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The Bidirectional Relationship Between Psychiatry and Type 2 Diabetes Mellitus

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1. Introduction

The relationship between DM and Psychiatry is becoming obvious and may be traced through a huge research material over the last few decades. However the nature of the relationship is still an unanswered question: is there a causal relationship or is it a mere comorbidity? As the relationship is becoming more and more complicated with the discovery of antipsychotic induced DM all over the world, biologically based research is still needed to clarify the obscure areas of this relationship.

2. Psychological stress predisposing to DM

Diabetes mellitus has reached epidemic proportions and affects more than 220 million individuals worldwide (WHO, 2009). These figures are expected to rise to 366 million by 2030 (Wild et al., 2004). In more developed societies, among obese white adolescents 4% had diabetes and 25% had abnormal glucose tolerance (Sinha et al, 2002). Some 90% of diabetic individuals have type 2 (non-insulin-dependent) diabetes mellitus, and within this category no more than 10% can be accounted for by monogenic forms such as maturity-onset diabetes of the young (Fajans et al, 2001) and mitochondrial diabetes (Maassen et al, 2004) or late-onset autoimmune diabetes of the adult, which is actually a late-onset type 1 diabetes (Pozzilli and Di Mario, 2001). Thus, most diabetes in the world is accounted for by “common” type 2 diabetes, which has a multifactorial pathogenesis caused by alterations in several gene products.

To understand the cellular and molecular mechanisms responsible for type 2 diabetes it is necessary to conceptualize the framework within which glycaemia is controlled. Insulin is the key hormone for regulation of blood glucose and, generally, normoglycaemia is maintained by the balanced interplay between insulin action and insulin secretion. Importantly, the normal pancreatic β cell can adapt to changes in insulin action—ie, a decrease in insulin action is accompanied by upregulation of insulin secretion (and vice versa). (Bergman 1989) Deviation from this hyperbola, such as in the patients with impaired glucose tolerance and type 2 diabetes occurs when β -cell function is inadequately low for a specific degree of insulin sensitivity. Thus, β -cell dysfunction is a critical component in the pathogenesis of type 2 diabetes. This concept has been verified not only in cross-sectional studies but also longitudinally. (Weyer, et al, 1999)

Although lifestyle and overeating seem to be the triggering pathogenic factors, genetic elements are also involved in the pathogenesis of type 2 diabetes. Positive family history confers a 2.4 fold increased risk for type 2 diabetes. 15–25% of first-degree relatives of patients with type 2 diabetes develop impaired glucose tolerance or diabetes. The lifetime risk (at age 80 years) for type 2 diabetes has been calculated to be 38% if one parent had type 2 diabetes. (Pierce et al, 1995) If both parents are affected, the prevalence of type 2 diabetes in the offspring is estimated to approach 60% by the age of 60 years. (Tattersal and Fajans, 1975)

Since dizygotic twins share the environment (both intrauterine and extrauterine) but only 50% of their genes, concordance rates in monozygotic twins in excess of those in dizygotic twins have been used to distinguish genetic from non-genetic contributions. In individuals older than 60 years, concordance rates for diabetes were 35–58% in monozygotic twins, compared with 17–20% in dizygotic twins. (Kaprio *et al.*, 1992; Newman et al, 1987). Inclusion of impaired glucose tolerance markedly increased the concordance in monozygotic twins to 88%. (Henkin et al, 2003). Nevertheless, concordance rates in monozygotic twins might produce an underestimate of genetic effects, because the monochorionic intrauterine nutrition of monozygotic twins has been shown to result in growth retardation compared with dizygotic twins. And low birthweight itself is associated with increased risk of type 2 diabetes later in life. (Beck-Nielsen et al 2003; Hales and Barker, 1992; Hattersley and Tooke, 1999)

The exact causes of type 2 diabetes are still not clear. Since the 17th century, it has been suggested that emotional stress plays a role in the etiology of type 2 diabetes mellitus. So far, review studies have mainly focused on depression as a risk factor for the development of type 2 diabetes mellitus. Yet, chronic emotional stress is an established risk factor for the development of depression. Results of longitudinal studies suggest that not only depression but also general emotional stress and anxiety, sleeping problems, anger, and hostility are associated with an increased risk for the development of type 2 diabetes. Conflicting results were found regarding childhood neglect, life events, and work stress. Moreover, a considerable number of depressed patients suffer from high levels of diabetes-specific emotional stress (Pouwer et al., 2005; Kokoszka et al., 2009). Important factors contributing to the increasing prevalence of type 2 diabetes are obesity, physical inactivity, and an increase in the number of individuals older than 65 years (Wild et al., 2004).

Interestingly, stress has long been suspected as having important effects on the development of diabetes. More than 400 years ago, the famous English physician Thomas Willis (1621–1675) noted that diabetes often appeared among persons who had experienced significant life stresses, sadness, or long sorrow (Willis, 1675). One of the first systematic studies testing Willis's hypothesis was described in 1935, by the American psychiatrist Dr. W. Menninger, who postulated the existence of psychogenic diabetes and described a “diabetic personality” (Menninger, 1935). More recently, numerous studies have been performed, elucidating the role of emotional stress as a risk factor for the development of type 2 diabetes. The majority of these studies focus on depression. However, there is growing evidence that other forms of emotional stress contribute to the development of type 2 diabetes as well.

Nowadays, the term “stress” is commonly used in the psychological, biological, and medical sciences. The concept of stress has been developed in the 1930s by the endocrinologist Hans Selye. In 1950, he has defined stress as “the nonspecific response of the body to any demand,” with the body going through three universal stages of dealing with the stressor:

the alarm phase (Cannon's fight-or-flight), the resistance phase (in which resistance to the stress is built), and the exhaustion phase (when the duration of stress is sufficiently long), together encompassing the "general adaptation syndrome." A more recent stress theory by McEwen (1998) is based on Selye's general adaptation syndrome, but incorporates additionally the notion that the body anticipates a stress response by shifting the homeostatic set point (allostasis, or stability through change). This comes at a price though, because shifting a set point of one system (e.g., blood pressure) affects other physiological systems (e.g., kidney function), a concept which is known as allostatic load.

However, the meaning of the word "stress" has changed during the past decades. Currently, stress usually refers to the consequence of the failure of an organism to respond appropriately to emotional or physical threats, whether actual or imagined (Bao et al., 2008). Stress symptoms commonly include a state of alarm. Signs of stress can be defined at a cognitive, emotional, physical or behavioral level. Cognitive signs are for example poor judgment, low self-esteem, poor concentration, and negative cognitions. Emotional signs include moodiness or even depression, feeling of anxiety, excessive worrying, irritability, agitation, and feeling lonely or even isolated. Physical symptoms are for example aches and pains, diarrhea or constipation, nausea, dizziness, chest pain, and rapid heart rate. Behavioral symptoms of stress can for example include: eating too much or not enough, sleeping too much or not enough, social withdrawal, procrastination or neglect of responsibilities, increased alcohol, nicotine, or drug consumption, and nervous habits such as pacing about or nail-biting.

Although the stress response of the body functions to maintain stability or allostasis, a long-term activation of the stress system can have serious, negative consequences for the body (Bao et al., 2008). Based on nine prospective epidemiological studies, Knol et al. (2006) were the first to conclude that depression increases the risk for type 2 diabetes by 37%. Two years later, Mezuk et al. (2008) were able to include a total of 13 studies that investigated depression as a risk factor for diabetes, representing 6,916 incident cases. In that meta-analytic review, the risk for incident diabetes was 60% higher in depressed participants, compared to non-depressed controls.

Engum (2007) has tested anxiety as a risk factor for the development of diabetes, using data from a large Norwegian prospective population-based study ($n=37,291$). Both baseline anxiety and depression were associated with an increased risk for the development of type 2 diabetes at 10 years follow-up. Among participants with a high level of depression/anxiety at both baseline and follow-up, the risk of type 2 diabetes was even higher (Engum, 2007).

Persons who had experienced significant life events during the past five years had a 1.6-fold increased risk to have type 2 diabetes compared to those who had not experienced life events. Interestingly, data from the Hoorn Study showed that life events were positively associated with the Waist-Hip-Ratio, an important risk factor for diabetes and cardiovascular disease (Mooy et al., 2000). Visceral adiposity does not seem to be the main link between stress and development of type 2 diabetes. Goodwin and Stein (2004) used data from the National Comorbidity Survey ($n=5,877$). In particular, a history of childhood neglect was associated with a higher risk of diabetes and this risk was higher among women, after adjustment for age, gender, race, marital status, income, and education. The first prospective study in this area has been described by Räikkönen et al. (2007) who used data from the Healthy Women Study ($n=523$) to test whether psychosocial factors predict the risk for the development of the metabolic syndrome. These researchers found that

among this group of middle-aged women, baseline depressive symptoms, feeling frequently intensely angry, tensed or stressed, and very stressful life events were all associated with an increased risk to develop the metabolic syndrome during the 15-year follow-up.

Several prospective studies have tested the hypothesis that “general emotional stress” is associated with an increased risk for the development of type 2 diabetes. Rod et al. (2009) analyzed data from the Copenhagen City Heart Study, involving 7,066 women and men, finding that particularly stressed men but not women were more than two times as likely to develop diabetes during follow-up. Interestingly, participants who had reported high levels of stress compared to those with low levels of stress were less likely to quit smoking, more likely to become physically inactive, and less likely to stop drinking during follow-up: all these factors are known to be associated with an increased risk for type 2 diabetes. In another Japanese study by Toshihiro et al. (2008) among 128 male Japanese with impaired glucose metabolism, a high score on a questionnaire assessing “stress in daily life” was associated with an increased risk for the development of type 2 diabetes after a 3-year follow-up. Golden et al (2005) have conducted a longitudinal cohort study of 11,615 non-diabetic adults aged 48-67 years at baseline. Anger, particularly anger temperament, appeared to be associated with onset of type 2 diabetes. Additional analyses showed that particularly a higher caloric intake and adiposity but not smoking behaviors and physical activity were potential mediators of this association. Finally, Zhang et al. (2006) analyzed data from 643 non-diabetic men with a mean age of 63 years, and found that the persons who reported a high level of stress and high hostility were more likely to have higher insulin resistance levels. This result is in line with earlier studies by Surwit et al. (2002) and Raikonen et al. (2003). In the study by Zhang et al., the association between hostility and insulin resistance was mediated by the stress hormone norepinephrine (Zhang et al., 2006).

Excessive overtime, probably due to over commitment to work has been reported to be associated with 4-fold higher risk of type 2 diabetes in Japanese men, independent of other risk factors (Kawakami et al., 1999). However, in the same study, job strain (defined as high work overload and low job control) was not significantly associated with incident diabetes. In the Whitehall II Prospective Study (Kumari et al., 2004), an imbalance in effort-reward, suggestive of significant work stress, was associated with a higher risk to develop diabetes in men but not in women. In a large (n=33,336) population-based sample, tense working situation related working stress was associated with onset of diabetes after, on average, 5 years, in women but not in men (Norberg et al., 2007). Burn-out, resulting from chronic work stress, has also been studied as a risk factor for the development of type 2 diabetes. Another study that was based on data from the Whitehall II Study (1991-2004) tested whether stress at work was associated with an increased risk of type 2 diabetes, in a sample of 5,895 middle aged civil servants (Heraclides et al., 2009). In that study, “psychosocial stress at work” appeared to be an independent predictor of the onset of type 2 diabetes among women, during a follow-up period of 15 years, but not in men. The strong association in the female group remained stable and decreased with only 20% after adjustment for life events, health behaviors, obesity, potentially confounding, and mediating factors (Heraclides et al., 2009).

Poor sleep can be an important indicator of emotional stress. On the one hand, emotional stress can easily affect different aspects of sleep, such as initiation of sleep, sleep duration, and sleep quality. Conversely, sleeping problems may not only be a consequence of emotional stress, but are often experienced as a significant source of stress. In their recent systematic review and meta-analysis, Cappuccio et al. (2010) tested whether habitual sleep

disturbances were associated with a higher incidence of type 2 diabetes. They included 10 studies, comprising a total of 107,756 male and females. Follow-up durations of the studies ranged from 4 to 32 years. It appeared that short duration of sleep (less than 5 to 6 hours per night) increased the risk for type 2 diabetes. Difficulties in initiating sleep also increased the risk for the onset of type 2 diabetes. Interestingly, persons with a long duration of sleep, more than 8-9 hours per night were at increased risk for incident type 2 diabetes. Difficulty in maintaining sleep was associated with an 84% higher risk to develop type 2 diabetes. A high body mass index (BMI) is an important potential confounder in studies that investigate sleeping problems and incidence of type 2 diabetes. Overweight is a major risk factor for type 2 diabetes that can also contribute to snoring problems and sleep apnea (and thus to sleeping problems). Therefore all 10 studies that were included in the meta-analysis of Cappuccio adjusted their analyses for BMI.

Emotional stress can increase the risk for the development of type 2 diabetes through different pathways. The first pathway is via behavioral mechanisms. Emotional stress was found to be associated with unhealthy lifestyle behaviors, i.e., inadequate eating behaviors in terms of quality and quantity of food, low exercise levels, smoking and alcohol abuse (Bonnet et al., 2005; Rod et al., 2009). All these factors are well-known risk factors for the development of type 2 diabetes. The second pathway is via physiological mechanisms. Chronic stress reactions and depression are often characterized by long term activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system which were found to be associated with the development of abdominal obesity, and this may explain why depression or chronic stress increases the risk of diabetes (Björntorp, 2001; Vogelzangs et al., 2008).

Chronic stress can also initiate changes in immune system activity. There is experimental and clinical evidence that a rise in the concentration of pro-inflammatory cytokines and glucocorticoids, particularly cortisol, in response to chronic stress, both contribute to the behavioral changes associated with depression (Leonard and Myint, 2009). In addition, activation of the immune system can provoke neuroendocrine and neurotransmitter changes that are similar to those provoked by physical or psychological stressors (Anisman, 2009). Sleep disturbance and depression were also associated to hypercytokinemia and activated innate immunity (Pickup, 2004). Interestingly, Pickup (2004) also described convincing evidence that an ongoing cytokine-induced acute-phase response is closely involved in the pathogenesis of type 2 diabetes. Thus, inflammatory processes may be a common antecedent of stress vulnerability, depression, and type 2 diabetes, which can develop in parallel or in succession. Although the above-mentioned potential pathways give a slight indication of what is happening, we still know very little about the mechanisms by which different forms of emotional stress increase the risk of diabetes incidence and progression.

In general, the above described research findings support the notion that different forms of emotional stress are associated with an increased risk for the development of type 2 diabetes, particularly depression, general emotional stress, anxiety, anger/hostility, and sleeping problems. Conflicting results were found regarding childhood neglect/abuse, life events, and work stress. In several papers, childhood traumata and life events have been linked with higher odds of type 2 diabetes, but these studies were all limited by a cross-sectional design. Moreover, results from longitudinal studies in that area had conflicting results. A longitudinal study based on data from the Healthy Women Study showed that persons who had experienced life events were at increased risk for the metabolic syndrome,

including impaired fasting glucose (Räikkönen et al., 2007), while another longitudinal study (Kumari et al., 2004) found no significant association between life events and incident diabetes.

3. DM predisposing to Psychiatric disorders

Chronic diseases e.g. Diabetes Mellitus commonly pose a heavy weight on the patients' resilience and psychological well being, and eventually affect their mental health negatively. Numerous studies have suggested that certain psychiatric disorders occur with increased frequency among adults with type 2 diabetes mellitus for several reasons (Anderson et al, 2001; Peyrot and Rubin 1997): diabetes is considered as one of the most psychologically and behaviorally demanding of the chronic medical illnesses. Because 95% of the management of diabetes is conducted by the patient himself, a diagnosis of diabetes can lead to increased levels of anxiety, depressive symptoms, and lowered self-esteem. This is often true in individuals who are predisposed to psychiatric disorders or those with limited social supports (Llorente et al, 2006). Further, the increased co-occurrence of diabetes and psychiatric disorders may be due to the medical consequences of diabetes, e.g. dementia.

At present, there is no cure, and people with diabetes have multiple self-care tasks such as administering insulin injections and oral medication, implementing specific diet, exercise, weight reduction, and injection sites regimens. Between one-third and one-half of patients with diabetes do not achieve targets for good metabolic control (which includes glycaemic levels as well as lipids, blood pressure, and weight control). Type 2 Diabetes (T2DM) is a progressive condition, so that even with optimized intensive medical regimens in controlled settings glycaemic control continues to worsen over time. A significant proportion of patients have clinically relevant difficulties with managing their self-care regimen despite receiving intensive medical, educational, and nursing input such as multiple injection regimens, continuous subcutaneous insulin infusion pumps, and structured education programmes for carbohydrate counting and insulin adjustment. There is now substantial evidence that certain aspects of self-management and suboptimal glycaemic control are associated with a variety of psychiatric and psychological problems. For instance, for people with T2DM, insulin therapy is associated with weight gain, which leads to a negative effect on body image and contributes to resistance to uptake of insulin treatment. (Ismail, 2009)

Depression is the most common psychiatric disorder associated with diabetes, and may occur at several stages of the natural history of diabetes. It is twice as common in diabetes as in the general population, with a pooled prevalence of 9% using diagnostic interviews and 26% using depressive symptom scores on self-report scales. Prevalence rates increase as the condition progresses, similar to those observed for other chronic medical conditions such as cardiovascular disease (Anderson et al, 2001). In a systematic review of mainly secondary analyses of retrospective community cohorts, depression was associated with an increased risk of 37% for subsequent diabetes (predominantly type 2) in adults, (Knol et al, 2006) suggesting a temporal association between the two conditions. There is around a three-fold increased risk of depression in people with diabetes complications (de Groot et al, 2001, Shehatah et al, 2010). There is a two to five fold increased risk of death in prospective cohort studies (Egede et al, 2005, Katon, *et al.* 2005). Elderly patients with T2DM and those with complications seem to represent a high-risk group. (Makine et al, 2009, Lustman et al, 2000, Lustman and Clouse, 2005, Zhang et al, 2005). A study by Shehatah et al, (2010), confirms the association of depression with complications of diabetes. Type 2 diabetic participants

reporting the presence of at least one diabetic complication scored significantly higher on the BDI-II than participants with no complications. (Shehatah et al, 2010)

Depression in diabetes is underdetected, underdiagnosed, and undertreated. For instance, a US study of more than 9000 primary care patients with diabetes found a recognition rate for major depression of 51%; less than half (43%) of these depressed patients were given one or more antidepressant prescriptions, and a small proportion (6.7%) were offered four or more psychotherapy sessions during a 12-month period. (Katon *et al.*, 2004). It has yet to be seen whether the introduction of screening for depression in diabetes and heart disease in primary care in the UK has led to improved depression outcomes.

About 10% of the patients with type 2 diabetes suffer from “subthreshold” or “subclinical” depression (Ali et al, 2006). This subtype is characterized by pervasive depressive symptoms, not meeting all criteria for the psychiatric diagnosis of a depressive disorder. Subthreshold depression is clinically relevant and has been identified as a risk factor for subsequent major depressive disorder (Cuijpers and Smit, 2004). In addition, it has also been recently pointed out in research outcomes that most diabetes patients that have high levels of depressive symptoms are not clinically depressed (Fisher et al, 2007) and that screening for depression seems reasonable for both depression and emotional problems (Hermanns et al, 2006).

Depression has a doubling effect on disability. Quality of life is reduced with respect to psychological, physical, and occupational functioning. (Moussavi et al., 2007; Schram et al., 2009; Pouwer et al., 2010). In people with diabetes, depression has been associated with hyperglycemia (Tilburg et al 2001, Roy et al 2007); lower levels of diabetes self-care (Tilburg et al 2001); complications, including coronary/cardiovascular disease (Olson et al 2000, Kinder et al 2002), neuropathy (deGroot et al 2001, Lustman et al 1997), and retinopathy (Roy et al 2007, deGroot et al 2001); and increased mortality (Zhang et al 2005). Diabetes-related burdens are perceived as more severe, and satisfaction with diabetes treatment is lower, when depression is present. Patients with depression and diabetes were less physically active, were more likely to smoke tobacco, had less healthful eating habits, and adhered less to diabetes treatment (Gonzalez et al, 2007) Depression is associated with a negative appraisal of insulin therapies in those who are insulin naive, (Makine et al, 2009) and this could delay diabetes treatment such as initiation of insulin therapy in type 2 diabetes. In a handful of selected clinic samples, the course of depression appears to be of longer duration, with more recurrences and of greater severity in people with diabetes. Diabetes is a costly condition, and co-morbid depression adds to the health care costs; in one study in the USA, there was a four-fold increase. (Ismail, 2009)

In an earlier study Pouwer et al (2005) have found that diabetes-specific emotional problems, such as feelings of guilt or anxiety when the patient gets off track with the diabetes management (26–56%), concerns about food (26–41%), fear of hypoglycaemia (21–62%) or worries about complications (29–74%) were particularly common in patients with high levels of depression symptoms. Diabetes-specific emotional problems might be a chronic source of stress that can contribute to the onset of (new episodes of) major depression. Yet the reversed causation might also be true; depressed patients may experience their diabetes more frequently as a burden, as a result of their comorbid depressive disorder. Most of the research done on depression in diabetes has focused on depression symptomatology and used only self-report measures of depression. As inclusion of diabetes-specific issues during psychotherapy could increase treatment success.

Several studies have examined the relative correlation of depressed mood to glycemic control compared to the contribution of other psychosocial factors such as adherence to prescribed regimen, coping strategies, and perception of control over diabetes to glycemic control. Lustman et al (1997) examined the relative contribution of nortriptyline and improvement in depression on glycemic control. While nortriptyline showed negative effects (hyperglycemic) on blood glucose levels, reduction in depressive symptoms had a positive effect (hypoglycemic) on blood glucose levels. Adherence with diabetes regimen was hypothesized by the authors to account for the relationship between depressive symptoms and HbA1c although small sample sizes prevented empirical validation of this hypothesis.

The direction of the relationship between depression, behavior, and glycemic control remains unclear. Depression may be the precipitant of poor glycemic control or the result of failed efforts to improve blood glucose control. A cycle of effects may occur where feelings of disappointment about poor glycemic control may affect adherence to one's prescribed regimen, in turn worsening glycemic control. Longitudinal studies that track the course of disease, psychiatric comorbidity, and glycemic control at multiple points in time are needed to distinguish the trajectory of impacts among these variables. Lustman et al (1997) reported five year follow-up data for patients undergoing a randomized clinical trial of antidepressant treatment, documented worsened glycemic control in patients with recurrent major depression compared to baseline. Measures of adherence to a prescribed regimen during the follow-up period were not reported, thus leaving open the question of the direction of impacts on glycemic control.

Depression can be effectively treated in diabetic patients through pharmacotherapy, cognitive-behavioral therapy, and collaborative care. Depression interventions may also improve glycemic control and survival. (Lustman et al, 1998, 2000, Katon et al, 2004, Bogner et al, 2007). However, effective treatment of depressive symptoms accompanying diabetes is limited by low rates of detection and treatment. Jones and Doebbeling concluded that depression screening for diabetes patients remains below those of patients without diabetes (Jones and Doebbeling, 2007).

Some studies indicate that the major problems for a large group of diabetes patients could be addressed with the usage of psychotherapeutic methods, for example a cognitive behavioral therapy. The lack of statistically significant differences in the rate of complications among the studied groups may indicate that other factors, instead of complications, might be the most important determinants of the emotional well-being of people with diabetes. Examples of these factors may be personality, social support, life events, etc... diabetes-specific emotional problems are common in patients with high levels of depressive symptoms. "Worrying about the future and the possibility of serious complications" appeared to be among the most common diabetes-specific emotional problems (Pouwer et al, 2005), worrying about hypoglycaemia was also frequently endorsed as a significant problem in the present sample.

As diabetes-specific emotional problems were particularly common in depressed patients with diabetes, we believe that psychiatrists should not only have good biomedical knowledge about diabetes, its complications and its management, but also about the diabetes-specific forms of distress that are common in depressed patients with T2DM.

The handful of randomized controlled trials that have tested an antidepressant against placebo has included nortriptyline, fluoxetine, sertraline, and paroxetine. All suggest that antidepressants are effective in improving major depression but not mild depression.

Sertraline has been shown to reduce the risk of relapse of depression in diabetes. (Lustman *et al.*, 2006)

A number of complex interventions have combined psychological and pharmacological treatments in comparison with standard care. The psychological components of these treatments included combining antidepressants with problem-solving training, (Williams *et al.*, 2004, Katon *et al.*, 2004), counseling (Stiefel *et al.*, 2008) or interpersonal therapy, (Bogner, *et al.*, 2007) given according to patients' preferences or following a predefined algorithm. The methodological quality of these studies was better than that of the single-treatment interventions. There appears to be evidence that combined interventions improve depression outcomes but not glycaemic control. (Bogner, *et al.*, 2007) These findings raise more questions than answers, for instance whether, and how, complex interventions for depression should include therapeutic components to improve diabetes self-care.

One interesting speculation is that depression and type 2 diabetes may have common origins. Shared developmental factors, environmental and genetic, may influence the onset of both. (Farmer *et al.*, 2008). Another suggestion is that dopamine reward systems are linked to obesity and a second suggestion is that dopamine reward systems are linked to obesity and impulsive disorders. (Wang *et al.*, 2001). Also, the well-known hypothesis that depressive disorders and chronic stress are accompanied by increased activity of the hypothalamic-pituitary-adrenal system, which increases cortisol and catecholamine levels, is receiving attention as they are associated with central adiposity. There is accumulating evidence that inflammatory factors such as high-sensitivity C-reactive protein and interleukin-6 are on the causal pathway to insulin resistance and emerging evidence that they may be increased in depression and related disorders. (Danese *et al.*, 2007). Hyperglycaemia may activate the sympathetic nervous system. Hyperglycaemia and hypoglycaemia may also lead to microvascular cerebrovascular disease, which may manifest as a depressive syndrome and/or increase the susceptibility for depression. (Ismail, 2009)

Importantly, there are two studies in the literature reporting hippocampal volume loss in T2DM (den Heijer *et al.*, 2003 and Gold *et al.*, 2007). Given the role of the hippocampus in HPA axis feedback regulation (Jacobson and Sapolsky, 1991) and the close link between cortisol and glucose metabolism (Khani and Tayek, 2001), it is not all that surprising there is also some indication for HPA axis disturbances in T2DM, although the order of events remains unclear. Both unstimulated plasma levels (Lee *et al.*, 1999), as well as dexamethasone-suppressed cortisol levels (Bruehl *et al.*, 2007) have been shown to be elevated in T2DM (Andrews *et al.*, 2002). In addition, elevated evening free cortisol salivary levels have been observed in T2DM relative to controls (Liu *et al.*, 2005).

Several mechanisms could account for hippocampal damage in T2DM, among which are, for example, the formation of toxic advanced glycation end-products (Rojas and Morales, 2004), increased production of superoxides via increased intracellular glucose metabolism (Brownlee, 2001), and endothelial dysfunction (Tooke and Hannemann, 2000).

This corroborates the findings of two previous reports in healthy young (Pruessner *et al.*, 2007) and older adults (Pruessner *et al.*, 2005)

The hippocampus may have a role in the regulation of the HPA axis, which extends beyond the feedback regulation of the axis (de Kloet, 2000 and Herman *et al.*, 2005). Studies on HPA axis have focused on the hippocampus as a regulatory entity with a *negative* feedback function or as a target structure for cortisol, and have generally yielded negative associations between hippocampal volume and cortisol levels (smaller volumes associated with higher cortisol levels).

T2DM, in addition to its recognized associated complications such as stroke, retinopathy, microvascular abnormalities, and neuropathy (Stumvoll et al., 2005), is also linked to cognitive dysfunction (Strachan et al., 1997 and Ryan and Geckle, 2000), with recent or declarative memory being the cognitive domain most frequently affected (Grodstein et al., 2001 and Gold et al., 2007), declarative memory impairments (Bruehl et al., 2007) and associated hippocampal volume reduction in late middle-aged and elderly patients with T2DM (Gold et al., 2007). Volume reductions of medial temporal lobe (MTL) structures, including the hippocampus and amygdala, have been reported in T2DM independent of atherosclerosis (den Heijer et al., 2003), hypertension and dyslipidemia even in individuals with well controlled diabetes of relatively short duration (Gold et al., 2007). The MTL structures, and in particular the hippocampus, have been shown to be highly vulnerable to damage (Cervos-Navarro and Diemer, 1991; Convit et al., 2003), and although the number of reports remains relatively small, it appears that they are affected by the metabolic dysregulation present in T2DM (Convit et al., 2003).

The reports of MTL abnormalities in T2DM have primarily come from gray matter volumetric assessments; however, the status of the MTL white matter remains unclear. WM assessment in T2DM has predominantly focused on gross overt structural changes, which is often accomplished using semi-quantitative methods (van Harten et al., 2006 and Manschot et al., 2007).

Emotional stimuli, particularly those of negative valence, are known to promote memory processing by, among other mechanisms, heightened arousal and attention (Kensinger, 2007). It has been shown that among women, brain activation associated with emotional arousal tends to be left lateralized and that stronger associations are found between emotional memory and activation of the left amygdala (Canli et al., 2002). Whether the observed blunted memory enhancing effects are related to amygdala dysfunction among these patients remains to be explored.

Another possible mechanism may be due to impaired cerebral perfusion and vasomotor reactivity, which has been demonstrated in diabetes (Novak et al., 2006) and which may result in diminished metabolic substrate delivery, particularly during periods of brain activation, thus contributing to the damage in T2DM (Convit, 2005).

Several prospective studies have found that obesity in middle age, as well as diabetes in later life, can increase the risk for developing dementia in at least two different ways. (Gustafson et al., 2003; Arvanitakis et al., 2004; Whitmer et al, 2005). First, animal studies have suggested that depletion of the neuronal insulin receptor mimics some aspects of the neurodegeneration seen in Alzheimer's disease. (de la Monte and Wands, 2005). This provides support for the idea that Alzheimer's disease may be caused in part by neuronal insulin resistance. Second, the presence of multiple cardiovascular risk factors at midlife substantially increases the risk of late-life dementia in a dose-dependent manner, (Whitmer et al, 2005), and T2DM is associated with a twofold increased risk of vascular dementia. (Hassing et al, 2002)

Although currently no guidelines exist regarding routine screening for cognitive disorders in older adults, memory deficits are not a part of normal aging. A clinician must have a high index of suspicion, particularly in an older patient who starts "forgetting" appointments, stops checking fingersticks, or inconsistently takes/refills prescriptions. Older adults who report memory problems merit a cognitive assessment. A cognitive screening instrument allows the provider to objectively document the deficit, and monitor the course of impairments. A laboratory dementia work-up, with complete blood count, metabolic profile,

rapid plasma reagin, thyroid function tests, B12, and folate serum levels, should also be completed to rule out treatable causes of cognitive impairment. (Llorente et al, 2006)

Additionally, the majority of patients with dementia will develop behavioral disturbances, including insomnia, agitation, and aggression, and as many as one-third will experience psychotic symptoms. Medical causes of memory problems, and associated behavioral disturbances, are important to consider in the older person with diabetes. Delirium, the sudden onset of impaired attention with a waxing and waning course, and, at times, associated visual hallucinations and agitation, may have multiple causes. In the patient with diabetes, hypoglycemia and hyperglycemia, as well as electrolyte and volume disturbances, and urinary or respiratory tract infections must be ruled out. Many medications taken commonly by older adults can result in cognitive impairment. These medications include those that have significant anticholinergic side effects (ie, opioids, diphenhydramine, olanzapine and conventional antipsychotics, incontinence medications, antispasmodics, antiparkinsonian medications, benzodiazepines, and histamine receptor antagonists. (Llorente et al, 2006)

In addition to poor self-care and greater health service use, mortality is also high in this group. In a population-based study of the elderly, adjusted 6-year relative risks of mortality in those with cognitive impairment and in those with diabetes were similar: 1.68 (1.53-1.86) and 1.62 (1.44-1.83), respectively. While no interaction was found between cognitive impairment and diabetes on risk of mortality, the proportion surviving with both illnesses after 6 years was approximately 50%.¹

There have been few reports that other psychiatric disorders may coexist with depression in diabetes. Anecdotally, such coexistence is a common problem, but more epidemiological surveys are needed to confirm this observation. (Das-Munshi et al, 2007) Although studied less extensively, prevalence rates of anxiety disorders (Grigsby et al, 2002) and eating problems. (Mannucci et al, 2002, 2005, Allison *et al.*, 2007) are also increased in diabetes compared with those in healthy controls. As these disorders tend to co-occur with depression in the general population, this is likely also to be the case in diabetes. The implications of multiple psychiatric morbidities in diabetes for the prognosis and management of depression, as well as of the diabetes, also remains unknown but is likely to be deleterious. (Ismail, 2009)

4. Psychiatric medications predisposing to DM

An iatrogenic problem relating psychiatric disorders to diabetes is the use of psychotropic medications which cause changes in the glucose tolerance test and were sometimes accused of causing T2DM and other metabolic hazards, called "the metabolic syndrome".

New generation "atypical" antipsychotic medications carry an increased risk of weight gain and new-onset T2DM (American Diabetes Association, 2004, Department of Veterans Affairs, 2002, Melkersen and Dahl, 2004, Cohen, 2004, Jin et al., 2002, Wirshing et al., 2002 and Caro et al., 2002). While the association between atypical antipsychotics and these metabolic side effects is clear, especially in patients with schizophrenia, information about comparative risks of weight gain and diabetes between specific atypical medications, the exact relationship between weight gain and diabetes, and comparative risks for patients with diagnoses other than schizophrenia remain important areas of concern (Kornegay et al., 2002, Koro et al., 2002, Kropp et al., 2004 and Beliard et al., 2003).

Olanzapine, risperidone, and quetiapine are the most frequently prescribed atypical antipsychotic medications. (Leslie and Rosenheck 2004). They found the risk for new-onset diabetes in schizophrenia patients was highest for clozapine (2.03%), with lower risks for quetiapine (0.80%), olanzapine (0.63%), and risperidone (0.05%) compared to a reference cohort of patients on haloperidol. Characteristics of the sample population such as older age, polypharmacy, and pre-existing obesity may increase the risk for development of diabetes. Costs of additional weight gain and DM on health, quality of life, survival, and health care expenditures are enormous (Wolf and Colditz, 1998 and Nasrallah, 2002).

In a study conducted by Lambert et al (2006), subjects in all groups developed newly diagnosed DM at a higher rate (10 to 130 per 1000) than the annual incidence reported by the U.S. Department of Health and Human Services (2002) among the general U.S. population (6.3 per 1000). Olanzapine subjects had a higher rate of new-onset DM than that reported in a previous study: 7.3% over a 12–24 month follow-up period (Leslie and Rosenheck, 2004). This difference may in part be due to the high prevalence of pre-existing obesity in study subjects increasing DM risk. On average the study population was near the cutoff for Class I Obesity and 42% met criteria for Class I Obesity at baseline. (McTigue, 2003). Clearly, patients prescribed olanzapine should receive careful laboratory monitoring for DM and relying on weight assessment alone is inadequate. Patients with additional risk factors, such as older age or pre-existing obesity should be very closely monitored for new-onset diabetes by baseline and repeat assessments of glucose status (fasting serum glucose, HbA1c).

Among the 13 large sample retrospective studies based on prescription or safety monitoring databases, eight compared the risk of developing DM directly or indirectly between AAP and conventional antipsychotics as groups. Seven of these reports (Sernyak et al., 2002; Koro et al., 2002; Gianfrancesco et al., 2002; Kornegay et al., 2002; Hedenmalm et al., 2002; Buse et al., 2003 and Fuller et al., 2003) suggested that certain atypical agents or atypicals as a group had a significantly increased risk of new-onset DM (or increased odds ratio for the case-control studies) compared to conventional antipsychotics. In evaluating the risk for new-onset DM among individual atypical agents, 8 of these 13 studies compared the risk among individual atypical agents or relative to conventional agents or non-users of antipsychotics. Seven of these studies (Caro et al., 2002; Sernyak et al., 2002; Koro et al., 2002; Gianfrancesco et al., 2002; Gianfrancesco et al., 2003a; Gianfrancesco et al., 2003b and Fuller et al., 2003) suggested that olanzapine was associated with a significantly greater risk of developing DM than either risperidone or non-users of antipsychotics. On the other hand, only one study (Buse et al., 2003) found that the risk of developing DM was significantly lower in patients taking olanzapine than in patients taking risperidone, and also found no difference between clozapine and haloperidol in the risk of new-onset DM. Two other studies which included clozapine found no increased DM risk (Lund et al., 2001 and Wang et al., 2001), while Sernyak et al. (2002) and Gianfrancesco et al. (2002) both suggested that patients on clozapine had a greater risk of developing DM than those on conventional antipsychotics or non-users of antipsychotics. The report by Biswas et al. (2001) found only eight cases of diabetes among 8858 patients on olanzapine between 1996 and 1998 reported by responding clinicians to a pharmacovigilance questionnaire.

Among the clinical studies, five found that the use of olanzapine was associated with a significantly greater risk of increasing blood glucose or insulin levels compared to those on risperidone or a control group (Melkersson and Hulting, 2001; Newcomer et al., 2002; Wirshing et al., 2002; Meyer, 2002 and Lindenmayer et al., 2003). Similarly, five clinical

studies that evaluated clozapine suggested that glucose levels or other markers of glucose/insulin homeostasis were significantly increased in the clozapine group compared to groups on conventional antipsychotics or controls (Melkersson et al., 1999; Melkersson and Hulting, 2001; Newcomer et al., 2002; Wirshing et al., 2002 and Lindenmayer et al., 2003), while, the difference did not reach significance in the Hagg study (Hagg et al., 1998). While ziprasidone has been available in the U.S. for 3 years, and aripiprazole for about a year, there are limited published data aside from that used in support of the submission to the FDA and a small number of studies. Kato and Goodnick (2001) published a review of the effects of AAP on lipid and glucose levels, and noted that ziprasidone appeared to be neutral in its effects on serum glucose. Kingsbury et al. (2001) published data from the cohort of 37 patients who were switched from various atypical and typical antipsychotics to ziprasidone, and noted no significant changes in serum glucose levels or weight, although there was improvement in serum total cholesterol and triglycerides. Cohen et al. (2003) also noted a non-significant decrease of 3.6 mg/dl among 40 persons with mental retardation after 6 months of ziprasidone treatment. Aripiprazole also appears to be metabolically neutral in its effects on serum glucose and lipids, but these data have only been published as part of a review of its safety profile (Goodnick and Jerry, 2002). Case reports and retrospective database analyses suggest that conventional and atypical antipsychotics are associated with significant increases in fasting glucose concentrations. This hyperglycemia can result in new-onset T2DM, metabolic acidosis or ketosis, and even hyperglycemia-related deaths. Most cases of new-onset T2DM occur within the first 6 months of treatment and are often, although not always, associated with significant weight gain or obesity. A family history for diabetes is also associated with an increased risk.

Several mechanisms of glucose dysregulation have been proposed to explain this association. The medications most associated with diabetes are also those that induce the greatest amount of weight gain. There are patients who develop diabetes, however, in the absence of weight gain, so other causes must be sought. These drugs may disrupt hypothalamic regulation of glucose serum levels through hypothalamic dopamine antagonism. Additionally, elevated insulin levels have been found in 46% of clozapine-treated patients, compared with 21% of those receiving conventional medicines (Melkersson et al, 1999) and 71% of a small sample of olanzapine-treated patients, suggesting that insulin resistance is a possible mechanism.

Johnson et al. (2005) found that in vitro low concentrations of olanzapine and clozapine (both potent muscarinic antagonists) inhibited cholinergics-induced insulin secretion by blocking muscarinic M3 receptor activity. risperidone and ziprasidone had no such effects. These findings suggest an added role for potent anticholinergic activity as a contributing factor for development of diabetes. This is consistent with early findings of a higher association between low-potency conventional antipsychotics and increased weight gain. The low-potency drugs, in general, are much more anticholinergic than high-potency medications.

The results of analysis of diabetic vs. nondiabetic patients suggest that use of phenothiazines, olanzapine, or clozapine is not the most important factor in determining risk of T2DM onset. Rather, body mass and psychiatric diagnosis were the most important determinants in our sample. (Regenold et al, 2000)

It is difficult to determine whether schizophrenia per se has an independent role in the development of abnormal glucose metabolism, as both conventional and atypical neuroleptics have been implicated in the pathogenesis of T2DM and impaired glucose tolerance (Mir and Taylor, 2001; Liebzeit et al, 2001; Lindenmayer et al, 2001). Prior to the

introduction of the first modern antipsychotics in the 1950's, several studies suggested that schizophrenia was associated with an increased risk of diabetes (Lorenz, 1922, Meduna et al., 1942, Braceland et al., 1945, Freeman, 1946, Langfeldt, 1952, Robinson and Shelton, 1940). Unfortunately, those studies did not use explicit diagnostic criteria for schizophrenia, and potentially confounding factors such as body mass index (BMI) and smoking were not considered. Some recent studies of newly diagnosed, antipsychotic-naïve patients with schizophrenia or non affective psychosis have had stronger methods, although problems with potential confounding by hypercortisolemia in the psychosis group, and incomplete matching for key demographic variables, have weakened some of the studies (Ryan et al., 2003, Arranz et al., 2004, Spelman et al., 2007). Despite these reservations, support for the hypothesis that schizophrenia and diabetes may be linked independently of medication comes from the observation that the rate of T2DM in family members of schizophrenic patients is between 18% and 30% (Mukherjee et al, 1989), which is far higher than the rate in the population at large (1.2%–6.3%) (Adams and Marano, 1994). Therefore, patients with schizophrenia and their first-degree relatives appear to be predisposed to developing T2DM.

Leaving aside the issues of medication and age, factors such as ethnicity, physical inactivity, and smoking and diet habits may also play a crucial role in the development of T2DM (Shaten et al, 1993; King and Rewers, 1993). Some researchers have contended that patients with schizophrenia who are severely ill with either negative or positive symptoms may have poorer glycemic control (Brambilla et al, 1976; Brown et al, 1999).

In a study conducted by Kirkpatrick (2008), newly diagnosed, antipsychotic-naïve patients with non affective psychosis and features of deficit schizophrenia were found to differ from other patients without deficit features on the GTT. The non deficit group had significantly higher two-hour glucose concentration than did the deficit group, and both the deficit and non deficit groups had higher two-hour glucose concentrations than did matched control subjects. Because, deficit and non deficit schizophrenia differ with regard to many variables, including those related to etiopathophysiology, the author tested the hypothesis that they would also differ in the results of a GTT. The evidence that diabetes has an increased prevalence in the relatives of people with schizophrenia, and that deficit and non deficit schizophrenia differ with regard to family history (Hong et al., 2003, Kirkpatrick et al., 2000a, Kirkpatrick et al., 2000b and Ross et al., 2000) provided support for this hypothesis. Consistent with other studies, the two groups would not differ at baseline, but would differ on two-hour glucose concentrations.

It was hypothesized that deficit schizophrenia was a separate disease within the syndrome of schizophrenia, based on studies that had shown that deficit and non deficit schizophrenia differed with regard to signs and symptoms, risk factors, course of illness, biological correlates, and treatment response (Kirkpatrick et al., 2001). The alternative interpretation of the many deficit/non deficit differences is that the deficit group simply has a more severe form of the same etiopathophysiology found in the non deficit group. The greater severity interpretation was based on poorer function and outcome, poorer treatment response, and poorer cognitive function, as well as the presence of two forms of serious pathophysiology (positive psychotic symptoms and primary negative symptoms) in the deficit group, compared to one (psychotic symptoms) in the non deficit group. Other studies have supported the separate disease hypothesis: Mucci et al. (2007) found a double dissociation in evoked potential variables; and more normal regional brain volume has been found in

deficit compared to non deficit patients by separate groups (Gur et al., 1994, Quarantelli et al., 2002 and Galderisi et al., 2008).

The improved tolerability of AAP compared to typical antipsychotics, and emerging data suggesting improved psychiatric outcomes (Csernansky et al., 2002), has led clinicians to begin prescribing these agents for other disorders such as bipolar disorder, post traumatic stress disorder, personality disorders, dementia with psychosis, conduct disorder and severe aggression in children. Now, 15 years after the first atypical antipsychotic entered the U.S. market, clinicians and researchers have gradually come to realize that while EPS and TD occur less frequently with atypical agents, these medications may present a different set of adverse effects than typical antipsychotics. Of particular concern are the metabolic side effects of excessive weight gain and obesity, glucose intolerance, new-onset T2DM, diabetic ketoacidosis (DKA) and hypertriglyceridemia (Meyer, 2002; Jin et al., 2002 and Meyer and Koro, 2004).

This heightened level of concern is reflected in the actions of various health regulatory authorities throughout the world that have issued warnings and recommend labeling changes for atypical antipsychotic medications (Japan Ministry of Health, Labour and Welfare, 2002; Pierson, 2003; Risperdal Package Insert, 2003; Seroquel Package Insert, 2004; Zyprexa Package Insert, 2003 and Abilify Package Insert, 2004). While regulatory agencies have failed at times to provide specific monitoring recommendations or guidance regarding differential risk for hyperglycemia or DM among various AAP, consensus guidelines are now being published which elaborate on the differences in risk between agents, and provide rational monitoring schemes (American Diabetes Association et al., 2004; and Marder et al., 2004)

Historical evidence of abnormal glucose metabolism in psychiatric patients has been accumulating since the early 20th century (Kooy, 1919). The evidence consists of numerous reports of increased rates of impaired glucose tolerance, insulin resistance, and frank diabetes mellitus among psychiatric patients (Braceland, 1945; Waitzkin, 1966; Mueller, 1969; Keskiner, 1973; Brambilla, 1976 and Winokur, 1988).

Eaton et al. (1996), following up on individuals who had been diagnosed with major depression in 1981, found that major depression was associated with a 2.23 relative risk of diabetes onset over the 13 years since diagnosis. In a study of spouses and first-degree relatives of probands, Moldin et al. (1993) found that individuals diagnosed and treated for major depression had a 1.87 relative odds of also having a diagnosis of diabetes.

Regarding bipolar disorder, there have been two chart review studies reporting an increased prevalence of diabetes in hospitalized patients. Lilliker (1980) found a threefold higher rate of diabetes in 203 "manic-depressive" inpatients compared to other psychiatric inpatients and to the general population. Cassidy et al. (1999) compared the rate of diabetes in 345 hospitalized "manic-depressives" to the expected general population rate weighted for age, race and gender and found a similarly increased rate.

A study by Newcomer et al. (1999) is worth noting, because it compared schizophrenic and bipolar patients to controls on a glucose tolerance test and matched subjects for age and body mass. This study found that schizophrenic patients had significantly higher plasma glucose levels than both bipolar patients and controls 75 min after a 50 g oral dextrose load; however, schizophrenic and bipolar patients were equally insulin resistant with significantly elevated insulin levels compared to controls.

Findings of increased prevalence of diabetes in bipolar I patients relative to the general population is consistent with the aforementioned chart review studies of Lilliker (1980) and

Cassidy et al. (1999) that found rates significantly greater than the general population in their younger patient samples (mean ages of 49 and 40.6 years, respectively). The increased rate of bipolar patients compared to schizophrenic patients and the lack of an increased prevalence in schizophrenic patients are also consistent with the findings of Lilliker (1980), a previously published large-scale study of diabetes prevalence that compared rates among inpatients with a variety of psychiatric diagnoses.

It is important to emphasize that while Newcomer et al (1999) did not find bipolar patients to be glucose intolerant, they did find them to be just as insulin resistant as their schizophrenic subjects, indicating that the glucose metabolism of their bipolar subjects was not normal. Continued and worsening insulin resistance is the typical pattern of disease that eventually results in hyperglycemia and the diagnosis of T2DM. Why the bipolar subjects in their study had not yet manifested plasma glucose levels indicative of frank glucose intolerance is unclear.

In addition to factors that are typically controlled in diabetes prevalence studies, such as age, race, and gender, diabetes prevalence in psychiatric patients can be affected by treatment with psychotropic medications, many of which can cause weight gain and several of which have been associated with new-onset diabetes. Psychotropic medications of a newer (e.g., clozapine and olanzapine) and an older (e.g., phenothiazines) vintage have been reported to be associated with new-onset diabetes (Thonnard-Neumann, 1968; Wirshing et al, 1998 and Goldstein, 1999).

The possibility raised by these studies that schizophrenia may be associated with diabetes independently of poor health habits and medication side effects has received indirect support from family studies. Mukherjee et al. (1989) found an increased prevalence of T2DM among first degree relatives of schizophrenia patients, although that study used norms from population data, rather than a comparison of patients with matched controls. Another study (Spelman et al., 2007) also found an increased prevalence of impaired glucose tolerance in an oral glucose tolerance test (GTT) in both newly diagnosed, antipsychotic-naïve patients with schizophrenia (10.8%) and their first degree relatives (18%) compared to healthy controls (0%). In a study with closer matching and without confounding by hypercortisolemia in the relatives group, increased two-hour glucose concentrations in first degree relatives were also found (Fernandez-Egea et al., 2008).

Shortly after the introduction of chlorpromazine, clinicians noticed that antipsychotics use led to weight gain. It was further noted that lower-potency agents (chlorpromazine and thioridazine) induced greater weight gain than the higher-potency drugs (fluphenazine and haloperidol). Conventional antipsychotics-associated weight gain appears to be comparable for oral and depot formulations of the same drug.

Among the atypical medications, varying degrees of weight gain have been reported. Hummer et al. (1995) reported that after 1 year of treatment, 36% of patients treated with clozapine had gained > 10% of their initial body weight. Seven patients continued to gain weight, reaching a maximum gain of 30% of their initial body weight. Clozapine-induced weight gain does not appear to plateau early in treatment, and it has been shown to continue for 30 weeks. Olanzapine, with a similar chemical structure, has also been associated with significant weight gain. In prospective, double-blind studies, olanzapine has led to nearly twice the weight gain of risperidone. This weight gain is not apparently related to dose and can persist for up to 1 year (Lindenmayer et al, 2003)

Weight gain for risperidone and quetiapine appears to be intermediate among the antipsychotic medications. Weight gain is reported to be lower than that seen with

olanzapine and clozapine but greater than that seen with conventional drugs. Weight gain associated with risperidone and quetiapine does appear to correlate with dose. Ziprasidone is associated with little weight gain, even after 1 year of treatment. Average weight gain associated with aripiprazole after 1 year of treatment was 2 kg. Among the atypical antipsychotics, the relative tendency to cause weight gain is as follows: clozapine > olanzapine > risperidone = quetiapine > ziprasidone = aripiprazole. (American Diabetes association, 2004)

Some studies also demonstrated positive correlations between indirect measures of visceral obesity, such as waist-to-hip ratio and waist circumference, and plasma levels of glucose and triglycerides. Although no comprehensive explanation has been put forward to account for the co-occurrence of this group of conditions, it would appear that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may play a role. Using a crude indicator of HPA axis activity Ryan et al (2003) have shown that many schizophrenic patients had hypercortisolemia, which in turn may explain why they have excessive visceral fat, hyperglycemia, hyperinsulinemia, and insulin resistance. Alternatively, the stress of hospitalization may lead to impaired fasting glucose tolerance, as in major depression, and the endocrine abnormality may resolve with successful treatment. In conclusion, 15.4% of the drug-naïve, first-episode patients with schizophrenia in their study had impaired fasting glucose tolerance, compared to none of the matched healthy subjects. The patients also had higher levels of plasma glucose, insulin, and cortisol and were less insulin sensitive than the comparison subjects.

Increased serum levels of total cholesterol, LDL cholesterol, and triglycerides are all associated with obesity and weight gain. Because several of the newer antipsychotics are associated with significant weight gain, one would expect that hyperlipidemia should also be associated with the use of these medications. Results of database analyses, chart reviews, and clinical trials indicate that clozapine and olanzapine use is associated with increased serum triglyceride levels. This hypertriglyceridemia correlates directly with weight gain. Findings are equivocal regarding changes in cholesterol levels.

The concept of metabolic syndrome (MetS) or Syndrome X as elucidated by Reaven (1988) is a reality today. Originally proposed as a link between insulin resistance and hypertension in the causation of cardiovascular disease (Levitt and Lambert, 2002), it has now been extended to psychiatry and is seen as an adverse effect of psychotropic drugs, especially second-generation antipsychotics. Recent comprehensive reviews have well established that metabolic syndrome is indeed the concern of the future, with prevalence ranging between 20%–60%, at least double the prevalence in the general population (Toalson, 2004, Thakore, 2004, Shirzadi and Ghaemi, 2006, De Hert et al, 2006, Haupt, 2006 and Newcomer and Haupt, 2006). Added to this is the increasing recognition that MetS is escalating in economically developing countries (Saw, 1997 and Gu, 2005). On the other hand, several studies have also shown a link between psychiatric illnesses and a vulnerability to developing metabolic syndrome (Thakore, 2004, Thakore et al., 2002, Brugha et al., 1989 and Kendrick, 1996). The picture is therefore far from clear.

Atypical antipsychotic medications have many useful applications for patients other than those with schizophrenia. In our clinical experience, the mood-stabilizing and calming effects are useful in patients with mood disorders, PTSD, and in some patients with unstable personality disorder. Additional research is needed to identify the specific effect of diagnosis on relative risk of diabetes and weight gain with these medications. At the current

time, only schizophrenia has been identified as frequently having an independent risk of T2DM (Citrome et al., 2005).

Multiple studies indicate that patients with severe mental illness are not highly motivated to address obesity (Meyer, 2002), and, when motivated to enter a behavioral program for weight loss, experience high drop-out rates with limited success (Loh et al., in press). The outcomes data from CATIE address the medication-related issues in a prospective manner, and thereby provide useful information on the effects of antipsychotic switching on medical comorbidity and associated symptom and quality of life measures. Clinicians are advised to heed the recent expert consensus recommendations on metabolic and general health monitoring for patients with schizophrenia (American Diabetes Association et al., 2004 and Marder et al., 2004), and be attentive to the psychic impact which medical comorbidity may have on their patients with severe mental illness.

Clinicians need to be concerned not only about the development of DM, but also about impaired glucose tolerance in the non diabetic range which represents a source of ongoing cardiovascular risk even if the patient does not develop overt DM. Recently, the ADA reduced the upper limit of fasting normoglycemia from 109 to 99 mg/dl, and thereby increased the range of impaired fasting glucose to 100–125 mg/dl (Expert Panel, 2004).

All clinicians who prescribe AAP must be aware of the additive risk posed by the traditional risk factors for type 2 DM aside from obesity. These are:

1. Age 45 and older,
2. High risk ethnicity (African American, Hispanic, Asian, South Asian, Native American, Pacific Islander),
3. Gestational diabetes, or delivery of infant weighing >9 lbs,
4. Hypertension,
5. Dyslipidemia,
6. Previous history of impaired fasting glucose or impaired glucose tolerance.

The increased obesity, smoking, and unhealthy dietary habits and the inadequate utilization of preventative and primary health care in psychiatric patients underscore the importance of comprehensive medical and behavioral assessments. Patients should have baseline weight and BMI measured, as well as laboratory studies to screen for diabetes, lipid abnormalities, and thyroid disease. In addition, inquiries concerning exercise habits, eating patterns, caffeine usage, and smoking should be included in an initial evaluation. (McIntyre et al, 2005)

Weight loss is a particular challenge for patients with mental illness. (Devlin et al, 2000). Diet and exercise counseling should be provided to all patients, preferably before weight gain, and definitely once weight gain has occurred. (Fagiolini et al, 2003). Behavioral therapies are also effective adjuncts in weight loss treatment. (Devlin et al, 2000; McElroy, 2009) weight gain is clearly related to a specific medication, switching to an alternative agent or lowering the drug dose, if possible, should be considered. (Newcomer, 2009). Pharmacotherapy for obesity may be appropriate for obese patients who have failed to lose weight through diet and exercise alone. Surgical treatment, such as gastric bypass, should be considered in patients with a BMI >40 kg/m² who have not responded to other methods of weight reduction and who present with obesity-related comorbid conditions such as hypertension, diabetes, and obstructive sleep apnea. (Snow et al, 2005). Patients who smoke should be provided with smoking cessation support, counseling, and pharmacologic treatment, if appropriate. (Newcomer, 2007)

The National Cholesterol Education Program recommends screening of all adults over age 20 with a fasting lipoprotein profile every 5 years. (NCEP, 2001). Since patients with psychiatric disorders who take atypical antipsychotics associated with weight gain tend to have a greater prevalence of metabolic syndrome, (Fiedorowicz et al, 2008), more frequent metabolic monitoring has been recommended in these patients. Modifiable risk factors should be evaluated at or near baseline and serially after prescription of antipsychotics. Patients should have their weight and BMI evaluated at baseline and assessed at 4, 8, and 12 weeks after initiating or changing an atypical antipsychotic medication (then quarterly thereafter at the time of routine visits). Fasting plasma glucose, lipid levels, and blood pressure also should be assessed 3 months after initiation of antipsychotic medications. Thereafter, blood pressure and plasma glucose values should be obtained annually, or more frequently in those who have a higher baseline risk for the development of diabetes or hypertension. In patients with a normal lipid profile at 3 months, repeat testing should be performed at 5-year intervals, or more frequently if clinically indicated. (American Diabetes Association, 2004)

Results of numerous studies, suggest that physicians should counsel their patients that risk of T2DM can be significantly reduced by lifestyle changes involving diet and exercise. Some studies may also suggest that bipolar I and schizoaffective disorder patients could be inherently prone to T2DM, suggesting that caution is indicated when prescribing potentially hyperglycemic medications, or any medication that might promote weight gain, to patients with these disorders.

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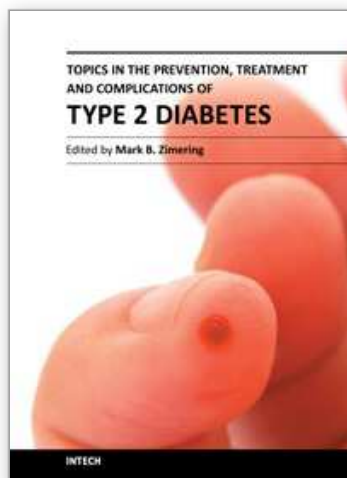
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Type 2 diabetes is estimated to affect 120 million people worldwide- and according to projections from the World Health Organization this number is expected to double over the next two decades. Novel, cost-effective strategies are needed to reverse the global epidemic of obesity which is driving the increased occurrence of type 2 diabetes and to less the burden of diabetic vascular complications. In the current volume, Topics in the Prevention, Treatment and Complications of Type 2 Diabetes, experts in biology and medicine from four different continents contribute important information and cutting-edge scientific knowledge on a variety of topics relevant to the management and prevention of diabetes and related illnesses.

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