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## DECLARATION

*I declare that this thesis is my original copyrighted work. All literature and other resources I used while processing are listed in the bibliography and properly cited.*

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## ACKNOWLEDGEMENT

Special thanks to my supervisor

## ABSTRACT

The aim of this review is the investigation of the relationship between metabolic abnormalities and psychiatric disorders analyzing the similarities in their biological pathways. Evidence shows that obesity and mood disorders share common molecular pathways.

Also, it has been suggested that antipsychotic medication causes significant weight gain through its effect on hormones such as leptin ~~levels~~, the activation of TNF-α~~a~~ system and cytokine receptors.

The present review is focused on the factors that contribute to the pathophysiology of obesity and mood disorders, their common pathways and the weight gain effect of antipsychotic medication, antidepressants, and mood stabilizers.



**Keywords:** mood disorders, obesity, BMI, schizophrenia, MDD, BP, leptin, cortisol, antipsychotics, antidepressants, mood stabilizers


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## ABSTRAKT

Cílem této přehledové práce je zkoumat vztah mezi metabolickými abnormalitami a psychiatrickými onemocněními nalézáním podobností v jejich biologických cestách. Existují důkazy, že obezita a duševní poruchy mají některé molekulární mechanismy společné.

Rovněž bylo navrženo, že antipsychotika způsobují významný váhový příbytek přes ovlivnění hormonů, jako je leptin, aktivací TNF-α a cytokinových receptorů.

Tato přehledová práce se zabývá faktory, které přispívají k patofyziologii obezity a duševních onemocnění, společnými cestami podmiňující tato onemocnění a účinkem antipsychotik, antidepresiv a stabilizátorů nálady na zvýšení hmotnosti.



**Klíčová slova:** antidepresiva, antipsychotika, BMI, duševní poruchy, kortizol, leptin, MDD, obezita, schizofrenie, stabilizátory nálady, TK.


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# Content

# 1. Introduction

Evidence shows that mood disorders and obesity have an unbreakable relevance as they share genetic, neurobiological, clinical and environmental agents presenting co-morbidity. Various empirical studies have attempted to demonstrate the correlation between those health situations and more specifically have tried to describe the subtypes of mood disorders that develop obesity and metabolic problems. Despite the efforts, the knowledge about this correlation is limited, exceptions in the evaluation of mood and metabolic disorders exist.

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Questions persist about the generalizability and validity of the findings in several studies evaluating metabolic-mood syndrome. The limitation factor is the heterogeneity, phenotypic and pathophysiological, of metabolic mood disorders. In the field of psychopathology there is an effort to categorize domains focused on pathogenic substrates, as suggested by the National Institute of Mental Health Research Domain Criteria Project. The existence of metabolic-mood syndrome is possible due to accumulating evidence showing an association of multiple abnormalities in neuropsychology and brain abnormalities concerning metabolic dysfunction. (Mansur, Brietzke & McIntyre, 2015).

Research data support an increased incidence of mood disorders in obese people, including major depression, dysthymia, manic and hypomanic episodes. The connection between mood disorders and obesity is stronger regarding women, while the relationship between higher BMI and alcohol abuse is more connected to men. Depression may be the result of obesity, but it might be related to its occurrence and development. The association between obesity and mood and anxiety disorders may be a result of stress on the hypothalamic-pituitary-adrenal axis (HPA), which reacts by releasing cortisol and other hormones that regulate sympathetic nervous system activity. In chronic stress, the HPA axis activity is deregulated and this deregulation classifies depressive and anxiety disorders and obesity (Collins & Bentz, 2009; Carr & Friedman, 2005).

Metabolic abnormalities related to weight gain have shown a linkage to various psychiatric disorders including bipolar disorder, major depressive symptoms, schizophrenia and anxiety disorders. It is speculated that a bi-directional relationship exists, developed by a series of genetic, environmental, clinical and neurobiological factors. Treatment of mood disorders can be more complicated in the presence of overweight and obese individuals. However, obesity alone increases the risk of depressive symptoms and manic attacks.

Additionally, depressive symptoms are observed in individuals regardless of age, sex and race who aim in obesity treatment or developed medical conditions associated with obesity like T2DM, coronary artery disease, cerebrovascular disease, musculoskeletal disorder and several forms of cancer. Drugs used in the therapy of other medical conditions that co-exist with obesity may influence and induce mood depressive behaviors. Referring to the high impact of psychiatric diseases and obesity in morbidity and disability, the concomitance of these conditions indicates the arousal of accumulative effect in the burden of illness (Mansur, Brietzke & McIntyre, 2015)

Several mechanisms are involved in the explanation of the relationship between obesity and psychiatric disorders and have been investigated for a long period of time, in order to find a way to render them more understandable. The most common dysregulated biological pathways include disturbances in HPA axis, an increase in oxidative and nitrosative stress, reduced antioxidant defenses and dysregulation of inflammatory pathways leading to apoptosis, mitochondrial abnormalities, neurodegeneration and reduced neuronal plasticity and neurogenesis (Lopresti & Drummond, 2013a).

All the above-mentioned abnormalities are influenced by environmental, genetic, psychological factors, as well as social and lifestyle parameters.

The present review is focused on the relationship between metabolic abnormalities and psychiatric disorders analyzing the similarities in their biological pathways.

# 2. Epidemiology

Obesity, which causes a series of physical problems in patients, shows a dramatic increase over the past three decades. The disease of obesity is one of the most important disorders of the human body that affects the modern developed societies and represents the large increase in the atomic weight and a particularly excessive increase in body fat; approximately 15 to 20 pounds above the normal weight (Oken & Gillman, 2003). Obesity is a modern scourge that tends to get the global epidemic. The incidence of obesity is increasing rapidly and more than 30% of adults in Western society are obese while equally worrying is the increase of obesity in childhood and adolescence.

Research studies have focused either on the examination of obesity prevalence in people with mental disorders or on the examination of mental disorders in obese people (Taylor et al., 2008; Scott et al., 2008).

Epidemiologic data suggest an association between obesity and mood disorders while few of them have investigated the relationship between BMI and psychopathology. Simon et al (2006) and Onyike et al (2003) found that BMI increases the risk of major depression even when controlling for demographic characteristics and that obesity is linked to increased odds of anxiety disorders. There are gender differences in obesity among men and women. Men are more likely to be overweight (Hedley et al., 2004), while on the other hand women tend to be obese (Poulose et al., 2005).

Barry, Pietrzak & Petry (2008) have found that BMI>30 is associated with increased odds of developing any mood disorder (including major depressive disorder and dysthymic disorder and specific phobia) both in women and men. They also found that obese women were at risk of developing bipolar I and II disorders and social phobia unlikely men. Desai et al (2009) study aimed to investigate the gender differences and the association between BMI and psychopathology based on data from the National Epidemiologic Study of Alcohol and Related Conditions. They found that both obese men and women were more

likely to develop anxiety disorders, but the association was more statistically significant for women.

Carpenter et al (2000) investigated the gender impact on the association of obesity and depression on data over 40.000 American adults and concluded that a significant positive association between BMI and depression in women exists and a significant negative association in men. Simon et al (2006) epidemiological study concluded that obesity (BMI $\geq$ 30) elevates the odds of developing anxiety and mood disorders both in men and women in contrast to non-obese (BMI < 30) men and women.

Simultaneously, women with a lifetime history of the disorder or major depression had been associated with greater likelihood of developing obesity (McIntyre et al., 2006). Also, obese adolescent and young female are of greater likelihood of experience anxiety disorders (Anderson et al., 2007; Lamertz et al., 2002). According to Weissman et al (1993) women are more likely to experience mood disorders. Chen, Jiang & Mao (2009) study have identified that obesity is associated with 30-40% increase in depression, mainly in women of age 18-39 years.

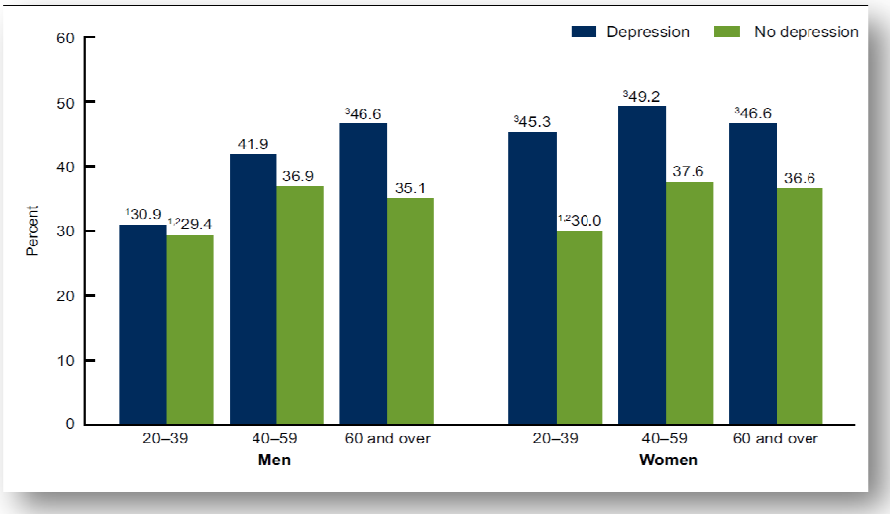
Based on this evidence it could be mentioned that BMI and psychopathology seem to be more strongly associated in women than in men (McIntyre et al., 2006; Carpenter et al., 2000). Also, Atlantis & Baker (2008) systematic review have argued that longitudinal studies show that obesity increases the risk of developing depression. The review results regarding the association between obesity and depression for U.S. population were referred to women and not men.

Several studies have mentioned the existence of obesity in adults with mental disorders (Zhao et al., 2009; Onyike et al., 2003), stating the use of some antidepressants is positively related to obesity (Aronne & Segal, 2003). CDC statistical data shows that adults with depression were more likely to be obese than adults without depression. Furthermore, women with depression have higher odds to be obese than women without depression. For men with depression those who are aged over 60, there are higher odds to develop obesity while for both

genders the younger adults aged 20–39 are less likely to be obese in contrast to people over 40 (Pratt & Brody, 2014).

Few studies have reported the association between age and increased odds of developing obesity and mental health disorders (Ma & Xiao, 2009; van der Merwe, 2007). The age group, which is at greater risk, is young women while older people could be also at greater risk given the health problems arising from age (Kivimaki et al., 2009).

Regarding ethnic groups, it has been suggested that the association of obesity and mood disorders, especially depression, varies across ethnic groups. Women citizens of U.S. non-Hispanic white and black women are at greater risk of developing obesity-related to depression (Gavin, Rue & Takeuchi, 2010). Simon et al (2006) did not note gender differences between obesity and mood disorders association. However, their study identified differences across racial groups and education levels.

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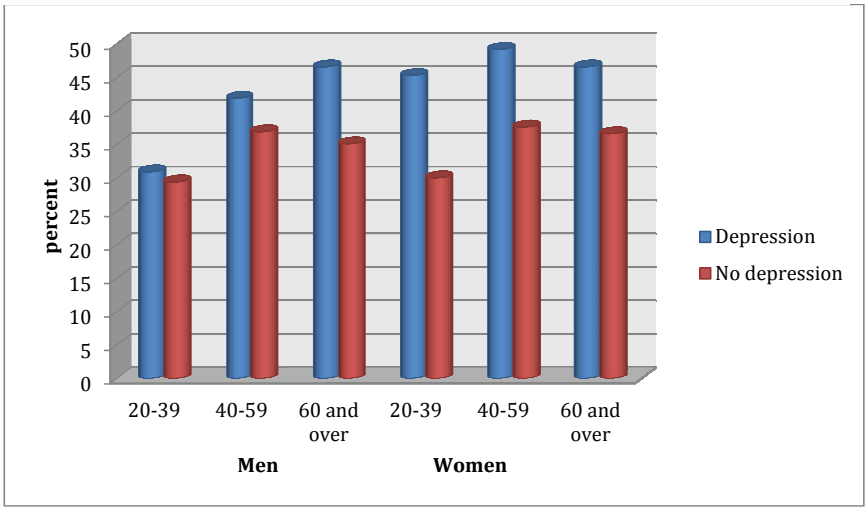


The association between depression and obesity has been studied among Western countries population and the meta-analysis of de Wit et al (2010) have shown the positive association in general adult population which has been more markedly pronounced among women than men. Another two meta-analyses of longitudinal studies found that depression is positively associated with abdominal obesity (Xu, Anderson & Lurie-Beck, 2011; Luppino et al., 2010).

Abou Abbas et al (2014) meta-analysis was based on the synthesis of data from observational studies and aimed to evaluate the association between depression and obesity in Middle Eastern countries. The meta-analysis of 8 observational studies suggests the positive association between depression and obesity among adults in Middle Eastern countries while it has been found that the association is statistically more significant among women.

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Pratt & Brody (2014) study for U.S. adults have shown that 45% of non-Hispanic white women with depression were obese and among Mexican-American and non-Hispanic black men and women obesity rated did not differ by depression status.

Regarding the association between antidepressant medication and obesity, 50% of U.S women with severe depressive symptoms were obese while more than 50% of both gender adults with moderate to severe depressive symptoms who were also treated with antidepressant medication were obese (Pratt & Brody, 2014).

Finally, the association between obesity and socioeconomic status seems to be still unclear while Minet Kinge & Morris (2010) study reported the association of lower socioeconomic status with a greater risk of obesity and depression (Chen, Jiang & Mao, 2009). On the other hand, Simon et al (2006) and Moore, Stunkard A, Srole (1962) have found that high socioeconomic status is related to obesity and depression.

# 3. Metabolic abnormalities involved in mental disorders

Metabolic syndrome is involved to risk factors for development obesity, insulin resistance, glucose intolerance, and dyslipidemias. Recent evidence shows that patients with mood disorders, such as schizophrenia, have higher odds to develop metabolic syndrome (Stubbs et al., 2015; Zhang et al., 2015; Harris et al., 2013).

Figure 2, represents the pathways through which obesity and psychiatric disorders are associated

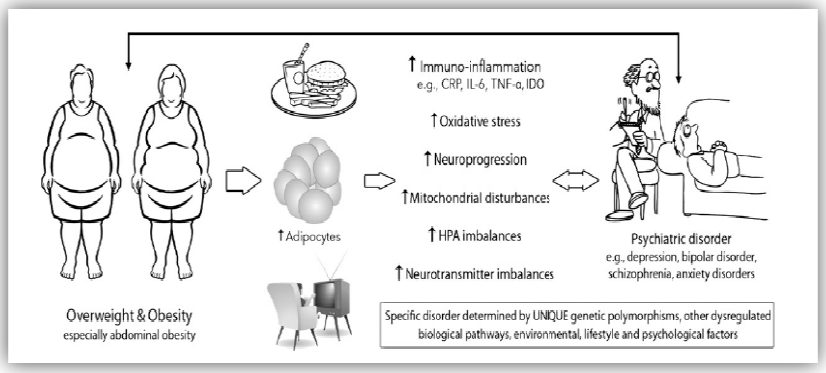



**Figure 1:** Obesity and its influence on pathways associated with psychiatric disorders.

## Dyslipidemia

The metabolic syndrome is the result of the complex of metabolic abnormalities and is correlated with obesity while evidence shows that psychosocial environment conduces to obesity development (Iwasaki et al., 2008).

| | ATP III<br>3 out of 5 criteria required | ATP III A<br>3 out of 5 criteria required | IDF<br>waist + 2 criteria required |
|---|---|---|---|
| Waist (cm) | M>102, F>88 | M>102, F>88 | M≥94,F≥80 |
| Blood pressure | ≥130/85* | ≥130/85* | ≥130/85* |
| HDL cholesterol (mg/dl) | M<40, F<50 | M<40,F<50 | M<40,F<50 |
| Triglycerides (mg/dl) | ≥150 | ≥150 | ≥150 |
| Fasting glucose (mg/dl) | ≥110** | ≥100** | ≥100** |

**Table 1:** The definitions of metabolic syndrome (Saravane, 2012).

*or treated with antihypertensive medication
**or treated with insulin or hypoglycemic medication

While the prevalence of metabolic syndrome in the general population is estimated 2-6% (is more frequent in men) (Maumus et al., 2005), in patients with schizophrenia and mood disorders estimates up to 36%. More specifically, the recent meta-analysis of Mitchell et al (2013) on 25.692 total patients showed that the overall rate of metabolic syndrome in mood disorders and schizophrenia is 32.5%. De Hert et al (2006) reported an estimated range of 36% in schizophrenics taking antipsychotics and Yumru et al (2012) reported 32% bipolar patients with metabolic syndrome.

The main feature of metabolic syndrome is obesity which leads to dyslipidemia and insulin resistance. Wysokinski, Kowman & Kłoszewska (2012) have mentioned that dyslipidemia and raised fasting plasma glucose is common in schizophrenics and individuals with mood disorders. It should be highlighted that

many patients with mood disorders and schizophrenia do not receive the appropriate treatment for metabolic abnormalities.

Nasrallah (2008) reports that the 88% of patients with dyslipidemia were not receiving treatment of metabolic syndrome as 38% of that had diabetes and 62% hypertension.

This evidence is leading to the suggestion that lipids and blood levels of mood disorders and schizophrenia patients should be frequently monitored (Wysokiński, Strzelecki & Kłoszewska, 2015).

Bipolar disorder and schizophrenia are linked to metabolic abnormalities, which include obesity, increased glucose blood levels and raised lipids. Metabolic syndrome seems to be more frequent on patient with mood disorders taking psychotropic agents including antidepressants, mood stabilizers and antipsychotics (McIntyre et al., 2010; Teixeira & Rocha, 2007; De Hert et al., 2006).

Wysokiński, Strzelecki & Kłoszewska (2015) research study aimed to examine the differences in HDL, LDL, glucose, cholesterol and triglycerides levels in patients with schizophrenia and bipolar disorder. The research study involved 2305 Caucasian patients with schizophrenia, bipolar depression, bipolar disorder and bipolar mania and found that there is a high prevalence of lipid and glucose abnormalities in schizophrenics and mood disorder patients.

Also, it has been shown that patients with schizophrenia and bipolar depression presented the higher level of TGA while schizophrenia and bipolar disorder are linked to increased risk of TGA level exceeding the upper normal limit (150 mg/dL). De Leon et al (2007) had found higher TGA level in schizophrenics than Wysokiński, Strzelecki & Kłoszewska (2015) (139.8 mg/ dL).

The main feature of the metabolic syndrome is the resistance to insulin action or *insulin resistance, which* is frequent in obese people. Insulin resistance is defined as the situation in which the tissues of the body do not react to insulin secretion from pancreas as it is expected in normal conditions. Insulin resistance results from the reduced clearance of free fatty acids in plasma. Overall the lipid profile of an obese individual, because of the insulin resistance, is likely to have

higher levels of VLDL and LDL cholesterol, triglycerides and decreased levels of HDL cholesterol (Wilson et al., 2002; Ferrannini et al., 1991).

The metabolic syndrome causes the abdominal fat distribution (mainly visceral adiposity), which is a risk factor for glucose intolerance, insulin resistance, and dyslipidemia. Additionally, adipose, muscle, nervous, adrenal and hepatic tissues could be affected and vasculature could be significantly affected. Lipoprotein abnormalities and insulin resistance are a major problem caused by metabolic syndrome and the insulin resistance contributes to glucose intolerance.

The unchecked lipolysis could lead to raised delivery of free fatty acids to the liver for triglyceride synthesis and packaging into very low-density of VLDL particles. Lower HDL levels are associated to higher VLDL as the reciprocal exchanges between these lipoproteins mediated by cholesterol ester transfer protein.

Also, visceral obesity is an initial marker of metabolic syndrome while insulin resistance is linked to increasing plasma triglycerides, increased blood pressure, impaired glucose control, reduced high-density of HDL cholesterol, increased markers of inflammation and increased risk of blood clotting. Thus, elevated fasting plasma triglycerides as an indicator of insulin resistance could be used as a key point for monitoring patient's risk (Nasrallah, 2008).

As LDL is formed small and thick because of increased neutral transfer between different classes of lipids and consequent increased activity of CETP enzyme (protein transfer of cholesterol esters), the risk of atherogenesis is increased. Insulin stimulates the formation of various growth factors such as Insulin-Like Growth-factor I, which contributes to atherosclerosis (Wilson et al., 2002; Ferrannini et al., 1991).

## Glucose disturbances

There is a debate between scientists for whether metabolic syndrome is a result of antipsychotic medication or schizophrenia per se (Britvicet al., 2013). There is a suggestion of the existence of glucose and lipid metabolism abnormalities at the onset of psychosis.

More specifically, Wu et al (2013) have found that in first-episode schizophrenia patients there was higher insulin, insulin resistance and C-peptide levels and lower total cholesterol, high-density lipoprotein cholesterol and apolipoprotein A1 levels.

The insulin resistance is characterized by the impaired response to insulin action in relation to the metabolism of carbohydrates and is regarded as a key atherosclerotic risk factor. Several studies indicate the relationship between major depression disorder and insulin resistance. One of the pathophysiological mechanisms correlates insulin resistance with depression caused by the overactivity of HPA axis (Ramasubbu, 2002).

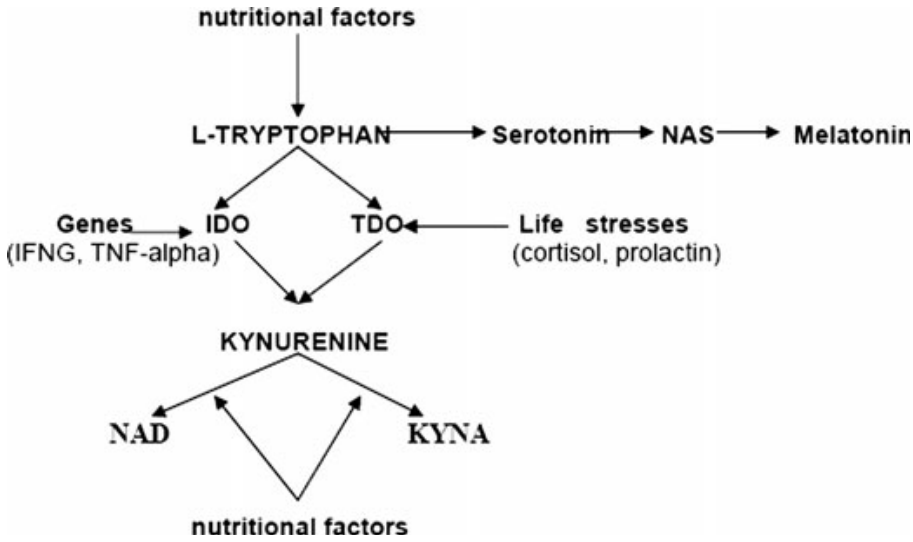
There is a recent suggestion that schizophrenics have impaired fasting glucose tolerance and were more insulin resistant and had higher fasting 2-h plasma glucose levels (Fernandez-Egea et al., 2009; Spelman et al., 2007; Ryan et al., 2003). Guest et al (2010) have found that first onset schizophrenia patients had increased circulating levels of insulin-related peptides and the secretory granule protein chromogranin A. Their later study showed that schizophrenics (both first and recent onset schizophrenia patients) had increased serum concentrations of insulin and chromogranin A.

## The role of kynurenine pathway

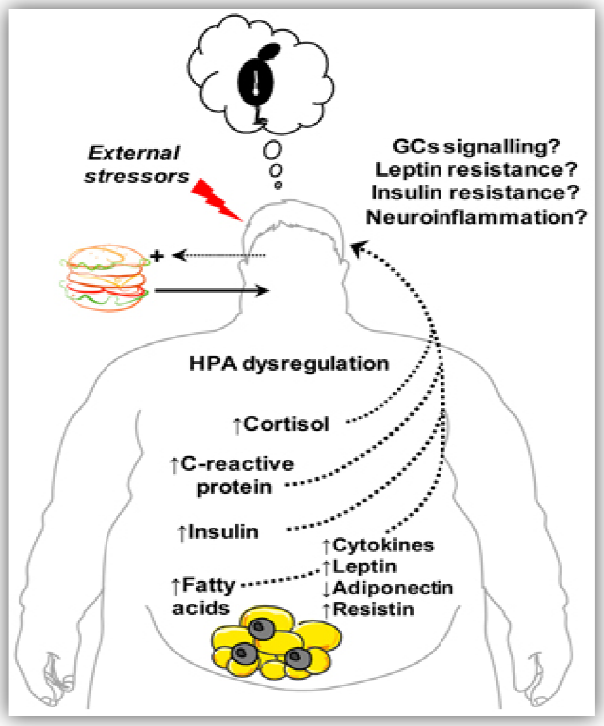
Obesity is associated with upregulation of the kynurenine pathway, evidenced by decreased concentrations of plasma tryptophan and an increased kynurenine/tryptophan ratio (Brandacher et al., 2007). Upregulation in the kynurenine pathway affects neurotransmitter production, especially serotonin. Moreover, it is associated with increased oxidative stress and neurodegeneration. The dysregulation of this pathway is suggested to be important in depression, schizophrenia and bipolar disorder (Myint et al., 2012; Lopresti et al., 2013b).

The tryptophan catabolite pathways (TRYCAT) are an important mediator of the association of oxidative and nitrosative stress and immuno-inflammatory activation with alterations in glia-neuronal interactions and neuronal activity. An emerging concurrence proposes that oxidative and nitrosative stress is interacting with changes in immuno-inflammatory activity, increasing levels of proinflammatory cytokines, in turn activating indoleamine 2,3-dioxygenase (IDO). This forces tryptophan down the tryptophan catabolite pathways, decreasing serotonin and melatonin production, in sequence increasing depression and metabolic dysregulation . Here again alterations on leptin is proposed to be the mediator that driving changes in the tryptophan catabolite pathway, both centrally and peripherally and in the fragile balance between TRYCAT products and induction of metabolic regulators. This is a mechanism underestimating the metabolic syndrome and psychiatric disorders (Anderson and Maes ,2013).

Finkelstein et al., observed a decrease free tryptophan in the plasma of obese rats. Plasma tryptophan concentrations were decreased in obese patients regardless of dietary intake or weight reduction. (Brandacher et al.,2007). Preoperative kynurenine/tryptophan ratio in morbidly obese patients was significantly increased compared to the healthy individuals, and postoperative weight reduction did not normalize kynurenine/tryptophan ratio. In addition, these tryptophan metabolic changes may subsequently reduce serotonin production and cause mood complications, depressive symptoms, and impaired satiety ultimately leading to obesity (Brandacher et al.,2006; Oxenkrug,2010).



## HPA axis

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ying mechanisms of mood disorders immune-inflammatory and endocrine regulation hold a prominent position as HPA axis and glucocorticoids participate in the physiological response to acute stress. Its purpose is to redintegrate energy homeostasis through actions in the glucose and insulin regulation, adipose tissue and appetite. However HPA dysregulation is reported on obese people and a positive association between abnormal activation of HPA and abdominal adiposity has been found. This association is accompanied by lower or higher responses to

stress (Pasquali, 2012; Kubera et al., 2012; Jones et al., 2012; Mujica-Parodi, Renelique & Taylor 2009).

Hyperactivation of the hypothalamic– pituitary–adrenal (HPA) axis is induced by stress, which triggers the hypothalamic corticotropin-releasing hormone (CRH) secretion. That prompts the release of adrenocorticotropin hormone (ACTH) by the anterior pituitary ,which causes the adrenal secretion of cortisol (Gragnoli , 2014).

People who are exposed to excessive cortisol (i.e. to chonic stress) represent an increment in visceral adipose tissue, while HPA dysregulation have been present in mood disorders aetiology. Cervantes et al (2001) pointed out that patients with bipolar disease demonstrate hypersecretion of cortisol (in euthymia, depression and mania) and Daban et al (2005) found the existence of blunted cortisol response to stress. Several studies (Lamers et al., 2013; Gold & Chrousos, 2002; Wong et al., 2000) have found and overactivation of HPA to depressive patients that is correlated to melancholic features.

Many clinical indications confirm the participation of HPA axis in depression, as in approximately 50% of depressed patients an increase of cortisol is observed. Probably the increased secretion of CRH in hypothalamus is involved resulting in an increase of ACTH and cortisol (Ahlberg et al., 2002).

The dysfunction of adrenergic systems and the 5-HT system combination with hyperactivity of neurons that use the CRF agent are considered as the basic cause of depressive and anxiety symptoms. The precipitating agent release CRF corticotropin has been found in high prices in patients with depression (Plotsky, Owens & Nemeroff, 1998).

A 75% of patients with major depression shows hyperactivity in HPA axis and is characterized by hypercortisolism. The disturbance in the functioning of HPA axis is observed in generalized anxiety disorder, as it is disclosed by testing dexamethasone ( Manthey et al., 2011;Tiller et al.,1988).

Young et al, showed that depressed patients represent impairment on HPA axis during a test in which patients subjected to intense stress, with a consequent increase in cortisol. Several studies have investigate the effect of the HPA axis in

the CNS and evidence shows that clinical forms of Cushing's syndrome are present in some patients with major depressive disorder although cortisol levels are lower in depression than in Cushing syndrome (Brown, Varghese & McEwen, 2004).

Exogenous or endogenous cortisol increase (Cushing's syndrome) is often associated with insulin resistance and obesity, hypertension, hypercholesterolemia and hypertriglyceridemia. Glucocorticoids can reduce the vasodilation induced by insulin and they may also increase the lipolysis and the release of fatty acids, causing inhibition of protein lipase. Elevated fatty acids contribute to impaired glucose transport. Glucocorticoids also reduce insulin secretion from pancreatic beta-cells and inhibit or disrupt the connection with receptors. In the case of hypercortisolism causing insulin resistance in depressed patients, a study reports a significant correlation between insulin resistance and the evening-night cortisol levels of depressive patient's plasma (Andrews & Walker, 1999).

Vicennat et al (2009) have found that intense stress reactivity could predict metabolic syndrome development while there is an association between glucocorticoids and metabolic syndrome (Pasquali et al., 2006).

A well-described aetiology of mood disorders is dysfunction of HPA axis and depression pathogenesis is underlying on to a breakdown in glucocorticoid-receptor-mediated negative feedback mechanisms within the HPA axis (hypercortisolaemia) (Young, 2004).

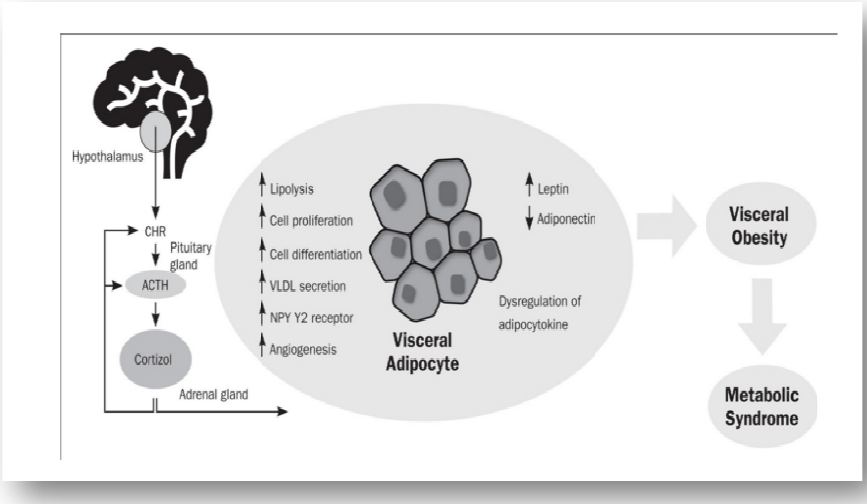


**Figure 3:** This figure describes the mechanisms which are involved in glucocorticoids release visceral adipose tissue accumulation and the pathogenesis of metabolic syndrome. Cortisol is excreted as a responder to stressful events under HPA axis control and affects adipocytes promoting the visceral obesity. These conditions lead to the manifestation of metabolic syndrome (Paredes & Ribeiro, 2014).

## Proinflammatory signals

Stetler & Miller (2001) stated that depressive patients show a raise in cortisol levels while Munkholm, Vinberg, & Vedel Kessing (2013) highlighted the existence of higher levels of pro- inflammatory markers such as IL-6, sIL-2R and TNF-a in bipolar disorder and major mood disorder patients. Thus, the contribution of immune-inflammatory dysregulation and mood disorders is emphasized by studies results (Dowlati et al., 2010; Howren, Lamkin, & Suls, 2009).

The adipose tissue constitutes a significant origin of cytokines and it has been stated that the inflammatory imbalances are present in mood disorders. The adiposity contributes as an immune-inflammatory dysregulation moderator as Choi, Joseph & Pilote (2013) highlighted and it has been found that obesity is related to a low-grade pro-inflammatory state with elevated levels of C-reactive protein.

At the same time, Hickman, Khambaty & Stewart (2014) compared individuals with atypical major depressive disorder, non-atypical major depressive disorder and with no major depressive disorder regarding to their serum C-reactive protein levels. The researchers found that participants with atypical features (compared to those with melancholic features) demonstrated higher levels of pro-inflammatory markers (TNF-a, CRP and IL-6).

Both metabolic abnormalities and mood disorders present an association with adipose-derived hormones in accordance to Wilhelm et al (2013). Barbosa et al (2012) have found that obesity is linked to lower levels of adiponectin while bipolar disorder and major depressive disorder to altered levels of adiponectin. Leptin, as it has mentioned before, is also associated with both obesity and mood disorders and it has been observed that high levels of waist circumference and leptin increase the risk of depression development (Milaneschi et al., 2012).

## Adipose derived hormones

The adipokines consist of polypeptides such as other non-protein products that are metabolically active molecules belonging to different categories, like immunization (additional agents, haptoglobin), endocrine function (leptin, steroid sex various growth factors) metabolic function (fatty acids, adiponectin, resistin) and cardiovascular functions (angiotensin, PAI-1) (Scherer, 2006).

The increase of adipose tissue is accompanied by changes in the distribution and morphology of fat cells, which differ between individuals because there is a genetic and an influence by lifestyle. The presence of large fat cells is accompanied by functional changes of which the most important are:

a) the increased production of adipocytes, the pro-inflammatory cytokines and reactive oxygen species (ROS),

b) the decreased storage of lipids capacity leading to ectopic deposition of fat,

That malfunction of adipose tissue causes activation against sympathetic nervous system (Scherer, 2006).

The research data that associates major depression disorder and adipokines is focused on leptin which is produced initially by differentiated adipocytes stimulating energy expenditure and repressing food intake (Munzberg, 2010). Primary leptin was identified as an antiobesity hormone as it was suggested to act as a negative feedback adiposity signal to control energy homeostasis by interacting with its receptors in the hypothalamus (Elmquist et al., 1998). Increased leptin levels are linked to obesity caused by leptin resistance (Munzberg & Myers, 2005).

Leptin and leptin receptors may be regarded as candidate genes for the development of obesity. Several polymorphisms in the coding region and the region 5 and 3 appear to be related to body weight, weight loss and BMI. The level

of leptin used as a measure of obesity and polymorphism in leptin receptor (Gln223Arg) is associated with the fat mass and body composition in many populations (Morris & Rui, 2009; Speakman, 2004).

The majority of research data highlights the importance of leptin in determining body weight. Leptin is a protein, such as insulin, produced in adipocytes from the gene «ob» (obesity gene) and acts through specific receptors in the hypothalamus (control center of appetite), achieving the adjustment of the sense of hunger or saturation. Leptin levels are an indicator of energy reserves in the adipose tissue. High levels of leptin lead to reduced food intake and increase of energy consumption (Morris & Rui, 2009; Speakman, 2004).

Leptin has been found to reduce appetite, increases energy consumption, stimulates the gonadotropins and is an important regulator of the body's insulin sensitivity and the metabolic rate of the body (Morris & Rui, 2009; Speakman, 2004).

However, the mechanism of leptin appears to be broken in obese people and despite the fact that they have increased production and concentration of leptin in their blood they are unable to control their body weight due to the resistance to leptin. A new term is the "leptin resistance" and it is believed to be the reason by which the high levels of leptin in obesity are unable to suppress appetite and result in weight loss. Various mechanisms have been discovered to act to this resistance; recently an unsaturation carrier has been discovered which appears to prevent the passage of leptin across the blood brain barrier, where concentrations exceeding the normal, thus reducing the availability of the hypothalamus. Also, studies indicate that the signal transduction pathway inhibitors of leptin such as protein tyrosine phosphatase 1B (PTP-1B), SH-contained protein tyrosine phosphatase (SH-2) and the signaling cytokines inhibitor 3 (SOCS- 3) contribute to leptin resistance. The fact that insulin can increase the inhibitor SOCS-3 leptin appearing to act competitively in leptin is quite interesting (Dotsch, Rascher & Meissner, 2005).

Generally, the problems related to leptin are mainly the following three: the leptinopenia wherein fat cells do not produce normal amounts of leptin; the absence of leptin receptors in the brain and leptin-resistance, i.e. the

desensitization mechanism of leptin recognition from the brain or the abnormal reaction of the brain to the stimulus that causes leptin when contacted with leptin receptors (Morris & Rui, 2009).

Stubbs et al (2016) study suggested that leptin has a significant role in the pathophysiology of schizophrenia and performed a systematic review and meta-analysis in order to compare leptin levels on control groups and schizophrenic patients. They collected scientific 27 articles which represented 2.033 control group individuals and 1.674 schizophrenic individuals. The follow figure shows the summary of the included studies.

Their analysis found that when one outlier was removed leptin levels maybe marginally higher in schizophrenia. Moreover, leptin levels were higher in females and multi-episode schizophrenia.

# 4. Factors involved in the correlation between metabolic abnormalities and Mood Disorders

The systematic review of longitudinal studies of Luppino et al (2010) have reported the bidirectional association between depression and obesity and more specifically they found out that obese people are at 55% increased risk of developing depression while depressed people are ~~on~~ at 58% increased risk of becoming obese. Gariepy, Nitka & Schmitz (2010) meta-analysis confirmed the association between anxiety disorders and obesity.

Obese women and men experience greater odds (OR from 1.21 to 2.08) of any mood and anxiety disorder (Petry et al., 2008) while Scott et al (2008) mentioned that obesity is associated with anxiety disorder (OR = 1.46), major depressive disorder (OR = 1.27) and mood disorder (OR = 1.23).

Obesity influences several biological pathways associated with psychiatric disorders including immuno-inflammatory processes, oxidative stress, neuroprogression, mitochondrial disturbances, HPA axis imbalances, and neurotransmitter imbalances. A bi-directional relationship likely exists (represented by the bidirectional arrow) between obesity and psychiatric disorders, as obesity increases the risk of psychiatric disorders, and suffering from a psychiatric disorder increases the likelihood of obesity. Suffering from both these conditions is likely to have an additive influence on these pathways. While psychiatric disorders share many commonalities in dysregulated pathways, genetic, environmental, lifestyle, and psychological factors will determine the specific disorder(s) suffered [C - reactive protein (CRP), interleukin-6 (IL-6), tumo~~u~~r necrosis factor-α (TNF-α), indoleamine 2, ~~3~~ 3-dioxygenase (IDO)].

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**Komentář [U3]:** What did you wanted to tell by listing these…?

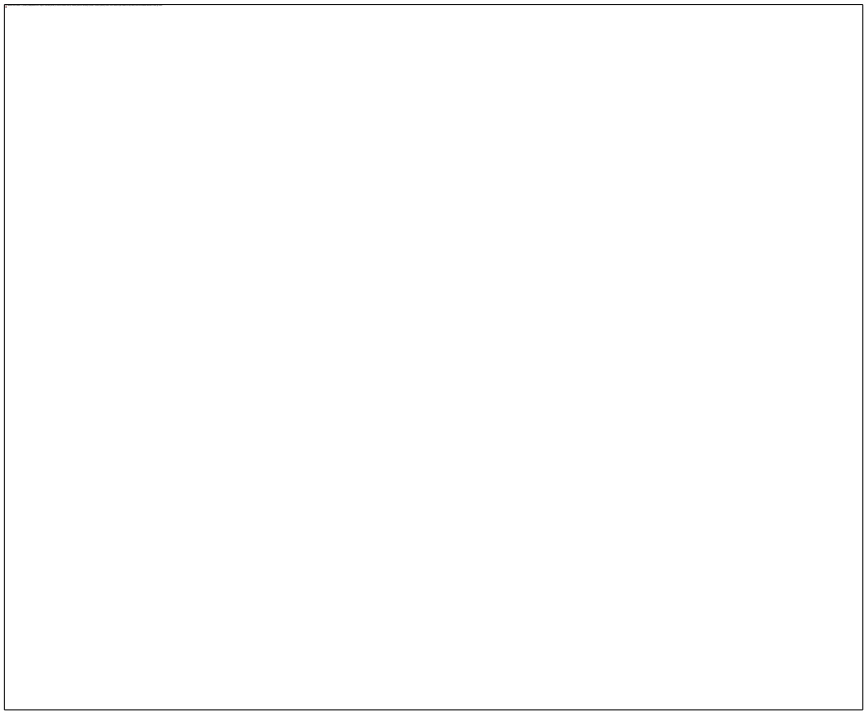

**Figure 4:** Stubbs et al (2015) representation of association between neuropsychological and metabolic phenotypes aspects.

The authors suggests that this phenotypical congruity is moderated by shared pathophysiological pathways which are underlied by environmental and genetic risk factors as it will be analyzed later in the this chapter. The existence of specific environmental and, epigenetic, and genetic factors, such as genetic vulnerabilities, stress, the inadequate or excessive food intake, or the childhood trauma, could lead to the negative impact on neural systems and peripheral homeostatic systems. This impact could be translated transferred into the damage on brain structures damage and functioning connectivity dysfunction. , on bBrain energy metabolism, and BDNF, and endocannabinoid system are affected caused by dysregulation of HPA axis, the existence of inflammation and adipocytes derived hormones are present. These alterations may lead on to

Komentář [U4]: You mean Stubbs et al?

phenotypical expression of metabolic phenotype and behavioral/emotional phenotype, ~~which~~ whose combination ~~constitutes~~ forms the metabolic-mood syndrome.

## Genetic

Generally, the genes affect the body weight to the extent that encodes molecular components of the normal setup system. The detection of rare mutations has raised new ground in detecting pathways involved in the regulation of body weight. The volatilities at the gene sequence adrenergic receptors of uncoupling proteins have the greatest scientific interest nuclear, also the PPAs receptors and the leptin receptor. The results of studies analysis of the genome shows that the key genes are located mainly in the ~~genes~~ chromosomes 2p, 3q, 5p, 6p, 7q, 10p, 11q, 17, and 20q (Loos & Bouchard, 2003).

Komentář [HK5]: syntax

Proopiomelanocortin (POMC) is a precursor of many neuropeptides and hormones of the hypothalamic~~-~~-pituitary~~-~~-adrenal axis ~~and neuropeptides~~ and participates in the regulation of energy consumption and food intake. The mutations of the gene encoding the synthesis of proopiomelanocortin affect~~inhibit~~ the synthesis of alpha-MSH, a neuropeptide that inhibits appetite in the hypothalamus, leading to severe obesity (Krubde et al., 1998).

Bell, Walley & Froguel (2005) have mentioned that obesity is heritable ~~for~~ ranging from 50 to 90% and Kendler et al (2006) and Smoller & Finn (2003) have stated that major depressive disorder is hereditary about 30-50%, while bipolar disorder is heritable about 50-70%. Kerner (2014) reports that obesity and mood disorders present a polygenic mode of inheritance as multiple genes are ~~conduced to their deployment~~involved in their pathophysiology.

Farmer et al (2008) have mentioned a relationship between increased BMI and depression, as their regression analyses have ~~showed~~ shown that metabolic syndrome was widely accounted for BMI. Newly studies indicate the potential shared aetiological factors (containing genetic factors) between obesity and unipolar depression (Rivera et al., 2012; Patten et al., 2005).

Komentář [U6]: ?

Barry, Pietrzak & Petry (2008) and Scott et al (2008) studies have investigated the *FTO* on BMI in a large sample of depressed patients to report the

Komentář [HK7]: Explain – next comment

association with obesity and psychiatric disorders. Rivera et al (2012) investigated the genetic influence of polymorphisms in FTO in relation to BMI ~~to~~ in control group (Radiant Study) and group with major depressive disorder. 88 polymorphisms have been analyzed and 8 of the top 10 single-nucleotide polymorphisms, showing the strongest associations with BMI, were followed-up in a population-based cohort. The results have shown a significant interaction between genotype and affected status in relation to BMI for seven SNPs in radiant indicating an association between mood disorders and obesity.

Several studies have reported that fat mass and obesity associated gene, *FTO* on chromosome 16q contribute to obesity (Loos & Bouchard, 2008; Dina et al., 2007; Frayling et al., 2007; Scuteri et al., 2007).

**Komentář [U8]:** Put this earlier to understand the abbreviation from the start.

Rivera et al (2012) have suggested that the association between FTO and obesity was mitigated by the ~~attendance~~ presence of depressive symptoms. A differentiation in gene TCF7L2 has been associated with protection to bipolar disease, but as BMI increases this outcome becomes weaker. Gene TCF7L2 encodes a transcription factor involved in the Wnt signaling pathway (Winham & Biernacka, 2013).

**Komentář [U9]:** Explain what is this.

## Developmental aspects

It has been suggested that obesity and mood disorders ~~are sharing~~share developmental pathways (Wu et al., 2012). Several studies have associated pediatric and adolescent obesity with ~~adulthood~~ depression in adults (Reeves, Postolache & Snitker, 2008; Anderson et al., 2007).

Reeves, Postolache & Snitker (2008) concluded that the investigation of childhood factors that influence the onset of ~~adulthood~~ depression and obesity in adults ~~and obesity~~ is needed.

Early child~~-~~hood malnutrition and low birth-weight have been linked to higher odds of developing depression during adulthood (or adolescence) (Wojcik et al., 2013; Sanchez-Villegas et al., 2012).

Grigoriadis et al (2013) have noted that mothers' depression due to pregnancy increases the risk of depression development in puberty, a fact that have been confirmed by Pearson et al (2013) and Raisanen et al (2014).

The exposure of fetus to maternal depression has been characterized as a risk factor ~~of~~ for childhood obesity development (Ruttle et al., 2014), while epigenetic processes such as DNA methylations causing changes in gene expression have been suggested as underlying developmental mechanisms. More specifically, Teh et al (2014) have found a link between mother~~'~~s' depression and obesity with epigenetic modifications.

Anderson et al (2007) have found that women who had experienced early childhood depression have had higher weight gain and BMI ~~z~~ scores in contrast to the women without depression.

A potential link between obesity and depression ~~could be~~ include altered stress system and increased inflammation, as obesity is regarded as a pro-inflammatory state. Both human and animal investigations have mentioned that

obesity increases adipose tissue expression and the secretion of pro-inflammatory cytokines.

Also it has been reported that treatment options that reduce obesity or insulin resistance have a moderating effect ~~of~~ on reducing inflammation (Ferrante AW Jr, 2007). In obese children the levels of the pro-inflammatory cytokine IL-6 and the C-reactive protein have been shown to be higher in comparison ~~as levels of C-reactive protein~~ to ~~overweight and~~ non-overweight youths (McMurray et al., 2007; Cindik et al., 2005).

Additionally, there is evidence that depression is linked to dysregulation of inflammatory system, where patients suffering major depressive disorder have higher levels of pro-inflammatory cytokines IL-6 and tumor necrosis factor alpha (Kim et al., 2007).

Those levels were also higher in patients with ~~treatment~~ treatment-refractory depression, as well as ~~and~~ in ~~as~~ euthymic individuals who were previously treatment~~-t~~ refractory in accordance to O'Brien et al (2007).

Charmandari et al (2003) based on Gold & Chrousos (2002) centering on the hypothalamic-pituitary-adrenal (HPA) axis argued that early childhood stress ~~effects on~~leads to the dysregulation of the stress system. This dysregulation causes hyperreactivity of the stress system and impaired glucocorticoid negative feedback showing a link between depression states and obesity.

The treatment used for pediatric depression (serotonin selective reuptake inhibitors - SSRI's) could play a role in the association of obesity and depression. It has been shown that serotonin affects appetite through food intake/preferences and mood states.

Wurtman & Wurtman (1995) have argued that underlying ~~decreases~~ serotonin decrease during mood episodes in seasonal depression could be a~~n~~ ~~explanation~~ factor explaining ~~for~~the preference for carbohydrates since they ~~which~~ increase~~s~~ the serotonin levels.

Gotlib et al (2008) assumed that ~~it~~ there could be a ~~potential~~n association between serotonin and HPA axis stress response through the ~~investigation of~~ discrepancies found in the promoter region of the serotonin transporter gene.

## Environmental

Mood disorders and obesity ~~share~~ have some common environmental risk factors ~~of~~ for their development such as the chronic psychosocial stress (Horesh & Iancu, 2010; Kyrou et al., 2006). One of the greatest risk factors for mood disorders is childhood trauma (i.e. physical, emotional and sexual abuse) (Watson et al., 2013; Carr et al., 2013; Nanni, Uher & Danese, 2012) ~~while~~ and recent evidence show~~s~~ an impact on metabolic health causing the increase of BMI and the risk of metabolic syndrome development in adulthood (Lee, Tsenkova & Carr, 2014a; Midei et al., 2013; Pervanidou & Chrousos, 2012; Midei, Matthews & Bromberger, 2010).

The scarcity of physical activity/exercise and ~~the~~ insufficient diet play a significant role ~~o~~in obesity onset while studies (Lai et al., 2014; Sanhueza, Ryan & Foxcroft, 2013; Lopresti Hood & Drummond, 2013a; Vancampfort et al., 2013) have argued that play a role ~~o~~in the onset of bipolar disorder and major depression disorder too.

Regarding ~~to~~ the socioeconomic risk factors, several epidemiological studies have found a positive association between obesity and mood disorders and unpropitious socioeconomic status. More specifically, poverty, isolation, low education level, and scarcity of support affect the onset of both obesity and mood disorders (Devaux & Sassi, 2013; Sassi, Devaux, & Church, 2009; Everson et al., 2002).

## Brain substrates

Functional connectivity problems and changes in brain structure are connected to mood disorders. Studies using neuroimaging have reported irregular probity in the neural tracts which connect the temporal and parietal cortices with the frontal cortex and sub-cortical regions in major depressive disorder in bipolar disorder (Liao et al., 2013; Vederine et al., 2011) while it has been shown that there is a decreased connectivity between limbic brain structures and ventral prefrontal networks (Vargas, Lopez-Jaramillo & Vieta, 2013; Strakowski et al., 2012). These networks may be involved in the formation of emotional control and cognition.

Obesity has also been considered to be subserved by abnormal brain networks (Mansur, Brietzke & McIntyre, 2015). In accordance to Garcia-Garcia et al (2012) obesity is considered to be linked to disturbed connectivity in neurocircuits which are involved in reward and motivation regulation including fronto-occipital and fronto-amygdala networks. These abnormalities, both at resting-state and in response to food and non-food rewarding stimuli, point out the extension beyond appetite regulation.

Bond et al (2011) found the increased BMI in bipolar disorder patients has been shown to mediate the decrease of brain white-matter volume and temporal lobe volume while Cole et al (2013) mentioned that in major depressive disorder patients, the reductions in subcortical and white matter areas were associated with increased BMI.

Serotonin, dopamine and opioids seems to be involved in mood regulation and brain reward circuitry. These neurotransmitters are also involved in homeostatic regulation of food intake (Russo & Nestler, 2013). Van de Giessen et al (2014) suggested that the abnormal dopamine signaling (low dopamine receptor availability) which is proportional to patient's BMI increased the sensitivity to conditioned stimuli and decreased sensitivity to rewarding effects.

Also, abnormities in cellular bioenergetics (focused on mitochondrial function) seem to be tangled in mood disorders aetiology (Manji et al., 2012) and in pathopsysiological mechanisms of obesity (Thrush et al., 2013).

Additionally, brain-derived neurotrophic factor (BDNF) is found to be a moderator of neuroplasticity and seems to be implicated in energy metabolism (Zagrebelsky & Korte, 2014; Marosi & Mattson, 2014). As Markham et al (2012)note, other functions that BDNF in part of are modulating neuronal glucose transport and mitochondrial function, energy homeostasis regulation, cellular bioenergetics, while the decrease of BDNF expression seems to be associated to obesity and hyperphagia in mouse model. BDNF expression in the hypothalamus was found to be inhibited by dietary restriction and enhanced by energy availability (Unger et al., 2007). Moreover, BMI has been associated with single nucleotide polymorphism Val66Met of BDNF gene (Shugart et al., 2009). Val66Met is a single nucleotide polymorphism which present a non-synonymous amino acid substitution of methionine (Met) for valine (Val) at position 66 of the BDNF protein (Bonaccorso et al., 2015).

Also, the endocannabinoid system (ECS) is suggested to be implicated in the regulation of energy metabolism and could be a factor in bipolar disorder and major depressive disorder pathophysiology (Ashton & Moore, 2011). ECS interacts with systems which are involved in the regulation of weight and food intake and also with energy-related hormones (such as leptin) (Bermudez-Silva et al., 2012). In the case of ECS dysregulation a development of obesity could be triggered, as were found to be altered in adipose tissue and in the plasma and saliva of obese people (Matias et al., 2012).

The chronic antagonism of the CB1 receptor reduced body weight concomitant improvements of metabolic parameters (Christopoulou & Kiortsis, 2011). eCB signaling has been characterized as a crucial modulator of the stress response through modulatory effects in HPA axis activation and behavioral reactions (Hill & Tasker, 2012). A CB1 antagonist impairs the antidepressant effects of eCBs and is connected to molecular pathways mediating both mood and metabolism (Moreira et al., 2008).

A potential aetiology of obesity and depression is the dysregulation of the hypothalamic-pituitary-adrenocortical system which is present on both health situations (Collins & Bentz, 2009; Scott et al., 2008; McIntyre et al., 2006; Carr & Friedman, 2005; Faith, Matz & Jorge, 2002).

Gold & Chrousos (2002) based on hypothalamic-pituitary-adrenal (HPA) axis created a concise model that presumes 2 subtypes of depression, melancholic and atypical of the stress system by changes in the HPA axis and sympathetic arousal. The depressed patients show decrease of sympathetic activity and HPA axis a fact that cause the increase of appetite which is triggered by sympathetic stimulation and corticotrophin releasing hormone mediated glucocorticoid secretion. These metabolic effects of HPA down regulation cause the increase of fat mass and the decrease of insulin sensitivity and dyslipidemia. Insulin resistance could be an aetiology factor of the association of obesity and depression.

# 5. Psychotropic medication and the risk of metabolic abnormalities

There is a great concern focused, throughout the years, on the metabolic complications caused by psychotropic medications including antipsychotics, antidepressants and mood stabilizers agents (Chokka, Tancer & Yeragani, 2006, Correll, Lencz & Malhotra, 2011). During psychopharmacological therapy metabolic side effects are observed, such as changes in body weight especially increased body mass index leading to overweight and obesity, increased risk of development of diabetes mellitus and alterations on the lipid profile. All these factors may increase health risks of several medical problems including cardiovascular complications like coronary heart disease, ischemic stroke, osteoarthritis, respiratory problems, hypertension and also cancer (Ruetsch et al.,2005; Himmerich et al., 2015). As it has been studied in the present review, the weight gain is linked to insulin resistance development and results in metabolic syndrome while it seems that psychotropic medications affect neuronal circuits that regulate appetite and the systems that regulate energy homeostasis (Wysokinski & Knoszewska, 2014).

Komentář [k10]: to other CVS above

Bradshaw & Mairs in 2014, represented 4 studies which are focused on patients with schizophrenia, bipolar disorder and depression, investigating the BMI and the existence of metabolic risk factors and the prevalence of metabolic syndrome. The findings suggest that there is a higher prevalence of metabolic risk factors in patients with mood disorders and abnormally high prevalence of metabolic syndrome.

## Antipsychotics

Revolution in medical care to people suffering from mental disorders, including schizophrenia and other psychotics disorders, was noted when psychopharmacotherapy was developed in the 1950s. In the beginning, first generation antipsychotics (FGAs), called also typical, were introduced with the synthesis of chlorpromazine by Delay & Deniker in 1952. The first obstacle reffering their use, was the side effect concerning extrapyramidal symptoms including parkinsonian symptoms due to blockade on D2 receptor. This finding caused great difficulties to treatment adherence and tolerance. In 1990s, the introduction of second generation antipsychotics drugs, called also atypical, came to diminish this side effect. These drugs became increasingly popular due to their low potency to produce extrapyramidal symptoms. Although this class seems to be preferable due to this advantage and higher efficacy, metabolic effects came to add a disadvantage, raised as a villain consequence (Teixeira et al., 2006, Reynolds et al., 2010, Potvin et al., 2015, Santini et al., 2016).

Metabolic syndrome is present 2 times higher in adults taking antipsychotics comparing to general population (Wysokinski, Kowman & Knoszewska, 2012). Allison et al (2009) have found that metabolic side effects of antipsychotic medications contribute to the high levels of obesity in schizophrenics. Weight gain including dyslipidemia has been proved as a metabolic side effect of antipsychotic treatment as some antipsychotic agents are related to increased blood lipids, mainly triglycerides (Newcomer, 2005).

Bradshaw and Mairs in 2014 focused on weight gain resulting from taking antipsychotic medication in meta-analysis studies. The evidence shows that all antipsychotic agents could potentially cause weight gain (compared to placebo) while it seems that the first generation antipsychotics cause less weight gain. Olanzapine and clozapine, as second-generation drugs, seem to cause rapid weight gain in the early treatment stages (up to 17 kg at the first year). Furthermore, the meta-analysis of Leucht et al (2009) suggests that olanzapine and clozapine are the most important weight gain-inducing drugs administered to schizophrenia patients. Foley & Morley (2011) have noted that weight gain could

be underestimated by up to 50% because of methodological limitations in the studies (like failing to assess for the effects noncompliance with medication). Alvarez-Jimenez et al in 2008 and Allinson et al in 1999 have found that weight gain is more severe and rapid in younger people with first episode psychosis who had limited previous exposure to antipsychotics and those who have a lower BMI pretreatment and more co-medications and antidepressants. These studies blame for weight gain more firmly on the side effects of antipsychotic medication. Allinson et al. suggested that antipsychotic medication has long been associated with weight gain in people with serious mental ill health (SMI) while Foley & Morley (2011) suggested that weight gain is more rapid on second-generation. Also, Kluge et al (2007) have suggested that olanzapine may promote binge eating and Mitchell et al (2013) systematic review found that prevalence of metabolic syndrome in people with SMI were 32.5%.

**Komentář [k11]:** speling

**Komentář [k12]:** in

**Komentář [k13]:** what is SMI – use the full term

As it could be observed in figure 10, the extent of weight gain is linked to age and treatment history regarding BMI increase with risperidone in adults and youth. In adults and youth the weight gain-episode patients is greater than in patients with chronic illness (Parsons et al., 2009; Lieberman et al., 2009). Correll et al. (2009) study in 135 children and adolescents showed the heterogeneity of three-month weight gain receiving risperidone (figure 10b). Despite a mean weight gain of 5.3 kg, weight gain outcomes varied considerably: weight loss occurred in 4.4%; weight gain of 0–6.9% of baseline body weight occurred in 31.1%; of 7–13.9% in 39.6%; of 14–20.9% in 18.5%; and of ≥21% in 6.7% of youth.

**Komentář [k14]:** probably should be first-episode patients

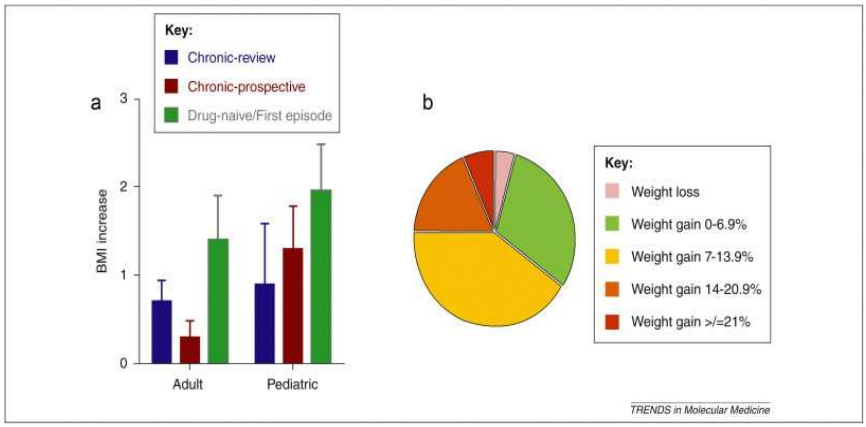


**Figure: a)** Effect of prior treatment exposure on BMI increase with risperidone in adult and youth.

**b)** Heterogeneity of weight gain in antipsychotic-naïve youth treated with risperidone for three months. Figure by Correll, Lencz & Malhotra, 2009.

Among typical antipsychotics, chlorpromazine as dopamine antagonist is associated with significant weight gain comparable to some of the second-generation agents (Adams et al., 2014). Chlorpromazine also affects serotonin (5-HT1 and 5-HT2), histamine (H1), adrenergic (α1 and α2) and muscarinic acetylcholine (M1 and M2) receptors. Phenothiazines represent an elevation of serum triglyceride and total cholesterol levels (Meyer, 2001). An analysis of four studies describing chlorpromazine treatment over 6 weeks in patients suffering from schizophrenia pointed out that about 24%of patients experienced significant weight gain (>7 % above their baseline weight) (Dossenbach et al., 2007).This typical antipsychotic agent is associated with high risk of developing hyperlipidemia and diabetes (Medici et al., 2016). Compared to chlorpromazine, haloperidol seems to be associated with moderate risk of weight gain and diabetes. Saddichha et al, when compared various types of antipsychotics including haloperidol, came to conclusion that the prevalence of metabolic syndrome related to this agent was the lowest among the others.

Regarding to atypical antipsychotics, clozapine and olanzapine, followed by quetiapine and risperidone are connected with greater incidents of diabetes,

hyperlipidemia and with the highest weight gain (Santini et al., 2016). Olanzapine and clozapine seem to be linked also with hypertriglyceridemia (Meyer, 2001). Medici et al. reported that the average weight gain associated with clozapine is 2.4 kg with a maximum reported of 10 kg. Olanzapine present a mean of 5.6kg in long term studies. This drug is connected with high risk of diabetes and increase serum lipid levels compared to other atypical antipsychotics. Patients with diabetes should use with caution olanzapine and monitor glycated hemoglobin (HbA1c) for signs of worsening glucose control. Increases in triglycerides, LDL cholesterol and total cholesterol and decreases in HDL cholesterol have been mentioned in the evaluation of studies for olanzapine and monitoring lipid levels during treatment is recommended (Proietto et al., 2004). In contrast to olanzapine and clozapine, the association of risperidone and weight gain is less significant .Sechter et al reported an average of 2.1 kg when risperidone was administered for 6 months to patients with chronic schizophrenia. High inter-individual variability is observed and is clearly demonstrated in published case studies as Fukui et al., which followed two patients treated with combination of risperidone and paroxetine. After 5 months of treatment, the raise of weight gain was up to 14kg.The suggested mechanism by authors was also a possible drug-drug interaction causing inhibition of cytochrome P450 enzyme 2D6. Less risk of developing diabetes is shown by aripiprazole and ziprasidone and that is due to low affinity at histamine receptors and partial antagonism on serotonin receptors (Medici et al., 2016).

**Potential mechanisms of antipsychotic drug-induced weight gain**

The atypical antipsychotics have an impact on several neurotransmitter systems. These drugs are exerting antagonistic actions at serotonergic, histaminergic, muscarinic, dopaminergic and adrenergic receptor subtypes. The neurotransmitters of the above systems are all implicated, directly or indirectly, in pathways associated with food intake regulation or metabolism (Teff et al., 2011, Panariello et al., 2011, Medici et al., 2016). Body weight gain, adiposity, dyslipidemia, impaired glucose homeostasis, insulin resistance, diabetes mellitus type II and leptin resistance are all factors arising from the use of atypical antipsychotics (Coccurello et al., 2010).

Dopamine plays an important role in feeding behavior. It affects the hypothalamus as well as other regions which determine the food intake. Its effects vary depending on the dose and on the site of administration in the hypothalamus. Atypical antipsychotics show affinity on dopamine binding sites of dopamine receptors (DA). The blockade of hypothalamic D2 can affect the feeding behavior with an increase in food consumption whether by direct action on nervous centers associated with appetite or by secondary hyperprolactinemia (Reynolds et al., 2010, Teff et al., 2011, Volpato et al., 2013, Panariello et al., 2011, Teixeira et al., 2006).

Circulating prolactin could be responsible for increase in food intake or stimulation of lipogenesis and this can be a consequence of blockade of the inhibitory effect of dopamine at the pituitary gland. Hyperprolactinaemia is connected with increased risk of obesity due to the fact that it is associated with insulin resistance and endothelial dysfunction which could improve after achieving normal levels of prolactin (Shibli-Rahhal et al., 2009). Hence, it may contribute to weight gain in patients treated with antipsychotics responsible for raising prolactin (Reynolds et al., 2010).

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In contrast, the involvement of other systems particularly of serotonin (5-HT2C), histaminergic (H1), adrenergic (α1, α2 and ß3) and muscarinic (M3) receptors located in central and peripheral pathways could play a stronger and prominent role than that of dopamine receptors (Coccurello et al., 2010).

Another important chemical messenger regulating a great variety of psysiological responses in the brain and peripheral organs including food intake, is monoamine histamine. The histaminergic system is involved in the reduction food intake through the histamine-induced activation of the H1 receptor. Blockade of H1 receptors is involved in increased appetite and consequent weight gain. The histaminergic system also influences the dopaminergic system. Histamine can suppress the mesolimbic dopamine pathway, responsible for controlling food intake, through the H3 autoreceptor and yet activates it through the histamine H1. Clozapine and olanzapine, are frequently used in the clinical setting due to their efficacy in treating the multiple domains of schizophrenia. These two atypical antipsychotics have a high affinity for the H1 receptor and olanzapine treatment has been demonstrated to decrease mRNA expression and H1 receptor binding

**Komentář [k17]:** of food intake

density in the hypothalamus (Brabant et al., 2010, Haas et al., 2008, Teff et al., 2011, Reynolds et al., 2010 ). The H3 histamine receptor also plays an important role in body weight and food intake. It acts as a heteroreceptor for other neurotransmitter signal pathways, such as noradrenaline, achetylcholine and serotonin (5-HT). Acts, moreover, as presynaptic autoregulator of histamine synthesis and release, which implicates in the regulation of eating behavior. However, whether the effect of weight-inducing antipsychotic drugs at the H3 receptor is unknown, Deng et al., 2010 proposed that the weight gain side effect of atypical antipsychotic drugs could be also a result of their effect on the H3 receptor.

Among neurotransmitters that contribute in food intake regulation, the serotonin system has been referred to as an important factor. That is why it is not surprising that it has been also under critical observation in the research for mechanism that is responsible for weight gain caused by antipsychotics. The 5-HT is a potent satiety signal. The 5-HT2C receptor is the most studied because this subtype is involved in the increase of weight gain through its physiological characteristics. Antagonism of this receptor is leading to induction of weight gain and also attenuates the decrease in food intake which is produced by 5-HT2C agonists (Himmerich et al., 2015, Hayashi et al., 2005, Panariello et al., 2011). However, ziprasidone, which is a strong antagonist of this receptor, has no evidenced association with weight gain and this could be explained by the compensatory anorexigenic action caused by noradrenaline reuptake inhibition (Wirshing, 2004). So the complex properties of a drug regarding the receptor profile play a key role. Murashita et al reported that risperidone blocks the HT2C receptor situated on hypothalamic arcuate nucleus (ARC) neurons, causing an alteration in the action of leptin.

A variation of sympathetic balance has been suggested to be a subject of obesity and diabetes development (Poyurovsky et al., 2003). Certainly, the relationship between sympathetic activity, noradrenaline secretion and role of the α1 receptor in energy metabolism, relating to the way of lipolytic activity, has been established. The role of α1 receptor in atypical antipsychotic induced glucose dysregulation could also be proposed by the hyperglycemic effects of α1 subtype

blockade (Coccurello et al., 2010). Furthermore, lipolytic activity by β-adrenergic stimulation was significantly inhibited by the administration of olanzapine. The study of other candidate genes in schizophrenic patients has resulted in the identification of genetic variants β3 adrenergic receptors as a possible risk factor for weight gain induced by olanzapine (Ujike et al., 2008). Association between polymorphism in β3 receptor and adiposity has been described in obese individuals as well as in schizophrenic individuals under clozapine medication (Coccurelo et al., 2010).

Zai et al in 2015, reported that among patients treated with olanzapine and clozapine with predicted weight gain, there is a potential role of genetic mutations involving the GABA alpha 2 receptor subunit variant.

It is widely known that parasympathetic nervous system and cholinergic transmission are involved in glucose-dependent insulin secretion. Additionally, type II diabetes mellitus results from the failure of glucose to stimulate insulin release from pancreatic ß-cells. Muscarinic receptors are distributed in pancreatic ß-cells and cholinergic dependent insulin release is under control of M3 receptors (Himmerich et al., 2015, Coccurelo et al., 2010). These receptors seem to be responsible for the regulation of insulin secretion, glucose homeostasis, and body weight and this can be an explanation for metabolic side effects and the large differences observed between high-to-moderate risk and low-risk antipsychotics. Among second generation antipsychotics, olanzapine, clozapine and quetiapine through its metabolite nor-quetiapine have an essential affinity at M3 receptors (Potvin et al., 2015). M3 receptor blockade from olanzapine in the brain may inhibit the acetylcholine pathway for insulin secretion (Weston-Green et al., 2012). The strong affinity of clozapine and olanzapine for the muscarinic M3 receptor is the mechanism which is suggested to be invloved in the dysregulation of glucose homeostasis and tendency to induce insulin resistance (Teff et al., 2011, Reynolds et al., 2010). Silvestre & Prous, proposed that this affinity is a great predictor to induce diabetes type II. In an in vitro study of isolated islet cells, there was supporting evidence highlighting the strong antagonism of olanzapine and clozapine at M3 sites and their inhibition of cholinergic stimulation of insulin secretion (Johnson et al., 2005).

As an extra factor, hyperleptinemia has been observed in schizophrenic patients. Many antipsychotic drugs could induce leptin resistance resulting to disinhibition of food intake. The disruption of hypothalamic function is provoked by antagonist action of antipsychotics at certain monoamine receptors (Reynolds et al., 2010). Panariello et al, suggested that there is an interaction between leptin and serotonin (specifically 5-HT2C). An important area of the brain, which is connected with food intake and body-weight regulation, is rich in 5-HT2C and the antagonism of these receptors attenuate the reduction in food intake produced by leptin. Furthermore, they suggested that hypothalamic histamine is a modulator of leptin activity. Leptin-induced food intake appears suppresses in H1 knockout mice.

Another one meta-analysis was performed aimed to examine the differential effect of antipsychotics on leptin levels in schizophrenia. Their findings shown an elevation on leptin levels produced by antipsychotics especially from olanzapine, clozapine, and quetiapine. Across their results, body mass index changes were significantly associated with hyperleptinemia. This suggests that leptin acts as a negative feedback signal in the event of fat increase. In addition, alterations in leptin were positively associated with changes in total cholesterol, LDL and triglycerides. These results have a close similarity to the known link between antipsychotic treatment, increased hyperlipidemia and adiposity (Potvin et al., 2015).

In the field of pharmacogenetics of antipsychotic drug-induced metabolic pathology, BDNF (as it was mentioned in the chapter brain substrates) plays a role in the regulation of food intake and one report has found a relationship with the functional Val66Met polymorphism of the BDNF gene of weight gain in male patients treated with antipsychotic drugs (Zhang et al., 2008). More recently, Bonaccorso et al. in 2015 hypothesized that this common functional variant, Val66Met, which has been shown to be linked with increased body mass index (BMI) in schizophrenia, is also associated with antipsychotic-induced weight gain in bipolar disorder. Moreover, this study measured the connection of this variant with other metabolic parameters, such as total cholesterol and triglycerides. It concluded that the expression of Val66Met is connected with a steady, long-term increase in BMI of bipolar patients within a 6-month period treatment with

**Komentář [k18]:** syntax

**Komentář [k19]:** delete „one“

**Komentář [k20]:** and

risperidone and olanzapine. Additionally, there was an increase in the triglycerides/high density lipoprotein ratio after a 3-month period treatment with risperidone.

As it could be seen below on table 2 clozapine and olanzapine produce the most weight gain, quetiapine and risperidone produce intermediate weight gain, and ziprasidone and aripiprazole produce the least weight gain. The differences in weight gain are linked to the risk of dyslipidemia, insulin resistance, and glucoregulatory dysfunction (American Diabetes Association et al., 2004).

Komentář [k21]: in

Komentář [k22]: I added coma

| | Risk of metabolic abnormalities | | |
|---|---|---|---|
| **Antipsychotic agent** | Weight | Risk for diabetes | Lipid profile alterations |
| **Clozapine** | +++ | + | **+** |
| **Olanzapine** | +++ | + | **+** |
| **Risperidone** | ++ | D | **D** |
| **Quetiapine** | **++** | D | **D** |
| **Ziprasidone** | +/- | - | **-** |
| **Aripiprazole** | **+/-** | **-** | **-** |

**Table 2:** Atypical antipsychotic drugs and metabolic disturbances (adapted from, American Diabetes Association et al., 2004).

D = discrepant results

## Antidepressants

Weight gain is an important factor that contributes to patient non-compliance and may lead to medical comorbidity. However, each person separately responds to antidepressants in a different way. Some people seem to gain weight, when treated with a certain antidepressant, while others don't. There is a growing interest in the last two decades, regarding the effect of psychotropic medication on

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body weight. Despite the fact that the relationship between weight gain and new generation antipsychotics, is verified, the interest on the effect on body weight from antidepressants on the literature is more limited (Uguz et al.,2015). Furthermore, the depression itself could be associated with increased body weight in adults, and this is a parameter that should be taken into account from any study that attends to examine the causal of weight gain from antidepressants (Patten et al., 2011).

Both hyperglycemia and hypoglycemia were observed in patients taking antidepressants. Referring to hyperglycemia, the association with antidepressants is probably due to the high binding affinity on 5-HT2c receptor and norepinephrine reuptake transporter. Additionally, hyperglycemia could be a consequence of the association between disturbances of glucose homeostasis and antihistaminergic antidepressants. Blockade of H1-R might cause such metabolic abnormalities due to counteracting the central anorexigenic effects of histamine or increasing adipose tissue deposition (Derijks et al., 2008a). Hyperglycemia has also been induced by drugs acting as agonists on central serotonin receptors (5-HT2A and 5-HT2B) (Khoza et al., 2011; Chaouloff et al., 1992). The inhibition of insulin signaling cascade by antidepressants, which leads to insulin resistance has also been hypothesized to induce hyperglycemia (Levkovitz et al., 2007). Khoza et al. proposed that antidepressants may provoke the elevation of cortisol through HPA-axis, thus resulting in insulin resistance and hence to hyperglycemia. In contrast, hypoglycemia was observed in diabetic patients taking antidepressants for over 3 years. The possible underlying mechanism is the affinity for the serotonin reuptake transporter (Derijks et al., 2008b).

Salvi et al, the most recent study in 2016, aimed to assess the prevalence of metabolic syndrome in patients with bipolar disorder exposed to different types of antidepressants. More precisely, they investigated whether the prevalence of metabolic syndrome is affected by the H1-R affinity of antidepressants. They classified the antidepressants according to their H1-R affinity in 2 groups. The first one included antidepressants with low affinity on H1 receptors (selective serotonin reuptake inhibitors plus venlafaxine, duloxetine, clomipramine, reboxetine and bupropion) and the second group drugs with high affinity in H1 receptor (amitriptyline, imipramine, nortriptyline, trimipramine, and mirtazapine). Finally,

**Komentář [k24]:** change to receptor as in other sections

**Komentář [k25]:** and

**Komentář [k26]:** receptor

**Komentář [k27]:**

their results are showing that the the prevalence of metabolic syndrome is almost identical reaching the 24 % among patients treated with H1-R low-affinity antidepressants and on the other hand, the prevalence of metabolic syndrome was substantially higher reaching the 53% among patients treated with H1-R high-affinity antidepressants. Throughout the years, this is the first time that this is observed in a clinical setting.

For a long time is known that tricyclic antidepressants and monoamine oxidase inhibitors have shown metabolic side effects related to weight gain and obesity development (Garland, Remick & Zis, 1988). Tricyclic anti-depressants, including nortriptyline, amitryptiline, doxepin, and desipramine, are first-generation anti-depressants acting by inhibiting serotonin and norepinephrine reuptake, with consequent elevation in synaptic concentration of neurotransmitters. High affinity for the H1 receptor, high antimuscarinic action and alphalytic action, are associated with a high incidence weight gain (Harvey et al., 2000). The exact mechanism that leads to weight gain is unknown, but there are probably many contributing factors. Tricyclic antidepressants can increase appetite and carbohydrate cravings. Amitriptyline is associated with short-term (4–8 weeks) and long-term (more than 3 months) weight gain, with a mean gain of about 2 kg. Amitriptyline appears to be the drug associated with the most significant weight gain in its category (Vanina et al., 2002). Moreover, in vitro studies in human culture hepatocytes have demonstrated that amitriptyline upregulates sterol regulatory element-binding protein (SREBP), associated with activation of hepatic lipid deposition (Raeder et al., 2006). These findings are concerning for potential lipotoxicity, even though there is no evidence that amitriptyline is associated with worsening fatty liver.

Monoamine oxidase (MAO) inhibitors, have shown greater potential on weight gain, when compared to selective serotonin reuptake inhibitors (SSRIs). Results from Pande et al. study, on patients with depression showed that the monoamine oxidase inhibitor, phenelzine, over a 6 weeks of treatment was connected with greater likelihood for weight gain than fluoxetine. Fava et al., suggested that from this class, phenelzine seems to be the drug most likely associated with weight gain, because it exerts its effects on mechanisms controlling appetite.

**Komentář [k28]:**

**Komentář [k29]:** so how do you mean „identical" – 24 vs 51 % is a difference

**Komentář [k30]:**

**Komentář [k31]:**

**Komentář [k32]:** of

**Komentář [k33]:** delete „a"

Selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, are first-line medicines prescribed for depression and plenty of alternative conditions together with panic attacks, chronic anxiety and post-traumatic stress disorder. Zimmermann et al. (2003) found that SSRIs (selective serotonin reuptake inhibitors) induce weight loss rather than weight gain. Mirtazapine, paroxetine, amitriptyline, citalopram and escitalopram have been associated with weight gain (Dent et al., 2012). The mechanism of action is also based on the binding of post-synaptic 5-HT receptors, resulting in increased serotonin levels and increased stimulus conductivity. SSRIs are related to weight gain less often than other anti-depressants, when used in short-term treatment of 2–3 months in length (Michelson et al., 1999). In contrast, during long term treatment, of 6-30 months, paroxetine has been shown to be associated with the highest risk of weight gain, while fluoxetine has been linked to the lowest risk (Fava et al., 2000). The underlying mechanism which was suggested to be the cause of increased appetite and carbohydrate cravings, is the direct role of SSRIs on 5-HT, that contribute on appetite regulation (Harvey et al., 2000). Lustman et al., in a randomized double-blind placebo-controlled trial, evaluating the increased risk of developing diabetes mellitus from SSRIs, found that fluoxetine showed a great profile on improved glycemic control. In 2013, Andersohn et al., proposed that among SSRIs, paroxetine was associated with increased risk of diabetes. Notwithstanding, clinical studies lack development of visceral obesity and fat distribution, in an *in vitro* study on murine islet cells incubated with SSRIs, Isaac et al in 2013 suggested that the underlying mechanism that shows approval of the development of diabetes mellitus, is the triggered beta cell death and the inhibition of insulin secretion.

Another drug that shows a greater potential on weight gain in relationship with SSRIs, is mirtazapine, a specific serotonergic and noradrenergic antidepressant (Watanabe et al., 2011). A possible mechanism explaining the correlation between metabolic and psychotropic effects of mirtazapine is the relationship between insulin sensitivity and 5-HT2-antagonism. A direct effect on 5-HT receptors could have a consequence on lipid metabolism. Increase in body weight and hypercholesterolemia were observed when mirtazapine was added to

**Komentář [k34]:** delete, this section is focused on SSRI

**Komentář [k35]:** I added

**Komentář [k36]:** related to

**Komentář [k37]:** I changed to italic

first generation antipsychotics for the treatment of schizophrenia. Similarly to clozapine, mirtazapine inhibits also the histamine H1 receptors and this effect could be an observation of its metabolic changes (Terevnikov et al., 2013). The patient's weight gain is observed in the beginning stages and during long-term therapy and this is most likely associated with increased appetite. Versiani et al. on 2005, during a double-blind clinical trial, compared mirtazapine and fluoxetine in severely depressed patients for 8 weeks. Mirtazapine-treated patients gained up to 2,7kg, whereas fluoxetine-treated patients lost up to 2,1kg. Studies from 2011 evaluated that the increase in weight from mirtazapine was linked to hyperglycemia and glucose metabolism dysregulation (Khoza et al., 2011). An experimental study found that 4 weeks of treatment with mirtazapine led to an increase in leptin plasma levels and weight gain. Here the leptin resistance could be explained by the antihistaminergic activity of this drug, interfering on hypothalamic nuclei integrating signals relevant for energy balance (Schilling et al., 2013). In one case report, significant elevated levels of plasma glucose were observed by the use of mirtazapine accompanied by a significant weight gain of 15.9 kg in 5 months of treatment (Fisfalen et al.,2003). Duncan et al in 2015 presented a case study of a man 75 years old, suffering from dementia, who was being treated with mirtazapine to improve his mood. High levels of triglycerides were noticed, consequently followed by hyperglycemia. Eventually, after the discontinuation of mirtazapine, hypertriglyceridemia still persisted.

Komentář [k38]: I added

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Komentář [k40]: in

Psychotropic drugs are found to activate the TNFa system and leptin by increasing plasma levels of these cytokines and cytokine receptors. A research study investigated the effect of amitriptyline and paroxetine on weight and on leptin, TNF-α, and TNF receptors and concluded that weight gain induced by psychotropic agents may occur without increased circulating levels of leptin (Himmerich et al., 2015, Hinze-Selch et al., 2000). The increase of leptin concentration could also be present on antidepressants medication as Kraus et al. have observed a small raise of leptin in depressive patients treated with mirtazapine.

Uguz et al. in 2015, investigate the weight gain in 362 patients under antidepressants treatment for 6 to 36 months. The results have shown that 55.2% of patients presented weight gain while 40.6% of them had a weight gain of 7% or

more compared to the baseline. Also, citalopram, escitalopram, sertraline, paroxetine, venlafaxine, duloxetine and mirtazapine, but not fluoxetine, were associated with significant weight gain.

Conversely, paroxetine and mirtazapine but not the other newer antidepressants were associated with a greater risk of weight gain in Serretti & Mandelli (2010) research study.

Wise et al (2010) analyzed 10 clinical studies to finding that long-term use of duloxetine and paroxetine is significantly associated with weight gain. Dannon et al (2004) reported an average weight gain of 5.06 kg by paroxetine treatment while Dannon et al (2007) suggested that mean increase in body weight was significant at 6.1 kg. More specifically Dannon et al (2007) reported that fluoxetine, citalopram, paroxetine, and fluvoxamine have respectively weight gain .2, 6.9, 8.2 and 6.3 kg. Patten et al (2009) mentioned that after 12 years the average weight gain is 7.2 to 7.6 kg.

**Komentář [k41]:** the lenght of treatment should be indicated in this paragraph when you explicitly report th number of kg

| Medication | Effect on Weight |
|---|---|
| **Tricyclics** | Most produce weight gain |
| **SSRIs:** | |
| Citalopram fluoxetine, fluvoxamine and sertraline | Neutral |
| Paroxetine | Gain |
| **Bupropion** | Loss |
| **Mirtazapine** | Gain |
| **Venlafaxine** | Neutral |

**Table 3:** Effects of Pharmacotherapy for Depression on weight (Stunkard, Faith & Allison, 2003)

## Mood stabilizers

Drug-induced weight gain has long been associated with antipsychotic medications. Another major class of drugs causing a significant risk in weight gain is mood stabilizers. They are used for the treatment of bipolar disorder and agents included in this class are lithium, valproic acid, carbamazepine and lamotrigine. (Wirshing, 2004; Zimmermann et al.,2003). Among these aforementioned drugs lithium and valproic acid cause the greatest increase in weight, carbamazepine to a lesser degree and lamotrigine does not seem to be associated (Teixeira et al., 2006).

| Medication | Effect on Weight |
|---|---|
| Lithium | Gain |
| Valproate | Gain |
| Carbamazepine | Neutral |
| Lamotrigine | Neutral |
| Topiramate | Loss |

**Table 4:** Effects of Pharmacotherapy for Bipolar Disorder on Weight (Stunkard, Faith & Allison, 2003).

Lithium is one of the most frequently used treatments for bipolar disorder and despite its characterization as a gold standard it seems to have serious effects on thyroid and parathyroid glands, BMI and kidneys (Eker & Eker, 2010). One of the most common adverse effects of lithium is weight gain and how exactly this occurs is not clearly understood. Lithium stimulates in a direct way the appetite at

the hypothalamus and the proposed mechanisms involved are: an insulin-like action causing increased fat deposition in the initial stages of treatment resulting in glucose tolerance and an increase in insulin sensitivity, edema caused by sodium retention, subclinical hypothyroidism, reduced adiponectin and increased appetite connected with mood improvement (Garland et al., 1988, Gracious and Meyer, 2005,Teixeira et al., 2006, McKnight et al., 2012, Medici et al. 2016). It has also been noted that weight gain caused by lithium occurs even in the presence of high leptin levels and as a result, it has been proposed that mood stabilizers could reduce hypothalamus sensitivity to the action of leptin (Wirshing, 2004; Holt, Peveler & Byrne, 2004; Zimmermann et al., 2003).

**Komentář [k42]:** the oposite probably NO?

The increase in weight caused by lithium is variable ranging from 4 to 12kg (Chengappa et al., 2002). Garland et al. reported that during chronic treatment, there was an increase of 10kg in 20% of the patients while during a small eight-week study by Atmaca et al. a mean weight gain of 5.9kg was found. Gracious and Meyer suggested that risks for weight gain included female gender, nephrogenic diabetes insipidus, history of obesity and combination with antipsychotic drugs.

**Komentář [k43]:** for how long – lenght of treatment?

Regarding valproic acid-induced weight gain, the mechanism of its effect in the hypothalamus is poorly understood and it is suggested that it could enhance secretion of insulin from pancreatic beta cells and reduce insulin clearance by the liver resulting in hyperinsulinemia which leads to weight gain (Pylvanen et al., 2006, Verrotti et al., 2011). Another mechanism suggested by Qiao et ali, is the down-regulation of adiponectin gene transcript levels in adipocytes. The study of Gracious and Meyer noticed that 57% of adults treated with valproic acid gained more than 4kg while the rest remained in a stable weight. Medici et al. mentioned that the increase in weight by valproic acid is dose-related and the maximum increase is observed at 6 months of therapy.

**Komentář [k44]:** I added

**Komentář [k45]:** lenght of tretament

| Antidepressants | Relative incidence | Antipsychotics | Relative incidence | Mood stabilizers | Relative incidence |
|---|---|---|---|---|---|
| Amitriptyline | +++ | Aripiprazole | + | Carbamazepine | + |
| Bupropion | +/- | Asenapine | + | Lamotrigine | + |
| Citalopram | + | Chlorpromazine | ++ | Lithium | ++ |
| Duloxetine | + | Clozapine | +++ | Valproate | ++ |
| Escitalopram | + | Haloperidol | + | | |
| Fluoxetine | + | Olanzapine | +++ | | |
| Mirtazapine | +++ | Risperidone | ++ | | |
| Paroxetine | ++ | Quetiapine | ++ | | |
| Sertraline | + | Ziprasidone | + | | |
| Venlafaxine | + | | | | |

**Table 5:** The relative incidence of weight gain with selected psychotropic medication, antidepressants, antipsychotics and mood stabilizers (adapted fromWhite et al., 2013).

**Komentář [k46]:** I added

# Conclusion

The present study aimed to investigate the relationship between metabolic abnormalities and psychiatric disorders analyzing the similarities in their biological pathways. In conclusion, several research data indicates the impact of certain risk factors, such as genetic, psychological, environmental and lifestyle factors in abnormalities which are finally expressed as metabolic syndrome.

As it has been studied, the relation between mood disorders and obesity is indeed bidirectional as obesity could cause mood disorders and mood disorders and its pharmacological treatment could cause weight gain and metabolic syndrome.

Certain abnormalities, such as the stress or the dysregulation of HPA axis, the dyslipidemia, the abnormalities on leptin, insulin and cortisol levels, the insulin resistance, the impaired glucose control and glucose disturbances, the adipokines and the broken mechanism of leptin, the higher levels of pro- inflammatory markers, are involved in the process of obesity and metabolic syndrome development which are present in patients with mood disorders. It is remarkable that these patients have twice higher odds to develop obesity (Stubbs et al., 2015).

Finally, drugs such as antidepressants, antipsychotics, and mood stabilizers are strongly associated with weight gain and metabolic syndrome. The following table summarizes the risk of mood disorders medication regarding weight gain, obesity, and development of metabolic syndrome. As it can be seen, amitriptyline, mirtazapine, clozapine and olanzapine (as depression and schizophrenia treatment) are the most inculpatory for weight gain, while mood stabilizers constitute a moderate risk for obesity
(White et al., 2013; Serretti & Mandelli, 2010; Torrent et al., 2010; Muench & Hamer, 2010).

Dopamine-2 receptor antagonism may be a common factor in antipsychotic-induced weight gain (Balt et al., 2011). The interactions of histamine-1, serotonin-

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**Komentář [k49]:** impaired

**Komentář [G50]:** Inserted: d

**Komentář [G51]:** Deleted:nt

**Komentář [G52]:** Inserted: ,

**Komentář [G53]:** Inserted: ,

**Komentář [G54]:** Deleted:to

2C and muscarinic cholinergic receptors seem to be related to weight gain at antidepressants use. Paroxetine constitutes the most commonly associated with weight gain agent by the selective serotonin reuptake inhibitors (Serretti & Mandelli, 2010). Finally, as lithium is associated with hypothyroidism it seems to result in obesity development by the slowed metabolic rate (McKnight et al., 2012).

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**Komentář [G56]:** Inserted: h

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