreased to 8.1% again in December 2006. It was 8.7% in June 2007, 8.1% in September 2007, 8.2% in January 2008, 7.6% in April, 8.2% in July, and 7.8% in September. The value was 8.6% in April 2009, 8.4% in June, and 8.9% in September. The glycosylated hemoglobin was 8.4% in March 2010, and 8.0% in July. The glycosylated hemoglobin was 8.4% at the last blood examination in October 2010.

Body weight of the patient was 79 kg at the beginning of the treatment (May 2005), 80 kg after 3 months, than it decreased to 72 kg and stayed until May 2006. It increased to 77 kg in September 2006 and 80 kg in April 2009. It was 82 kg in the end of the follow-up in February 2011. The body weight of the patient thus decreased at the beginning of the treatment, it returned to its original value after 4 years and subsequently kept gradually increasing.

Blood pressure of the patient hovered around 120/60 torr during the whole treatment. It did not change due to antidepressant therapy.

Her serum triglyceride level was 0.76 mmol/l at the beginning of the treatment and 0.59 mmol/l in the end of the follow-up, it did not change owing to the psychiatric treatment. Serum cholesterol level was 5.58 mmol/l at the beginning of the treatment and 5.95 mmol/l in the end of the follow-up, there was no significant change due to the psychiatric treatment.

Mental state of the patient improved, although very slowly, since the beginning of the treatment. It was necessary to change repeatedly her psychiatric drugs for insufficient effect and intermittent decompensations of her mental state. Even her glycemic control was slightly improving at the beginning, subsequently, a tendency of glycosylated hemoglobin to fluctuate was observed at times of varying mental state compensation as well as in long periods of mental stability. Her mental state, despite periods of subcompensation, is significantly improved after several years of psychiatric treatment than it was before treatment commencement. Glycosylated hemoglobin level is also lower than prior to treatment despite its fluctuations. It did not return to the original high value.

This case demonstrates the influence of fluctuating mental compensation on fluctuation in long-term glycemic control, although it is not possible to observe a direct temporal relationship. It is acknowledged that a change in glycosylated hemoglobin always occurs with a delay after a change in condition of a patient, i.e. treatment change, attitude towards treatment change, better self-monitoring, etc. The delay duration ranges usually in weeks. No exact correlation of individual changes in time can be observed in the relationship of mental compensation and glycemic control.

Patient No. 3 was born in 1966. She was diagnosed with diabetes mellitus in 1989, i.e. in her 23 years. Regarding organ complications of diabetes she suffers from diabetic nephropathy and retinopathy. She was also diagnosed with pulmonary fibrosis, she went through a lung biopsy in 1989. Her condition is stable with no functional impairment. She has been treated

for iron deficiency anemia since 1995. Her grandfather had a diabetes mellitus type II. Regarding psychiatric family history, her sister had collapse states and epilepsy in her childhood and her father suffers from dementia. The patient is married and has three children. She was just after maternity leave at time of psychiatric treatment. She did not work, she took care after her ill father. She was employed as a secretary in past. She was content in her partner life, but she was overburdened by care of her father and had conflicts with her mother-in-law.

She herself requested psychiatric care for feelings of anxiety/depression and painful diabetic polyneuropathy in May 2005, i.e. in her 39 years. She reported progressing feelings of anxiety, fear of closed-in places and tight clothing, tearfulness, sleeping disorder, hypobulia, constipation and headache for about one and a half year on the first examination. She felt overburdened, hurried and tired. She was losing her sexual appetite.

A psychomotor retardation, depressive mood, apathy, hypobulia and labile emotionality was evident in contact. The patient was significantly influenced by an apparent inner tension. CGI-S – 5 points.

A diagnosis of anxious depressive disorder was made and sertraline treatment at a daily dose of 100mg with a gradual titration from 50mg per day was started (May 2005).

At a visit the following month (June 2005) the patient reported an alleviation from anxiety. She was less agitated and more satisfied, she did not get disturbed so easily, but her anxiety prevailed in stress situations. The headache disappeared almost completely. CGI-S – 2 points. She was in an even better condition in July 2005; even sleeping and sexual appetite normalized. She was able to manage better her stress situations and was able to look for their solutions in more tranquility. In September, she complained about a slight deterioration of anxiety as a reaction to a stress at home, she was tearful and subdepressive. CGI-S – 3 points. Sertraline dose was therefore increased to 150mg per day. Consequently, her mental state stabilized again.

In January 2006, the patient complained about gastric problems that lasted for about a week and came always after sertraline ingestion. The problems comprised of a stomachache, nausea and even vomiting. From the psychiatric point of view, her mental stability prevailed, anxious states came occasionally and she was able to solve them easily. Withdrawal of the psychiatric medication was impossible owing to the short duration of mental state stabilization. Sulpirid at a daily dose of 50mg was added because of tendencies of the patient to somatize her problems.

Then in February, the patient complained about deterioration of her problems with vertigo, which she had had before, but had never spoken about. Meanwhile, her diabetologist changed the medication to 25mg of amitriptyline per day. After all examinations performed during hospitalization to find the origin of the vertigo, it was found to be psychogenic. The change in medication caused a mental decompensation of the patient, the symptoms of anxiety, tearfulness and inability to solve common problems returned, the headache came back. Moreover, she was terrified by her mental state deterioration, it was completely unexpected for her and she lost confidence in the medication. CGI-S – 4 points. Amitriptyline was continued and the dose was increased to 50mg per day. The patient was educated in

detail regarding the action of the medication and encouraged to endure until onset of antipsychotic medication effects. She felt already well at a visit next month, in March 2006; she was without depression and headache, the vertigo attenuated. CGI-S - 2 points. In May, she was without depression and sleeping disorder, however the headache worsened slightly and occasionally she had an episode of anxiety, which was difficult to manage. Sometimes she was more easily distressed. CGI-S - 3 points. The dose of amitriptyline was thus increased to 75mg per day. In July 2006, the mental state of the patient was well compensated, she was without depression, sleeping disorder and headache, occasional anxiety was well tolerated. CGI-S - 2 points. The patient was satisfied and asked for termination of psychiatric consultations. She wished to continue the medication under a supervision of her diabetologist. She promised she would come for a psychiatric visit in case of mental state deterioration or for treatment withdrawal after about one year. In the end, amitriptyline was discontinued by her diabetologist in January 2008, because of fatigability and insufficient effect on pain in lower extremities from diabetic painful polyneuropathy.

Glycosylated hemoglobin was 14.6% prior to psychiatric treatment commencement in May 2005. It was 14.1% in June, 12.4% in November. It was 10.3% in February 2006, 11.4% in May, 10.8% in August and 10.9% in December 2006. Glycosylated hemoglobin was 9.7% in March 2007, 10.5% in June, and 14.3% again in October 2007.

Psychological status (treatment)	Time	HbA1c	CGI-S
anxiety depression problems (sertraline treatment initiation)	05 / 2005	14.6	5
anxiety only in stress	06 / 2005	14.1	2
Improvement	07 / 2005		2
anxiety improvement, subdepression (sertraline dose increase)	09 / 2005		3
without problems	11 / 2005	12.4	3
gastric problems (sulpiride initiation)	01 / 2006		3
vertigo (amitriptyline initiation), deterioration	02 / 2006	10.3	4
Improvement	03 / 2006		2
deterioration (amitriptyline dose increase)	05 / 2006	11.4	3
without problems, cooperation termination	07 / 2006		2
	08 / 2006	10.8	2
	12 / 2006	10.9	
	03 / 2007	9.7	
	06 / 2007	10.5	
	10 / 2007	14.3	
medication withdrawal	01 / 2008		

Table 4. Timeline of mental state and glycosylated hemoglobin level development - patient No.3

Body weight of the patient was 78 kg at the beginning of the treatment (May 2005), it was gradually increasing to 80 kg during the year, in the course of the next year it was decreasing to 74 kg in the end of the year (January 2010).

Blood pressure of the patient ranged from 120/70 to 130/70 torr during the whole course of the treatment. It did not change owing to the antidepressant drug treatment.

The serum triglycerides level was 1.66 mmol/l at the beginning of the treatment, 2.2 mmol/l in the end, there was therefore a mild increase observed. Serum cholesterol was 5.68 mmol/l at the beginning of the treatment and 5.84 mmol/l in the end, the increase due to psychiatric treatment was thus only insignificant.

Mental state of the patient slowly improved, it was necessary to change medication because of insufficient effect, but also due to the fact that the patient reported only a part of her problems, negated the rest and these emerged later as chronic problems. Later, the patient refused to attend psychiatric out-patient clinic. She explained it by good stability of her state. She wanted to be followed only by her diabetologist, where the psychopharmacological treatment continued for another year and a half and was then withdrawn. The mental state in a long-term is not stable, neither on medication, nor after its withdrawal, however, she did not come back to psychiatrist's care. Her glycemic control improved significantly at the beginning of the treatment, however, it returned to its original value after the antidepressant withdrawal.

In this case the effect of supportive counseling was quite substantial, although it was not the case of systemic psychotherapy. The patient was in a difficult life situation and apart of medication she was receiving the support she needed. It can also be seen here, that the patient did not have the insight into her mental problems, it was necessary to keep asking about them repeatedly.

Patient no. 4 was born in 1970 and suffers from diabetes mellitus type 1 since 1996, i.e. since his 26 years. He did not have any organ complications diagnosed at time of psychiatric treatment. He is also treated for arterial hypertension and hypercholesterolemia. There was no family history of diabetes nor mental disorder. The patient works a clerk, is single, childless, lives alone.

He has been in psychiatric care since December 2005, i.e. since he was 35 years old. He was referred by his diabetologist for about 2 years of incompliance in diabetes treatment, active refusal of maintaining the daily regimen and hospitalization for treatment correction. The diabetologist referred him to psychiatry for a suspicion of a mental illness.

The patient admitted a deterioration of his mental state lasting for about 2 years on examination. He is afraid of a large number of people, gets easily distressed, is emotionally labile, has depressive moods with feelings of hopelessness that come unreasonably. He has his insight into the fact that he lacks the motivation for diabetes treatment. This condition lasts for about 2 years already. He used to cope with his disease well before. At present he has conflicts with the doctors at the department of Diabetology.

In contact he was tense, anxious, with labile emotionality, depression, even resonant mood, apathetic. CGI-S – 5 points.

A diagnosis of anxiety depression disorder was made and a sertraline treatment at a dose gradually up to 100mg per day was initiated. At a visit two weeks after, the patient felt better, he was subdepressed, less anxious, but he complained that he was not motivated by any life goal; he lives from one day to another, is indifferent. CGI-S – 3 points. He felt significantly better in January 2006, he reported better cooperation with doctors at the

department of Diabetology. He was getting insight into his share in the conflicts. CGI-S - 2 points. The mental state of the patient was completely restituted in February, he felt happy, he perceived occasional fluctuation of his mood as natural, he reported significant improvement in his glycemic control. He was very satisfied with the improvement and it motivated him to further improve the cooperation. Again, he found meaning in good treatment and control of his basic disease. CGI-S - 1 point. At a visit in August 2008, he reported that apart from further improvement he is successful in losing weight - he gained a few kilograms in previous two years. After mutual agreement, the patient was referred to diabetology out-patient clinic with set medication. He should come for a psychiatric check up if needed. He did not come and spontaneously discontinued the medication in the end of 2007, supposedly for financial reasons.

His long-term glycemic control at the beginning of the treatment was very unsatisfactory, the glycosylated hemoglobin level was 10.7% in January 2006, it decreased to 9.3% already in March, 9.6% in June, 9.9% in October. In January 2007 the level was 10.1%, followed by 9.9% in April, 9.6% in August, 10.1% in November, and finally 10.8% in March 2008.

Psychological status (treatment)	Time	HbA1c	CGI-S
anxiety depression problems (sertraline treatment) initiation	12 / 2005		5
Improvement	01 / 2006	10.7	2
full compansation	02 / 2006		1
	03 / 2006	9.3	1
	06 / 2006	9.6	1
compliance improvement	08 / 2006		1
cooperation termination	10 / 2006	9.9	
continuation in medication	01 / 2007	10.1	
	04 / 2007	9.9	
	08 / 2007	9.6	
	11 / 2007	10.1	
medication withdrawal	12 / 2007		
	03 / 2008	10.8	

Table 5. Timeline of mental state and glycosylated hemoglobin level development - patient No.4

Body weight of the patient was 97 kg at the beginning of the treatment (December 2005), it was 93 kg in the end (March 2008). A weight loss 4 kg was thus observed in the course of the treatment.

Blood pressure of the patient ranged from 140/80 torr at the beginning of the treatment to 130/70 torr in its end. It thus mildly decreased owing to the antidepressant drug therapy in the course of the treatment.

Serum triglyceride level was 1.28 mmol/l at the beginning of the treatment, 1.23 mmol/ in the end, it did not change due to the psychiatric therapy. Serum cholesterol level was 4.56 mmol/l at the beginning of the treatment, it decreased significantly to 3.58 mmol/l after 3 months and then mildly increased again up to 5.1 mmol/l in the end of the treatment.

The mental state of the patient improved quite rapidly and a significantly better cooperation in maintaining diabetic regimen was associated with it. Glycosylated hemoglobin at the beginning of the treatment decreased significantly, however, after the antidepressant medication withdrawal it returned to its original value prior to the treatment.

This case demonstrates that a mental disorder can induce incompliance of a patient and poor glycemic control. It is also evident here that the mental state deteriorated after the termination of the cooperation with a psychiatrist, or psychotherapy withdrawal.

3. Discussion

To our knowledge, there has not been found another scientific work that would deal with mechanisms of the effect of antidepressant drugs on glycemic control. The effect of mental state improvement using antidepressants is doubtless. It leads to attenuation of chronic stress and improvement in compliance with the diabetes treatment. Biochemical context is surely also in play. More research needs to be done in this field.

The medication of choice in all patients was sertraline for its efficacy against a wide spectrum of anxiety-depression symptoms. We often choose it for its safety regarding adverse effects and drug interactions. The individual patients were subsequently treated by various antidepressant drugs as individualized care was emphasized. The medication was thus selected according to specific problems and history of patients. Patients with varied initial glycemic control and a different change in glycemic control in course of the treatment and after the treatment termination are deliberately described here in order to be able to show multiple aspects of antidepressant drug effect in diabetic patients with a mental disorder. This variability was also chosen in order to enable demonstration of several possible pitfalls in treatment of these patients.

In spite of the fact that evaluation of the effect of individual groups of antidepressants in diabetic patients was not an objective of this work, it is suitable to share some experience from our psychiatric out-patient department. Drugs of choice are antidepressant drugs from the group of SSRI, especially aforementioned sertraline, for their effectiveness in the treatment of anxiety and depression problems, low risk of drug interactions and a small influence on body weight of patients. A potential contribution of SSRI to blood glucose decrease can also be beneficial in these patients. [Češková, 2004] Another commonly used drug is trazodone (SARI) for its good hypnotic and anxiolytic effect as well as the fact that it has no influence on body weight and sexual appetite. Venlafaxine (SNRI) is also frequently used for its good therapeutic effect on anxiety and depression symptoms and minimal metabolic adverse effects. Duloxetine from the same group of antidepressants is used for its effect on neuropathic pain alleviation. Unfortunately, it is not available to psychiatrists in the Czech Republic, only to neurologists. Tricyclic antidepressants, especially amitriptyline, are used mainly in the patients with painful diabetic neuropathy and associated sleep disorders. However, a frequent appetite and body weight increase limit their use. Antidepressants from the MAOI group (moclobemide) are scarcely used for their unconvincing clinical antidepressant effectiveness although they do not have any negative metabolic adverse effects. Bupropion (NDRI) has a good effect on inhibitedness and does not influence body weight, nonetheless, quite common and considerable increase in tension and anxiety constitute limiting adverse effects for its use. Mirtazapine (NaSSA) is an

unsuitable drug for diabetic patients for augmented appetite, weight gain and glycosylated hemoglobin level increase. [Šabaková, 2008]

Other somatic and metabolic parameters, which could have been influenced by the treatment, were monitored in the course of treatment of all abovementioned patients. [Svačina, 2004] The most significant change in monitored parameters was in the measurements of body weight of the patients, although the change was completely inconsistent. In the first patient, the body weight gradually increased. In the second one, it decreased at first, then returned to its original value. In the next patient, it slowly increased at first and then decreased significantly. In the last patient, the body weight significantly decreased during the whole course of the psychiatric treatment. The blood pressure values remained basically unchanged, as well as their blood cholesterol level. Only the serum triglyceride level increased in two patients in the course of the treatment, however, it was not possible to prove a direct association with antidepressant drug treatment here.

The focus of this work on antidepressant drugs does not allow broader addressing of issues concerning the origin of the mental problems, e.g. the influence of diabetes as a chronic disease, life crisis, etc. [Rossová, 1992] Even these factors undoubtedly significantly influence the treatment using antidepressant drugs and their effect on glycemic control.

Another important factor in this context is premorbid personality structure. It is acknowledged that antidepressant drug treatment of mental state decompensation is controversial in personal psychopathology. It could thus also have a smaller effect on glycemic control.

The psychiatric care cannot be perceived merely as the effect of psychotropic drugs. The counseling with a doctor have a certain psychotherapeutic potential, although it is not a form of systemic psychotherapy. A certain part of the session is psychoeducation and motivational and supportive interview. [Beran, 2000] Even this aspect needs to be taken in account when we evaluate the effect of antidepressants on a glycemic control in patients in psychiatric care.

Some patients with the described problems can profit from antidepressant medication, some from the systemic psychotherapy, some from the combination of the two. The indication of both should be wise. The antidepressant drugs are especially important in patients with a somatic disease as is diabetes mellitus, as these patients require quite lengthy psychotherapeutic work because of their significant orientation on somatic problems and laboratory findings. The need for mental state improvement, cooperation and glycemic control is often urgent. The treatment is thus often started with antidepressants and the psychotherapy is added after at least a partial improvement of the mental state.

Another issue is the eventual withdrawal of the medication. This is commonly dictated by the same rules as in other patients with mental illness. For some patients a long-term medication is beneficial, in spite of the fact that their mental problems long have disappeared. However, it was demonstrated that the patients should be left in the care of a psychiatrist during the whole time of medication administration.

Also, when initiating psychotherapeutic medication, all patients should be examined and educated by a psychiatrist. It is beneficial when the treatment can be indicated by a diabetologist to enable a fast treatment initiation, however, it has been proven that even psychoeducation and education regarding treatment is a very important part of a successful therapy and should therefore be performed by a professional. The advantage of a psychiatrist is also the ability to choose from a broader spectrum of psychiatric drugs.

4. Conclusion

The case studies demonstrate that the effect of an antidepressant drug on glycemic control improvement in patients with comorbid psychiatric disorder is possible.

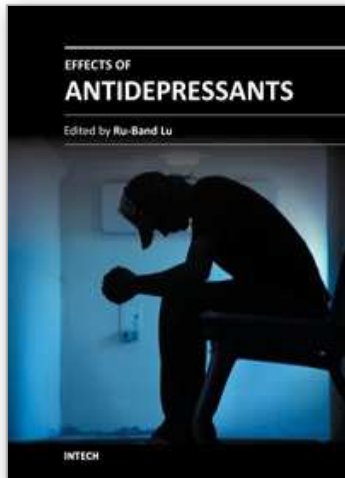
Mental state of diabetic patients when treated by antidepressant drugs changes similarly as in the rest of the population, i.e. rapidly in some, slowly in others, and in some a change in medication is needed. The glycemic control improvement is associated especially with the mental state improvement. In most patients the improvement in glycemic control was evident at the beginning of the treatment. The fact that the diabetic patient is introduced with a completely new treatment modality of his disease, i.e. psychiatric treatment, plays a positive role. The patients with a lasting improvement in their mental state have a high probability of persisting improved glycemic control. The deterioration of the basic disease can be expected in the diabetic patients, who mentally deteriorate some time after the antidepressant treatment withdrawal.

It is necessary to treat mental disorders in diabetic patients, as the antidepressant drug treatment has a positive effect not only on their mental state, which is associated with their compliance, but also it can positively influence the glycemic control, which is desirable even if the improvement were only temporary. Correctly selected antidepressants should not have an adverse effect on other somatic and metabolic parameters. Mental problems of diabetic patients should be treated by a psychiatrist educated in the problems of diabetes, because psychoeducation and a support of the patient are appropriate parts of the treatment.

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Over the last fifty years, many studies of psychiatric medication have been carried out on the basis of psychopharmacology. At the beginning, researchers and clinicians found the unexpected effectiveness of some medications with therapeutic effects in anti-mood without knowing the reason. Next, researchers and clinicians started to explore the mechanism of neurotransmitters and started to gain an understanding of how mental illness can be. Antidepressants are one of the most investigated medications. Having greater knowledge of psychopharmacology could help us to gain more understanding of treatments. In total ten chapters on various aspects of antidepressants were integrated into this book to help beginners interested in this field to understand depression.

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