Review

Insulin resistance in major depressive disorder and the effects of psychotropic medications

Jennifer S Mason[1], Heather A Kenna[1,2] & Natalie L Rasgon*[1,2]

Practice Points

- Studies suggest a positive correlation between depression and insulin resistance.
- Depression may be associated with physical inactivity and poor dietary habits, which may contribute to weight gain and thus, increases the risk of developing insulin resistance, diabetes and cardiovascular disease.
- Cortisol may mediate effects of insulin in the CNS, and in a state of hypercortisolemia, may lead to insulin resistance among persons with depression.
- Tricyclic antidepressants in particular have been shown to increase carbohydrate craving and appetite, which can result in moderate-to-significant weight gain. Selective serotonin reuptake inhibitors have less significant effects on weight.
- Only 50–60% of depressed patients will respond to antidepressant treatment alone, with only 30% of depressed patients achieving full remission.
- Atypical antipsychotics as an adjunctive treatment with antidepressants have shown promise in alleviating treatment-resistant depression. Adverse metabolic side effects, including insulin resistance, have been associated with atypical antipsychotic medications.
- There is a significant need for more prospective and longitudinal studies examining the complex relationships and mediational pathways between depression and insulin resistance.
- Analyzing the impact of adjunctive and monopsychotropic intervention will be an important area of investigation as their use continues to rise.

[1]Pacific Graduate School of Psychology, Palo Alto University, Palo Alto, CA 94304, USA
[2]Department of Psychiatry & Behavioral Sciences, Stanford University, Stanford, CA 94305-5717, USA
*Author for correspondence: nrasgon@stanford.edu

Future Medicine part of fsg

SUMMARY Major depression is a serious medical condition with an estimated lifetime prevalence rate of 16.6% (32.6–35.1 million) within the USA. High comorbidity exists between major depression and chronic medical conditions, such as Type 2 diabetes, cardiovascular disease and polycystic ovary syndrome. These diseases are, in turn, pathophysiologically linked by a metabolic state of insulin resistance, characterized by hyperinsulinemia, hyperlipidemia and often overweight/obesity. Many common psychiatric medications, such as antidepressants, anticonvulsants and antipsychotics, used in the treatment of major depression are associated with metabolic dysfunction indicative of insulin resistance. This article provides a review of data specific to major depression and insulin resistance, discusses shared health-related problems seen in both conditions, and examines adverse side effects of antidepressant and antipsychotic medications used to treat depression.

Depression is a serious medical condition with an estimated lifetime prevalence rate of 16.6% (32.6–35.1 million) within the USA [1]. Nearly 7% (13.1–14.2 million) of Americans will experience depression within a 12-month period, with 88% reporting moderate impairment and approximately 19% reporting severe impairment in domains such as self-care, cognitive function, social engagement and work performance [1]. Women are significantly more likely than men to experience depression and often have a more chronic course [2,3]. Furthermore, the lifetime risk of developing depression increases to as high as 40% when comorbid chronic medical illnesses such as diabetes and cardiovascular disease are present [4]. Insulin resistance (IR) is believed to be one of many physiological conditions that may link depression and chronic health conditions such as Type 2 diabetes and cardiovascular disease [5–7].

Little is known about the causality of the relationship between prediabetes IR and depression. Depression in some cases is associated with physical inactivity and poor dietary habits, which may increase the risk of developing IR, diabetes and cardiovascular disease. Studies suggest that many psychotropic medications used to treat depression may increase the risk of developing metabolic problems including IR, thus exacerbating poor health outcomes. This article will provide a review of depression and IR, discuss shared health-related problems seen in both conditions and examine side effects of antidepressant and antipsychotic medications that are often used to treat depression.

Insulin resistance: overview

Insulin is necessary for proper cell function and for the maintenance of blood glucose levels within the body. Insulin regulates glucose homeostasis at several sites by allowing glucose to enter the liver where it is converted into glycogen and stored for later use. Insulin also decreases hepatic glucose production and facilitates glucose disposal (entry) into both adipose and skeletal muscle cells where it is converted into energy. Insulin regulation of blood glucose disposal is vital for cell function because glucose is a cell's primary source of energy, which is necessary for proper functioning [8]. After an individual eats a meal, glucose is released by the liver into the bloodstream. In response to elevated blood glucose levels, insulin is released from β-cells located within the pancreas in an effort to reduce hepatic production of glucose and increase glucose disposal in adipose and skeletal muscle cells [7].

Insulin sensitivity refers to the ability of insulin to maintain glucose homeostasis through its effects on insulin-sensitive cells (e.g., adipose and skeletal) and organs (e.g., liver). Thus, when functioning properly, glucose is efficiently disposed of through the action of insulin [7]. IR occurs when 'normal' levels of insulin are no longer able to modulate glucose disposal [8]. This condition subsequently leads to elevated blood glucose levels. As a consequence, the pancreas receives signals to release more insulin, thus elevating insulin levels within the bloodstream as a compensatory effort. As long as the pancreas is able to produce adequate amounts of insulin, blood glucose levels will remain normal even though insulin levels are higher than they should be. This physiological condition is referred to as hyperinsulinemia. When the pancreas can no longer produce enough insulin,

blood glucose levels begin to rise and remain elevated even at fasting states. This is referred to as hyperglycemia. When cells are exposed to high levels of glucose, metabolic dysfunction of cellular processes occurs due to elevated levels of glucose both outside of and within the cells. The combination of IR, hyperinsulinemia and hyperglycemia increases the chances of developing a combination of physiological abnormalities and health problems that Reaven refers to as IR syndrome (IRS) [6].

Insulin resistance syndrome

IRS is not a disease in itself [6]. Rather, it is a combination of the physiological abnormalities mentioned above. Abnormalities seen in IRS are often the result of obesity [9]. The majority of obese individuals have elevated levels of free fatty acids. It is thought that elevated levels of free fatty acids are deposited within the liver, which contributes to an increase in the production of glucose and triglycerides. Elevated levels of free fatty acids are also thought to increase the secretion of smaller low-density lipoprotein (LDL) particles, also known as 'bad' cholesterol, from the liver. Decreases in the amount of high-density lipoprotein (HDL), often referred to as 'good' cholesterol, are also of consequence. HDL cholesterol is responsible for transporting cholesterol and triglycerides through the bloodstream to the liver where they can either be reprocessed for reuse as an energy source or eliminated from the body through bile. Thus, lower levels of HDL and higher concentrations of LDL leads to the accumulation of cholesterol plaques along blood vessel walls, leading to blockages.

Free fatty acids also reduce insulin sensitivity by inhibiting insulin-mediated glucose disposal within cells. Consequently, increases in blood glucose levels trigger the release of insulin from the pancreas resulting in a chronic hyperinsulinemic state [8]. A cluster of these abnormalities significantly increases the risk of developing hypertension, atherosclerosis, cardiovascular disease, polycystic ovary syndrome (PCOS) and/or Type 2 diabetes [5–7].

While this review focuses upon IR, the diagnostic category of metabolic syndrome warrants a brief mention. Unlike IR, which is indicated by proxy markers of insulin and glucose or direct measures of insulin sensitivity, metabolic syndrome is indicated by elevated weight circumference, triglycerides, blood pressure and fasting glucose, as well as low HDL [5,6]. The complete clinical characteristics of metabolic syndrome are beyond the scope of this review. However, many investigators have asserted that IR is the underlying pathophysiology of metabolic syndrome [6]. Indeed, many of the characteristics of the two syndromes are highly correlated (e.g., elevated triglycerides and diminished insulin sensitivity). However, epidemiological evidence does not indicate the presence of IR in all patients with metabolic syndrome. Rather, data suggest that obesity in metabolic syndrome initiates or worsens IR. Further, IR is not thought to play as strong of a role in the development of hypertension as it does in causing hyperglycemia and dyslipidemia.

IRS & related health problems

The consequence of medical illness and mortality associated with IRS is significant. Data from the National Health and Nutrition Examination Survey 2005–2008 indicate that 33.5%, or 76.4 million adults within the USA over the age of 20 years, have hypertension [101]. An estimated 82.6 million American adults have one or more types of cardiovascular disease, including hypertension, stroke, coronary heart disease, heart failure and congenital cardiovascular defects. More than 800,000 Americans die of cardiovascular disease every year, 150,000 of whom are under the age of 65 years.

Furthermore, according to the American Diabetes Association, an estimated 25.6 million American adults 20 years and older have been diagnosed with diabetes, representing approximately 11.3% of the adult population [102]. It is also estimated that an additional 7.1 million American adults have undiagnosed Type 2 diabetes and 79 million are prediabetic. Moreover, nearly 2 million adults were diagnosed with diabetes in 2010 alone [102].

Many health-related complications are associated with diabetes. For instance, diabetes is the leading cause of blindness, lower-limb amputations and kidney failure within the USA [102]. The risk of stroke is two-to-four times higher among diabetic individuals, with up to 68% of diabetic deaths associated with cardiovascular disease in 2004. In addition, 60–70% of adults with diabetes suffer from peripheral neuropathy, an often painful condition, which may result in mild-to-severe nerve damage [102].

The monetary costs of diabetes and cardiovascular disease are also significant. In 2007, the total cost of cardiovascular disease and diabetes, including prediabetes and undiagnosed diabetes, within the USA was estimated at US$503 billion [10,102]. This figure includes direct healthcare expenditures including the cost of physicians, hospital services, prescribed medications and home healthcare, in addition to indirect costs due to lost productivity resulting from mortality. Thus, these are very costly conditions.

IR is part of many somatic diseases, such as PCOS, the most prevalent endocrine dysfunction in women of reproductive age with nearly 5 million women suffering from PCOS in the USA. Legro, Castracane and Kauffman [11] estimate that 50–70% of women with PCOS are insulin resistant, particularly those who are overweight. However, more research is needed to confirm these findings. What seems to be clear is that women with PCOS are at increased risk of developing high cholesterol, impaired glucose tolerance and cardiovascular disease, with insulin dysfunction seemingly being the common thread [12].

In summary, the cluster of metabolic abnormalities, which has been referred to as IRS, can lead to the development of serious comorbid health problems including Type 2 diabetes, cardiovascular disease and PCOS [6]. The societal costs of these medical disorders are a significant financial burden. They also cause significant human suffering as discussed previously [10,102].

IR & depression

Studies have indicated physiological associations between depression and Type 2 diabetes, cardiovascular disease and PCOS [13–15]. It is believed that IR may serve as one of many links between depression and these disorders [16,17]. The following section reviews the literature regarding the associations between depression and IR. The last part of this section presents theories that are believed to link IR and depression.

Interest in the relationship between IR and depression has been an area of investigative interest for many years. Although studies examining the association between these constructs are sparse, overall findings suggest a positive correlation between depression and IR [15,18–27]. Okamura examined IR and depression in nondiabetic middle-aged males and females in their 40s whose fasting glucose was normal based on criteria set forth by the American Diabetes Association (<100 mg/dl) [21]. The primary goal was to explore changes in insulin sensitivity and glucose metabolism during the clinical course of depression. In addition they examined whether a relationship between insulin sensitivity and severity of depression was present. The minimal model analysis was used to assess insulin sensitivity and the oral glucose tolerance test was used to measure glucose metabolism. Patients were administered the Hamilton Rating Scale for Depression (HRSD) to assess severity of depressive symptoms. Results showed that depressed patients had impaired insulin sensitivity regardless of symptom severity and that insulin sensitivity increased when depressed symptoms improved.

Larger studies have also revealed an association between IR and depression. Everson-Rose and colleagues conducted a longitudinal study over the course of 3 years that examined changes in IR, depression and the risk of developing Type 2 diabetes in a community-based sample of 2316 nondiabetic, ethnically diverse women, ages 42–52 years [18]. IR was measured using homeostasis model of assessment of IR (HOMA-IR) and depression was assessed using self-report measure Center of Epidemiological Studies Depression (CES-D) Scale [18]. Baseline and annual assessments were obtained throughout the duration of the study.

Results showed that depressed women had higher rates of IR than nondepressed women ($p = 0.038$). In addition, the depressed women with IR were at increased risk of diabetes, wherein diabetes was 66% more likely to develop in depressed women than healthy controls during follow-up. However, more severe depressive symptoms did not predict an increased risk of IR. Rather, obesity seemed to mediate the relationship. Although IR tended to increase in both depressed and nondepressed groups over 3 years, depressed patients showed larger increases. No significant differences in IR were found between ethnicities. However, depression predicted a more than a 2.5-fold risk of developing diabetes in the African American group.

Three studies to date have looked at younger populations to determine if age plays a role in the relationship between IR and depression. In a cross-sectional study of 2609 nondiabetic, young adult males in the Northern Finland 1966 Birth Cohort study [28], IR increased with depressive

symptom severity (p = 0.003). These results are consistent with another study that found that moderate-to-severe depression was predictive of the presence of IR in 1054 19-year-old males [29]. Pearson and colleagues also studied IR in 833 men and 899 women (ages 26–36 years) [23]. Results indicated that depressed men and women had a significantly higher occurrence of IR (p = 0.04 and p = 0.02, respectively) compared with healthy controls even after controlling for smoking, alcohol consumption, use of oral contraceptives and antidepressants and level of physical activity. Furthermore, depressed women tended to have a larger waist circumference and be less physically active.

Although many studies show associations between IR and depression, a few studies have indicated that such associations between these constructs do not exist [30–32]. In a cross-sectional study Adriannese and colleagues studied glucose, IR and depression in a total of 504 men and women aged 50–75 years old [30]. In total, 260 of these participants had normal glucose tolerance 164 had impaired glucose tolerance, and 117 had a Type 2 diabetes diagnosis. They found a weaker, but significant association between depression, assessed using the CES-D Scale, and IR as measured by HOMA-IR and the Quantitative Insulin Sensitivity Check Index (r = 0.156; p = 0.001). No significant, weak correlations were found with normal glucose tolerance (r = 0.041; p = 0.509), impaired glucose tolerance (r = 0.112; p = 0.160) or those with Type 2 diabetes (r = 0.007; p = 0.942). Furthermore, no significant correlations were found between genders.

Larger studies have corroborated these findings. For instance, Roos and colleagues assessed IR and depression in 1047 women (ages 50–64 years) who had one or more biological markers that placed them at risk of developing Type 2 diabetes [32]. These risk factors included BMI, waist circumference, cholesterol, hypertension and family history of diabetes. IR was measured using HOMA-IR. All participants completed the Gothenburg Quality of Life self-report questionnaire, wherein a depression subscale was created to assess severity of depressive symptoms. Results did not show a direct relationship between IR and self-rated depression. Rather, women who reported more depressive symptoms had more abdominal fat and were less physically active. These results suggest that depression may lead to inactivity, which contributes to obesity and increases the risk of developing IR. Another large study did not reveal associations between IR and depression [33]. Interestingly, in a study of over 4000 women (ages 60–79 years) results showed that depression tended to decrease as IR increased in women without diabetes while depression increased slightly in women with diabetes, suggesting that a diagnosis of diabetes may drive depressive symptoms rather than IR. However, these last two studies utilized poor measures of depression.

Approximately 15 studies have been conducted that examine the relationship between IR and depression. There is a general consensus that an association exists with 12 of the 15 studies finding a positive correlation between depression and IR. Although one of the largest studies conducted did not find a relationship between IR and depression [33], the researchers created their own subscale for depression that has not been validated. Thus, it is questionable as to whether depression was measured accurately. **Table 1** provides a summary of group characteristics and depression and IR measures used in the studies previously mentioned.

Etiology of IR in depression

The general consensus is that there is a relationship between IR and depression. However, the directionality of the relationship remains largely unknown. Evidence suggests hyperactivity of the hypothalamic–pituitary-adrenal axis may be involved in both conditions [14,16]. This hyperactive state is thought to elevate levels of cortisol, which then increases glucose production within the liver, inhibits the secretion of insulin from the pancreas and prevents insulin from promoting glucose disposal into skeletal, adipose and muscular tissue; the latter two of which are both hallmarks of insulin-resistant states [34]. However, the mechanisms that underlie these processes are not well understood. Elevated concentrations of cortisol also seems to increase the quantity of fat cells, breakdown lipids which results in the release of free fatty acids into the bloodstream, and constricts blood vessels, thereby inhibiting the transport of glucose [16,35]. These metabolic abnormalities contribute to the development of obesity and IR that are linked to Type 2 diabetes, cardiovascular disease and depression [16,36].

Few studies have directly examined the relationship between IR, cortisol levels and

Table I. Measurement and group characteristics in insulin resistance/depression studies.

Study (year)	Depression measures	IR measure	Group characteristics	Ref.
Association between IR and depression in healthy general population				
Timonen *et al.* (2006)	HSCL-25 (symptom severity)	QUICKI	n = 2609 (males only)	[28]
Lawlor *et al.* (2005)	GHQ	HOMA	n = 2512 (males only)	[33]
Everson-Rose *et al.* (2004)	CES-D (>16 cut-off)	HOMA-IR	CES-D <16 = 2056 CES-D >16 = 606	[18]
Pearson *et al.* (2010)	CIDI	HOMA	Mild, moderate, severe depression = 150 HC = 1582	[23]
Timonen *et al.* (2007)	R-BDI (13 items; symptom severity)	HOMA-IR	Mild = 81, moderate-to-severe depression = 52, HC = 997	[29]
Timonen *et al.* (2005)	BDI (symptom severity)	QUICKI	n = 593 (elderly males)	[25]
Pan *et al.* (2008)	CES-D (>16 cut-off)	HOMA-IR	Depressive symptoms = 312 HC = 2973	[22]
Association between IR and depression in MDD patients				
Mueller *et al.* (1969)	Psychiatrist diagnosis	ITT	MDD = 5, PMD = 7, BP = 6	[20]
Heninger *et al.* (1975)	BPRS and psychiatrist diagnosis	GTT & ITT	MDD = 10, PMD = 22, BP = 8	[19]
Wright *et al.* (1978)	Zung Self-rating Scale & HRSD	GTT	MDD = 18, HC = 14	[27]
Winokur *et al.* (1988)	HRSD	GTT	MDD = 28, HC = 21	[26]
Okamura *et al.* (2000)	HRSD	Minimal model	MDD = 20, HC = 13	[21]
No association between IR and depression				
Lawlor *et al.* (2003)	EuroQOL	HOMA	n = 4286 (women only)	[31]
Adriaanse *et al.* (2006)	CES-D (>16 cut-off)	HOMA-IR QUICKI	n = 504 (measured number of depressive symptoms)	[30]
Roos *et al.* (2007)	GQL (self-report)	HOMA-IR	n = 1047 (women only)	[32]

BDI: Beck Depression Inventory; BP: Bipolar; BPRS: Brief Psychiatric Rating Scale; CES-D: Center of Epidemiological Studies Depression Scale; CIDI: Composite International Diagnostic Interview; EuroQOL: Euro Quality of Life Questionnaire; GHQ: General Household Questionnaire; GQL: Gothenburg Quality of Life; GTT: Glucose tolerance test; HC: Healthy controls; HOMA-IR: Homeostasis model of assessment of insulin resistance; HRSD: Hamilton Rating Scale for Depression; HSCL-25: Hopkins Symptom Checklist; IR: Insulin resistance; ITT: Insulin tolerance test; MDD: Major depressive disorder; PMD: Psychotic major depression; QUICKI: Quantitative insulin sensitivity check index.

depression. Of the existent literature, discrepancies in methodology make it difficult to draw any solid conclusions. Swami and colleagues found a significant correlation between IR and elevated plasma cortisol levels in the afternoon and evening in 50% of patients in the depressed group [37]. Furthermore, cortisol levels decreased and insulin sensitivity increased when depressive symptoms subsided. However, studies by Carroll [38] and Mueller *et al.* [20] did not find similar results. It should be noted that the latter study only obtained plasma cortisol levels during the morning, which may have influenced the results given that elevated cortisol levels are generally higher in the afternoon and evening [39].

Pathophysiological mechanisms that link IR and depression remain elusive. Nevertheless, it is generally agreed upon that the hypothalamic–pituitary–adrenal axis in conjunction with the actions of cortisol may play an important role. However, additional studies need to be conducted to confirm this hypothesis.

Pharmacological treatment of depression

A number of antidepressant and antipsychotic medications are used to treat depression. Some of these medications have been associated with weight gain, thus increasing the risk of obesity related illnesses such as coronary heart disease, hypertension, IR and diabetes [40,41]. The following section will highlight antidepressant and antipsychotic medications most often associated with weight gain in depressed patients.

Antidepressants

The effects of antidepressant medication on insulin function vary due to differences in their mechanisms of action [42]. Certain antidepressants are associated with increases or decreases in weight gain. Tricyclic antidepressants in particular have been shown to increase carbohydrate craving and appetite, which can result in moderate-to-significant weight gain [43].

Studies suggest depressed patients are more at risk of weight gain during the acute stages of tricyclic antidepressant treatment [44–46]. For example, Kazes and colleagues reported consistent weight gain over a 4–6 month period in depressed patients taking different tricyclics (e.g., amitriptyline, imipramine, clomipramine and maprotiline) [46]. A total of 37% of the patients in this study gained more than 11lbs, while 17% gained more than 22 lbs. Similarly, a meta-analysis examining weight gain in the use of antidepressants in both acute (4–12 weeks) and maintenance pharmacotherapy (>4 months) found the most significant relationship between amitriptyline and increases in weight in both phases of treatment, while weight gain was primarily seen in patients taking imipramine during acute stages treatment [41].

Mirtazapine, a newer antidepressant, has also been known to generally cause weight gain [43,47–50]. An increase in food cravings and appetite have been reported in 11–24% of depressed patients taking mirtazapine, with approximately 10% experiencing significant weight gain [43]. In contrast to mirtazapine and tricyclic medications, selective serotonin reuptake inhibitors (SSRIs) have less significant effects on weight [42], with the exception of paroxetine [51,52]. While paroxetine has been associated with slight decreases in weight earlier on in treatment, significant gains in weight have been reported after 8 months of treatment [41]. Vilazodone, a SSRI that received approval by the US FDA in 2011 as a newer treatment option for depression, demonstrated a favorable weight profile in short-term clinical trials [53]. However, long-term studies have yet to be conducted to rule out adverse affects on weight over time.

In addition to weight gain, researchers have proposed that long term use of tricyclics and some SSRIs, such as paroxetine, may lead to hyperglycemia through the inhibition of insulin signaling cascades, thus inducing IR [54,55]. Conversely, treatment of depression with SSRIs may increase insulin sensitivity and peripheral glucose utilization [56,57]. However, little remains known about the pathophysiology of antidepressants with regard to their affect on insulin function.

Antipsychotics

Although antidepressants have allowed for the improved treatment of depression, only 50–60% of depressed patients will respond to antidepressant treatment alone [58], with only 30% of depressed patients achieving full remission [59]. Consequently, there has been increased interest in discovering more effective treatment options [60]. The use of atypical antipsychotics as an adjunctive treatment with antidepressants has shown promise in alleviating treatment-resistant depression. Preliminary studies suggest that augmenting antidepressant medication with low-dose atypical antipsychotics increases brain-derived neurotrophic factor levels [61–63], which at low levels has been implicated in the pathophysiology of major depression [64]. However, many adverse metabolic side effects, including IR, have been associated with atypical antipsychotic medications [65].

In a study comparing fluoxetine plus placebo, olanzapine plus placebo and fluoxetine plus olanzapine (OFC), patients in the OFC group experienced a remission rate of 60% after 8 weeks of treatment compared with the olanzapine only group and the fluoxetine only groups, with remission rates of 25 and 20% respectively [66]. Similarly, Corya and colleagues reported a remission rate of 44% in treatment-resistant depressed patients and a 60% remission rate in nontreatment resistant patients taking combination olanzapine/fluoxetine [67].

Quetiapine XR has also demonstrated efficacy as an augmented treatment for treatment-resistant depression particularly at a dosage of 300 mg, with response rates falling just below 60% compared with about 47% for placebo [68,69]. Moreover, in a pooled analysis of two identical randomized control treatment studies of aripiprazole [70,71], depressed patients who added aripiprazole to their antidepressant (e.g., fluoxetine, sertraline, paroxetine, citalopram or venlafaxine XR) reported improvements of clinical significance in depressive symptoms, as measured by the Montgomery-Asberg Depression Rating Scale compared with aripiprazole plus placebo group. The aripiprazole plus antidepressant group also showed a 25.7% remission rate versus 15.4% in the aripiprazole plus placebo group [72].

However, olazapine, quetiapine and aripiprazole have been known to cause potentially serious metabolic side effects associated with significant increases in weight [66,69,73–75]. In a pooled analysis of OFC studies, the average weight gain in the treatment group was 10.8 lbs, with an average increase in nonfasting glucose

of +11.4 (mg/dl) [74]. Significant increases in weight, glucose, LDL cholesterol and triglycerides levels were also reported in patients taking quetiapine as adjunctive treatment [66]. Similarly, depressed patients taking an antidepressant plus aripiprazole gained an average of 3–4.5 lbs compared with 7–9 lbs in patients taking placebo. In addition, between 3.4 and 7.1% of patients taking combined antidepressant and aripiprazole gained a significant amount of weight (≥7%) compared with only 1.2% in the adjunctive placebo group [70,71]. While risperidone is another atypical antipsychotic associated with weight gain and related metabolic dysfunction, its use as an adjunctive medication in the treatment of depression has not been well studied and thus, has yet to be approved by the FDA to be prescribed for such means [60].

As with antidepressants, relatively little is known about the pathophysiology of antipsychotic-induced weight gain and alterations in insulin action. In general, studies suggest that antipsychotics may induce IR by inhibiting glucose transport while simultaneously promoting the accumulation of triglycerides, which may contribute to an increase in obesity [76]. However, additional human studies are needed to further elucidate the pathophysiological mechanisms between atypical antipsychotics, IR and related metabolic abnormalities.

Although there is increased interest in using atypical antipsychotics as an adjunctive treatment in treatment-resistant depression, it is unclear whether this has translated into an upward trend in prescribing these medications. While a recent review found that 12.9% of prescriber visits within the USA were for the purposes of adjunctive antipsychotic plus antidepressant medication [77], additional research needs to be conducted to explore whether there has been an actual increase in prescribing combination treatments.

Conclusion & future perspective

There is high comorbidity between depression and health-related medical conditions, such Type 2 diabetes. It is believed that IR may serve as one of many links between Type 2 diabetes and depression, although the relationship remains largely unknown. Even less is known about the directionality of the relationship between depression and IR, which may be a precursor to developing Type 2 diabetes. Findings from the available studies suggest a positive association between depression and IR, such that IR rises as the severity of depression increases. Thus, IR represents a significant comorbidity in depression that may complicate treatment. Given the association of IR to lifestyle factors such as poor diet and lack of exercise, improving insulin sensitivity serves as an important target for interventions and preventative measures that may improve psychiatric outcomes in depressed patients. Increased understanding of the etiology of IR in depression may also help elucidate more effective treatments. The impact of depression on psychosocial functioning combined with the use of antidepressant and/or antipsychotic medication present additional challenges in the prevention and treatment of IR. As a consequence, there is a significant need for more prospective and longitudinal studies examining the complex relationships and mediational pathways between depression and IR. Analyzing the impact of adjunctive and monopsychotropic intervention will be an equally important area of investigation as their use continues to rise.

In response to these issues, the authors speculate increased interest and use of thiazolidinediones to augment psychotropic interventions as these medications have shown to be effective in treating depression while improving metabolic biomarkers, including insulin sensitivity [78–80]. Furthermore, providing behavioral interventions that involve physical activity, dietary modification and sleep hygiene will likely gain traction as healthcare professionals continue to work toward enhancing treatment outcomes and lower healthcare costs. Lastly, continuing to improve screening techniques early in the doctor–patient relationship, including obtaining a family history of diabetes whenever possible, will allow for the implementation of preventive measures in predisease states.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- ▪ of interest

1 Kessler RC, Berglund P, Demler O *et al.* The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 289(23), 3095–3105 (2003).

2 Blazer D, Kessler R, McGonagle K *et al.* The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Am. J. Psychiatry* 151(7), 979–986 (1994).

3 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* 62(6), 593–602 (2005).

4 Melek S, Norris D. *Chronic Conditions and Comorbid Psychological Disorders.* Milliman Research Report, WA, USA (2008).

5 Reaven G. Pathophysiology of insulin resistance and human disease. *Physiol. Rev.* 75(3), 473–486 (1995).

6 Reaven G. The insulin resistance syndrome: definition and dietary approaches to treatment. *Annu. Rev. Nutr.* 25, 391–406 (2005).

▪ **Defines and discusses contributing factors of insulin resistance and pays special attention to the role of body weight.**

7 Sesti G. Pathophysiology of insulin resistance. *Best Pract. Res. Clin. Endocrinol. Metab.* 20(4), 665–679 (2006).

8 Jellinger P. Metabolic consequences of hyperglycemia and insulin resistance. *Clin. Cornerstone* 8(7), S30–S42 (2007).

9 Boden G. Effects of free fatty acids (FFA) on glucose metabolism: significance for insulin resistance and Type 2 diabetes. *Exp. Clin. Endocrinol. Diabetes* 111(3), 121–124 (2003).

10 Roger VL, Go AS, Lloyd-Jones DM. Heart disease and stroke statistics 2011 update: a report from the American Heart Association. *J. Am. Heart Assoc.* 123(4), e18–e209 (2011).

11 Legro R, Castracane V, Kauffman R. Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. *Obstet. Gynecol. Surv.* 59(2), 141–154 (2004).

12 Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Med.* 8(41), 1–10 (2010).

13 Lett HS, Blumenthal JA, Babyak MA *et al.* Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. *Psychosom. Med.* 66(3), 305–315 (2004).

14 Musselman D, Betan E, Larsen H, Phillips L. Relationship of depression to diabetes 1 and 2: epidemiology, biology, and treatment. *Biol. Psychiatry* 54, 317–329 (2003).

15 Rasgon NL, Rao RC, Hwang S *et al.* Depression in women with polycystic ovary syndrome: clinical and biochemical correlates. *J. Affect. Disord.* 74(3), 299–304 (2003).

16 Ramasubbu, R. Insulin resistance: a metabolic link between depressive disorder and atherosclerotic vascular diseases. *Med. Hypotheses* 59(5), 537–551 (2002).

17 Rasgon NL, Kenna HA. Insulin resistance in depressive disorders and Alzheimer's disease: revisiting the missing link hypothesis. *Neurobiol. Aging* 26(Suppl. 1), S103–S107 (2005).

18 Everson-Rose S, Meyer P, Powell L *et al.* Depressive symptoms, insulin resistance, and risk of diabetes in women at midlife. *Diabetes Care* 27(12), 2856–2862 (2004).

19 Heninger G, Mueller P, Davis L. Depressive symptoms and the glucose tolerance test and insulin tolerance test. *J. Nerv. Ment. Dis.* 161(6), 421–432 (1975).

20 Mueller P, Heninger G, McDonald R. Insulin tolerance test in depression. *Arch. Gen. Psychiatry* 21, 587–594 (1969).

21 Okamura F, Tashiro A, Utumi A *et al.* Insulin resistance in patients with depression and its changes during the clinical course of depression: minimal model analysis. *Metabolism* 49(10), 1255–1260 (2000).

22 Pan A, Ye X, Franco O *et al.* Insulin resistance and depressive symptoms in middle-aged and elderly Chinese: findings from the nutrition and health of aging population in China study. *J. Affect. Disord.* 109, 75–82 (2008).

23 Pearson S, Schmidt M, Patton G *et al.* Depression and insulin resistance: cross sectional associations in young adults. *Diabetes Care* 33(5), 1128–1133 (2010).

24 Rasgon NL, Carter MS, Elman S, Bauer M, Love M, Korenman SG. Common treatment of polycystic ovarian syndrome and major depressive disorder: case report and review. *Curr. Drug Targets Immune Endocr. Metabol. Disord.* 2(1), 97–102 (2002).

25 Timonen M, Laakso M, Jokelainen J, Rajala U, Meyer-Rochow B, Keinanen-Kiukaanniemi S. Insulin resistance and depression: cross sectional study. *BMJ* 330, 17–18 (2005).

26 Winokur A, Maislin M, Phillips J, Amsterdam J. Insulin resistance after oral glucose tolerance testing in patients with major depression. *Am. J. Psychiatry* 145(3), 325–330 (1988).

27 Wright J, Jacisin J, Radin N, Bell R. Glucose metabolism in unipolar depression. *Br. J. Psychiatry* 132, 386–393 (1978).

28 Timonen M, Rajala U, Jokelainen J, Keinanen-Kiukaanniemi S, Meyer-Rochow V, Rasanen P. Depressive symptoms and insulin resistance in young adult males: results from the Northern Finland 1966 birth cohort. *Mol. Psychiatry* 11, 929–933 (2006).

29 Timonen M, Salmenkaita I, Jokelainen J *et al.* Insulin resistance and depressive symptoms in young adult males: findings from Finnish military conscripts. *Psychosom. Med.* 69, 723–728 (2007).

30 Adriaanse M, Dekker M, Nijpels R, Heine R, Snook F, Pouwer F. Associations between depressive symptoms and insulin resistance: the Hoorn study. *Diabetologia* 49, 2874–2877 (2006).

31 Lawlor D, Smith D, Ebrahim S. Association of insulin resistance with depression: cross sectional findings from the British Women's Heart and Health Study. *Br. J. Med.* 327, 1383–1384 (2003).

32 Roos C, Lidfeldt J, Agardh CD *et al.* Insulin resistance and self-rated symptoms of depression in Swedish women with risk factors for diabetes: the Women's Health in the Lund area study. *Metabolism* 56, 825–829 (2007).

33 Lawlor D, Ben-Shlomo Y, Ebrahim S *et al.* Insulin resistance and depressive symptoms in middle-aged men: findings from the Caerphilly prospective cohort study. *Br. Med. J.* 330, 705–706 (2005).

34 Delaunay F, Khan A, Cintra A *et al.* Pancreatic β-cells are important targets for the diabetogenic effects of glucocorticoids. *J. Clin. Invest.* 100(8), 2094–2098 (1997).

35 Anagnostis P, Athyros V, Tziomalos K, Karagiannis A, Mikhailidis D. The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. *J. Clin. Endocrinol. Metab.* 94(8), 2692–2701 (2009).

36 Luppino F, Wit LM, Bouvy P *et al.* Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch. Gen. Psychiatry* 67(3), 220–229 (2010).

▪ **Provides an in-depth discussion regarding associations between obesity and depression in an attempt to identify factors that may influence both conditions.**

37 Swami N, Sachar E, Asnis G, Halbreich U, Halpern F. Relative insulin insensitivity and cortisol secretion in depressed patients. *Psychiatry Res.* 4, 291–300 (1981).

38 Carroll BJ. Hypothalamic-pituitary function in depressive illness: insensitivity to hypoglycaemia. *BMJ* 3, 27–28 (1969).

39 Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. *Psychoneuroendocrinology* 30, 1010–1016 (2005).

40 Kim SH, Nikolics L, Abbasi F *et al.* Relationship between body mass index and insulin resistance in patients treated with second generation antipsychotic agents. *J. Psychiatr. Res.* 44, 493–498 (2010).

41 Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. *J. Clin. Psychiatry* 71(10), 1259–1272 (2010).

- **Provides a comprehensive review of studies that have examined weight profiles associated with antidepressant medication. The authors compare the effects, both positive and negative, of specific antidepressants.**

42 Lindley SE, Schroder CM, O'Hara R *et al.* Insulin resistance in schizophrenia, major depression, and bipolar disorder. In: *Insulin Resistance Syndrome and Neuropsychiatric Disease.* Rasgon NL (Ed.). Informa Healthcare Inc, NY, USA, 49–86 (2008).

43 Zimmermann U, Kraus T, Himmerich H *et al.* Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients. *J. Psychiatr. Res.* 37(3), 193–220 (2003).

44 Altintoprak AE, Zorlu N, Coskunol *et al.* Effectiveness and tolerability of mirtazapine and amitriptyline in alcoholic patients with co-morbid depressive disorder: a randomized, double-blind study. *Hum. Psychopharmacol.* 23(4), 313–319 (2008).

45 Frank E, Kupfer DJ, Buhari A *et al.* Imipramine and weight gain during the long-term treatment of recurrent depression. *J. Affect. Disord.* 26(1) 65–72 (1992).

46 Kazes M, Danion JM, Grange D *et al.* Eating behavior and depression before and after antidepressant treatment: a prospective naturalistic study. *J. Affect. Disord.* 30(3), 193–207 (1994).

47 Weber-Hamann B, Gilles M, Schilling C *et al.* Improved insulin sensitivity in 51 nondiabetic depressed inpatients remitting during antidepressive treatment with mirtazapine and venlafaxine. *J. Clin. Psychopharmacol.* 28(5), 581–584 (2008).

48 Nutt DJ. Tolerability and safety aspects of mirtazapine. *Hum. Psychopharmacol.* 17(Suppl. 1), S37–S41 (2002).

49 Burrows GD, Kremer CM. Mirtazapine: clinical advantages in the treatment of depression. *J. Clin. Psychopharmacol.* 17(Suppl. 1), S34–S39 (1997).

50 Davis R, Wilde MI. Sertraline. A pharmacoeconomic evaluation of its use in depression. *Pharmacoeconomics* 10(4), 409–431 (1996).

51 Aberg-Wistedt A, Agren H, Ekselius L *et al.* Sertraline versus paroxetine in major depression: clinical outcome after six months of continuous therapy. *J. Clin. Psychopharmacol.* 20(6), 645–652 (2000).

52 Fava M, Judge R, Hoog SL *et al.* Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. *J. Clin. Psychiatry* 61(11), 863–867 (2000).

53 Citrome L. Vilazodone for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant – what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int. J. Clin. Pract.* 66(4), 356–368 (2012).

54 Levkovitz Y, Ben-Shushan G, Hershkovitz A *et al.* Antidepressants induce cellular insulin resistance by activation of IRS-1 kinases. *Mol. Cell Neurosci.* 36(3), 305–312 (2007).

55 Yamada J, Sugimoto Y, Inoue K. Selective serotonin reuptake inhibitors fluoxetine and fluvoxamine induce hyperglycemia by different mechanisms. *Eur. J. Pharmacol.* 382(3), 211–215 (1999).

56 Maheux P, Ducros F, Bourque J *et al.* Fluoxetine improves insulin sensitivity in obese patients with non-insulin-dependent diabetes mellitus independently of weight loss. *Int. J. Obes. Relat. Metab. Disord.* 21(2), 97–102 (1997).

57 Potter van Loon BJ, Radder JK, Frolich M *et al.* Fluoxetine increases insulin action in obese nondiabetic and in obese non-insulin-dependent diabetic individuals. *Int. J. Obes. Relat. Metab. Disord.* 16(2), 79–85 (1992).

58 Fava M. Diagnosis and definition of treatment-resistant depression. *Biological Psychiatry* 53, 649–659 (2003).

59 Trivedi MH, Rush AJ, Wisniewski SR *et al.* Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am. J. Psychiatry* 163(1), 28–40 (2006).

60 Connolly KR, Thase ME. If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies. *Drugs* 71(1), 43–64 (2011).

- **Discusses the limitations of antidepressants in terms of symptom relief and reviews the efficacy of augmenting/combination strategies to help improve clinical outcomes.**

61 Brunoni A, Lopes M, Fregni F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *Int. J. Neuropsychopharmacol.* 11(8), 1169–1180 (2008).

62 Yoshimura R, Ikenouchi-Sugita A, Hori H *et al.* Adding a low dose atypical antipsychotic drug to an antidepressant induced a rapid increase of plasma brain-derived neurotrophic factor levels in patients with treatment-resistant depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 34(2), 308–312 (2009).

63 Yoshimura R, Umene-Nakano W, Ueda N *et al.* Addition of risperidone to sertraline improves sertraline-resistant refractory depression without influencing plasma concentrations of sertraline and desmethylsertraline. *Hum. Psychopharmacol.* 23, 707–713 (2008).

64 Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biol. Psychiatry* 64(6), 527–532 (2008).

65 De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat. Rev. Endocrinol.* 8(2), 114–126 (2011).

66 Shelton R, Tollefson G, Tohen M *et al.* A novel augmentation strategy for treating resistant major depression. *Amer. J. Psychiatry* 158, 131–134 (2001).

67 Corya S, Andersen S, Detke H *et al.* Long-term antidepressant efficacy and safety of olazapine/fluoxetine combination: a 76-week open-label study. *J. Clin. Psychiatry* 64, 1349–1356 (2003).

68 El-Khalili N, Joyce M, Atkinson S *et al.* Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. *Int. J. Neuropsychopharmacol.* 13(7), 917–932 (2010).

69 Bauer M, Pretorius H, Constant E *et al.* Extended-release quetiapine as adjunct to an

antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. *J. Clin. Psychiatry* 70(4), 540–549 (2009).

70 Marcus RN, McQuade RD, Carson WH *et al.* The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J. Clin. Psychopharmacol.* 28(2), 156–165 (2008).

71 Berman RM, Marcus RN, Swanink R *et al.* The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J. Clin. Psychiatry* 68, 843–853 (2007).

72 Thase ME, Trivedi MH, Nelson CJ *et al.* Examining the efficacy of adjunctive aripiprazole in major depressive disorder: a pooled analysis of 2 studies. *J. Clin. Psychiatry* 10(6), 440–447 (2008).

73 Sanford M. Quetiapine extended release: adjunctive treatment of major depressive disorder. *CNS Drugs* 25(9), 803–813 (2011).

74 Thase ME, Corya SA, Osuntokun O *et al.* A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *J. Clin. Psychiatry* 68(2), 224–236 (2007).

75 Corya S, Williamson D, Sanger T *et al.* A randomized, double-blind comparison of olanzapine/fluoxetine combination, olazapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress Anxiety* 23, 364–372 (2006).

76 Newcomer, JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* 19(1), 1–93 (2005).

77 Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. *Arch. Gen. Psychiatry* 67(1), 26–36 (2010).

78 Sepanjnia K, Amirhossein M, Ashrafi M, Modabbernia MJ, Akhondzadeh S. Pioglitazone adjunctive therapy for moderate-to-severe major depressive disorder: randomized double-blind placebo-controlled trial. *Neuropsychopharmacology* 37(9), 2093–2100 (2012).

79 Kemp DE, Ismail-Beigi F, Ganocy SJ, Conroy C, Gao K, Obral S *et al.* Use of insulin sensitizers for the treatment of major depressive disorder: a pilot study of pioglitazone for major depression accompanied by abdominal obesity. *J. Affect. Disord.* 136(3), 1164–1173 (2011).

80 Rasgon NL, Kenna HA, Williams KE, Powers B, Wroolie T, Schatzberg AF. Rosiglitazone add-on in treatment of depressed patients with insulin resistance: a pilot study. *ScientificWorld J.* 10, 321–328 (2010).

Websites

101 CDC. National Health and Nutrition Examination Survey 2005–2008. www.cdc.gov/nchs/nhanes.htm (Accessed 16 July 2011)

102 American Diabetes Association. Data from the 2011 National Diabetes Fact Sheet. www.diabetes.org/diabetes-basics/diabetes-statistics (Accessed 23 July 2011)