Metabolic Influences of Commonly used Antidepressants on Blood Glucose Homeostasis

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Growing evidence has revealed a significant link between depression and diabetes, making it necessary to assess the glucose dysregulation that might have resulted due to individual antidepressant therapy in depressive patients, especially in patients with co-exiting diabetes. Although randomized, controlled trials are lacking and the underlying mechanism is poorly understood, the results from case reports and clinical observations have provided some clues as to how antidepressants possibly interfere in glucose metabolism. Escitalopram, fluoxetine and milnacipran may improve metabolic parameters while duloxetine, sertraline, mirtazapine, fluvoxamine and paroxetine may induce hyperglycaemia in some cases and worsen glucose control in depressed patients with diabetes; much less is known about the effects of some newer antidepressants such as, nefazodone, agomelatine and reboxetine on blood glucose levels. This review aimed to describe existing evidence of metabolic profiles involving glucose homeostasis following antidepressant therapy.

Key words: Antidepressants, depression, diabetes, metabolic parameters, glucose homeostasis

Depression is a mental illness characterized by a persistent sad, anxious and loss of pleasure in all activities, usually accompanied by a range of symptoms such as altered appetite, sleep disturbance, fatigue and suicidal tendencies. A combination of psychological and pharmacological therapies is the predominant option for depression; antidepressants are the mainstay of pharmacological intervention for moderate to severe depression. There are many antidepressants available now, including tricyclic's (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs) and other agents. These drugs produce therapeutic effects by pharmacologically blocking monoamine reuptake, down or up-regulating receptors, or affecting glutamatergic transmission, respectively[1]. Antidepressants also subsequently cause a variety of unwanted effects such as postural hypotension, dry mouth, constipation, memory or cognitive impairment and sexual dysfunction, which are mediated by affecting a number of neurotransmitter receptors.

It seems that antidepressants do not affect any targets involved in glucose metabolism and the only common risk factor for diabetes mediated by antidepressants is weight gain. There is a controversy regarding whether antidepressants and abnormal glucose metabolism are causally linked. Some studies reported that antidepressant treatments are associated with incidence of diabetes. For example, a nested case-control study showed that long-term use of TCAs or SSRIs was associated with an increased risk of diabetes in patients with depression[2]. Further studies confirmed that continuing use of antidepressants was associated with an increased relative risk of type 2 diabetes, although the elevation in absolute risk was modest[3]. However, other studies showed that the link between antidepressant use and diabetes risk may not be causal. In a prospective cohort study, during an 18-y period, antidepressant use was not associated with undiagnosed diabetes[4]. This finding is consistent with trials that antidepressants did not increase the risk of diabetes[5].

However, an association between depression and diabetes is also illustrated[6]. According to epidemiological data, prevalence of depression in

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patients with diabetes increased two-fold compared with the general population[7]. Existing evident to support co-occurrence of depression and diabetes is that inflammation and hypothalamic pituitary adrenal (HPA) axis dysfunction has been implicated in the pathogenesis of both diseases independently[6,8]. Thus, it is difficult to dissect the disease process from the secondary effects of antidepressants; the question whether antidepressants increase the incidence of diabetes remains need a large body of evidence from both human and animal studies.

Although potential dysglycemia risk is currently not taken into consideration in clinical guidelines for antidepressants, emerging evidence from case reports and clinical observation suggests that antidepressants have potential effects on blood glucose (Table 1)[9-32]. This review is aimed to draw together existing evidence to illustrate metabolic changes involving blood glucose and body weight during antidepressant treatment.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

Amongst antidepressants, currently SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) are the most commonly prescribed. SSRIs are generally better than TCAs in terms of tolerability[33], but not superior in terms of efficacy[34]. SSRIs exhibit their antidepressant action by selectively inhibiting serotonin reuptake. However, individual SSRIs have different affinities for other targets such as blockade of norepinephrine and dopamine reuptake, serotonin 2C agonism and muscarinic cholinergic antagonism. Thus, individual SSRIs have different side effect profiles. Although SSRIs are generally do not alter glucose metabolism, some evidence suggests a role for SSRIs in the dysglycemia.

Citalopram and escitalopram:

Both citalopram and escitalopram are SSRIs, and considered as first-line antidepressant treatment for moderate to severe major depression. Citalopram is a racemic dicyclic phthalane derivative and escitalopram is the S-enantiomer of RS-citalopram. The chemical structures of citalopram and escitalopram are unrelated to that of other SSRIs or of other antidepressants. Thus, citalopram and escitalopram are thought to have a more specific and selective pharmacological profile than other antidepressants. However, citalopram and escitalopram have their own characteristics, respectively. A systematic review by Cipriani and

colleagues on citalopram versus other antidepressants for efficacy and tolerability concluded that citalopram is more efficacious than other antidepressants (paroxetine and reboxetine) and more acceptable than other TCA antidepressants such as, reboxetine and venlafaxine[35]. A meta-analysis by Cipriani and colleagues showed that escitalopram was more effective than citalopram and fluoxetine and escitalopram was more acceptable than duloxetine[36]. In addition, citalopram has minimal potential for drug interactions and reasonably safe for special populations such as elderly patients and patients with renal impairment[37,38]. Although like RS-citalopram, escitalopram was expected to have a low propensity for drug interactions, escitalopram however, required dose adjustment in patients with chronic kidney diseases[38].

With respect to the metabolic effects of citalopram and escitalopram, the results were different. Although in animal models citalopram was shown to affect glucose and lipid metabolism in adipose tissue and resulted in enhanced release of glycerol and free fatty acids into the circulation[39], a firm consensus regarding alterations in glucose homeostasis/carbohydrate metabolism or lipid metabolism in patients associated with citalopram has yet to be established. In depressed euglycemic women, short-term treatment with citalopram failed to significantly change insulin sensitivity, cortisol secretion and leptin production[40], whereas triglyceride level was significantly increased in patients after 16 w of treatment[9]. In depressed patients with type 2 diabetes, citalopram improved depression with decrease of HbA1c[10]. However, based on those clinical studies, it seems difficult to determine whether the good control of HbA1c was a result of self-management behaviour after considerable improvement in depression or due to the direct influence of citalopram.

Metabolic effects of escitalopram were studied only to a limited extent, but available evidence indicated that escitalopram improved glucose and HbA1c levels in patients with comorbid depression and diabetes[11,12]. In a study of 36 patients with comorbid depression and diabetes who received escitalopram for 6 w, 47 % patients showed a reduction in glucose levels[12]. In an open-label study of 40 patients with comorbid depression and diabetes who received escitalopram for up to 12 w, patients had a corresponding decline in mean fasting and post-prandial plasma glucose level at 6 and 12 w, respectively and HbA1c at 12 w[11]. Of note, in another study with a smaller sample size showed that 14 patients who received open-label escitalopram

TABLE 1: INFLUENCE OF ANTIDEPRESSANTS ON GLUCOSE AND LIPID HOMEOSTASIS

Types	Antidepressants	Depressed patients without diabetes	Patients with comorbid depression and diabetes
SSRIs	Citalopram	Citalopram might increase triglyceride[9]	Citalopram improved depression with decrease of HbA1c[10]
	Escitalopram		Escitalopram improved glucose and HbA1c levels[11,12]
	Fluoxetine	In case reports fluoxetine induced hypoglycemia[13,14]	Fluoxetine resulted in weight loss, decreased fasting plasma glucose, reduced triglyceride[15]
	Sertraline	In case reports sertraline cause glucose dysregulation[16-17] In a prospective clinical trial, sertraline significantly increased insulin and triglyceride levels[18] In an observational cohort study sertraline contributed to higher LDL-C[19]	Sertraline improved HbA1c[20]
	Paroxetine	In a double-blind, randomized trial, paroxetine improved insulin sensitivity[21]	In a double-blind randomized trial, paroxetine was beneficial to HbA1c[22]
	Fluvoxamine	Fluvoxamine lowered total cholesterol in obese patients[23]	In a case report, fluvoxamine induced hyperglycemia[24]
SNRIs	Duloxetine		In three clinical trials, duloxetine resulted in modest increases in fasting plasma glucose in patients with DPNP[25]
	Venlafaxine	In three case reports, overdose of venlafaxine resulted in hypoglycemia[26-28]	
	Milnacipran		Milnacipran significantly improved HbA1c, fasting blood glucose, total and LDL-C and triglyceride levels in patients with type 2 diabetes and depression who received metformin for 6 months[29,30]
Other newer antidepressants	Mirtazapine	Mirtazapine is associated with weight gain[99-105]	Mirtazapine is associated with weight gain[101]
	Maprotiline		In two case studies, maprotiline was associated with hypoglycemia[31,32]
	Reboxetine	Reboxetine reduced a blood triglyceride and weight, but did not change cholesterol and glucose levels[116]	
	Bupropion		Bupropion improved weight changes in overweight/obese patients, which was accompanied with improvements in glycemic control[120]
	Nefazodone		In one case report, Nefazodone was associated with hypoglycemia and weight loss[121]
	Agomelatine	Case studies have showed that agomelatine reduced food-intake in night eating syndrome patients, which induced a net loss of weight and normalized levels of blood glucose, total cholesterol, and triglycerides[123,124]	

Antidepressants' influence on glucose and lipid homeostasis in depressed patients with or without diabetes. SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin-noradrenaline reuptake inhibitors

therapy for up to 16 w, had no significant reductions in fasting glucose and HbA1c in patients with depression and diabetes[41]. Reasons why escitalopram improved glucose levels in patients with depression and diabetes were not known. Based on studies in animals, possible hypotheses included escitalopram down regulated the increased HPA axis and reversed insulin resistance in both liver and muscle[42]; escitalopram has antihyperlipidemic, antioxidant and antiinflammatory properties[43]. These studies indicated that escitalopram

has potentially beneficial effects in controlling blood glucose in patients with comorbid depression and diabetes, at least escitalopram prevented diabetes syndrome from getting worse.

Fluoxetine:

Fluoxetine, one of the first new generation SSRIs, is a popular antidepressant. A meta-analysis study including 191 RCTs with 24868 people showed that fluoxetine was similarly effective but better tolerated than TCAs, whereas fluoxetine was less effective than sertraline and mirtazapine but better tolerated than reboxetine[44]. A study demonstrated that among the SSRIs, fluoxetine, citalopram, fluvoxamine, paroxetine, and sertraline, only fluoxetine increased extracellular concentrations of both norepinephrine and serotonin in the rat brains[45]. In addition, fluoxetine differs from other SSRIs regarding metabolic benefit in patients, which was thought to be independent of its antidepressant action.

A meta-analysis has shown that in patients with type 2 diabetes and depression, fluoxetine resulted in weight loss, decreased fasting plasma glucose, reduced triglyceride compared with placebo[15]. Although fluoxetine produced 0.78 % decrease in HbA1c, this effect was not statistically significant[15]. The reports confirmed fluoxetine might be beneficial in patients with comorbid depression and diabetes.

The fact that fluoxetine led to weight loss might be associated with decreased appetite and serotonin reuptake inhibition in patients[46]. Fluoxetine decreased body weight partly because of thermogenesis[47]. Fluoxetine increased basal thermogenesis and produced a significant increase in resting energy expenditure[48]. It also demonstrated a trend of body weight increase after long-term treatment with fluoxetine[49]. Of note, fluoxetine failed to attenuate olanzapine-induced weight gain[50,51].

In case reports fluoxetine was reported to induce hypoglycaemia in patients with diabetes or non-diabetic patients[13,14,52]. On the contrary, studies in obese patients have implicated that fluoxetine improved glycemic regulation and promoted peripheral and hepatic insulin action through increasing muscle glycogen synthase activity, independent of weight loss[53,54]. Meanwhile, there are studies indicating that fluoxetine might affect insulin secretion in major depressive patients[55]. In addition, fluoxetine amplified a wide spectrum of autonomic nervous system and metabolic counter-

regulatory responses during hypoglycaemia[56,57]. Fluoxetine defended against a reduced glucose level depending on the balance of glucose production and glucose utilization, but not amplifying glucagon responses during hypoglycaemia[57]. Together these data provided evidence that fluoxetine might induce beneficial effect on glucose control. Findings of animal studies on the metabolic effects of fluoxetine showed contradictory results. Studies in rats showed fluoxetine induced hyperglycaemia by inhibiting insulin release[58]. Fetal and neonatal exposure to fluoxetine resulted in increased adiposity, fatty liver and abnormal glycemic control in rats[59]. In this context, adverse metabolic outcomes in children who have been exposed to fluoxetine in utero should be considered.

Sertraline:

Compared with other SSRIs, sertraline is a potent and specific inhibitor of serotonin uptake into the presynaptic terminal[60]. For the acute phase treatment of major depression, sertraline was favoured, either in terms of efficacy (fluoxetine) or acceptability/ tolerability (amitriptyline, imipramine, paroxetine and mirtazapine)[60]. Because sertraline did not inhibit norepinephrine uptake and monoamine oxidase activity, and has no significant anticholinergic activity, sertraline is thought to have some activities that are different from some of the SSRIs[60].

Several reports have indicated that sertraline could affect metabolic outcomes in patients with diabetes or non-diabetic patients. In fact, one case study reported that one non-diabetic patient experienced multiple episodes of hypoglycaemia that resolved after discontinuation of sertraline[16]. Supporting this, sertraline has shown to improve HbA1c in depressed patients with diabetes[20] and significantly increased insulin levels[18]. In contrast, it was also reported that sertraline increased glucose levels in patients with type 2 diabetes[17]. In addition, sertraline was reported to contribute to higher LDL-C and triglyceride levels[18,19]. Sertraline failed to improve olanzapine-induced weight gain and elevated cholesterol and triglyceride levels[61]. All these results together indicted that that effects of sertraline on glucose and lipid metabolism were inconclusive. Animal studies showed that sertraline improved blood glucose levels[62-66]. Sertraline significantly reduced blood glucose levels in alloxan-induced hyperglycaemic mice, without affecting insulin levels[62]. However, in another study, sertraline increased glucose-stimulated insulin secretion without any change in peripheral

insulin sensitivity in normal rats under oral glucose overload[67]. Such contradictory results might be due to different animal models studied. As alloxan generates reactive oxygen species in pancreatic β cells to induce damage[68], which might lead to an absolute lack of insulin. In this context, sertraline had no effect on insulin levels; it also suggested that sertraline failed to protect and preserve β cells. In keeping with this, in cellular experiments, sertraline activated an apoptotic process and triggered β cell death[69]. Actually, the effect of sertraline on blood glucose and the underlying mechanisms need to be studied further.

Paroxetine:

Paroxetine is the most potent inhibitor of the reuptake of serotonin in all SSRIs. A meta-analysis showed that paroxetine was less effective than citalopram in improving response to treatment, and no clear evidence revealed paroxetine was more or less effective compared with other antidepressants[70]. During premarketing testing, the incidence of hyperglycaemia with paroxetine was 0.1 to 1 %; however, no evidence indicated paroxetine was its cause[71].

A meta-analysis showed that paroxetine use was associated with weight gain[49]; this effect was reported in several studies[9,72,73]. However, the effects of paroxetine on other metabolic parameters were inconsistent. Paroxetine increased body weight, BMI, waist circumference, fasting glucose, total cholesterol, low density cholesterol and triglycerides after 16 w of treatment in female patients aged 20-41 y without any metabolic comorbidity[9]. A case report showed that severe hyperglycaemia occurred in an obese depressed patient, which was correlated closely with the use of paroxetine[74]. Paroxetine and pravastatin had a synergistic effect on increased blood glucose; of note, neither drug administered singly was associated with changes in glucose levels[75]. However, in other studies paroxetine was reported to have a beneficial effect on glucose metabolism[21,22]. Paroxetine improved HbA1c after three months of treatment, and this effect is not sustained but transient[22]. In another clinical trial, paroxetine improved insulin sensitivity in non-diabetic patients with depression who remitted from major depressive disorder[21]. Together, these data suggested that paroxetine might have a side effect on weight gain and metabolic outcomes; the beneficial effects of paroxetine on blood glucose might be secondary to the improvement of depressive disorder.

Studies in animals and *in vitro* models provided further insight into the effects of paroxetine on glucose metabolism. Paroxetine inhibited insulin secretion via decreasing intracellular 5-HT and insulin biosynthesis[76]. On the contrary, paroxetine was thought to decrease blood glucose by increasing insulin secretion in diabetic mice[77]. In addition, paroxetine was shown to improve hyperglycaemic endothelial cell injury by its antioxidant effect[78], which suggested that paroxetine might be useful for diabetic cardiovascular complications.

Fluvoxamine:

Fluvoxamine is structurally different from TCAs, heterocyclics and other SSRIs. Thus, some differential clinical potency may be expected; however, a meta-analysis of 54 studies showed that fluvoxamine was either superior or inferior to any other antidepressants in terms of efficacy and tolerability in the acute phase treatment of depression[79]. However, fluvoxamine exhibited a different side effect profile[79]. An emerging body of evidence from both human and animal studies demonstrated that fluvoxamine has a potential to induce hyperglycaemia.

In a case report, fluvoxamine was found to induce hyperglycaemia in a patient with comorbid depression and diabetes[24]. When fluvoxamine was withdrawn, the glycaemia was normalized after two days[24]. In clinical trials, fluvoxamine was reported to lower total cholesterol and triglyceride levels[23,80]. In addition, fluvoxamine could attenuate clozapine-induced weight gain and metabolic disturbances by increasing plasma clozapine levels[81]. Although there were no findings from larger patient groups showing detrimental effects of fluvoxamine on glucose metabolism, results from animal studies provided more evidence about how fluvoxamine acted on glucose metabolism. One study showed that fluvoxamine induced hyperglycaemia in mice, which could be abolished by pretreatment with serotonin depleter, p-chlorophenylalanine[82]. These results suggested that fluvoxamine-induced hyperglycaemia was associated with serotonin levels.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

SNRIs are a class of antidepressants such as venlafaxine, duloxetine, desvenlafaxine, milnacipran, and levomilnacipran that inhibited reuptake of both serotonin and norepinephrine. These drugs have

different chemical structures with distinguished pharmacological characteristics. A systematic review showed that SNRIs were superior over SSRIs in terms of efficacy[83]. However, head-to-head comparisons of antidepressants showed that some SSRIs such as duloxetine was not as effective as some new antidepressant agents[84]. In terms of side effect, individual SNRIs also have their own profiles. For example, venlafaxine is associated with cardiovascular phenomena, which rarely occurred with duloxetine or milnacipran[85].

Duloxetine:

Duloxetine is a potent dual reuptake inhibitor of 5-HT and norepinephrine, which has high affinity to 5-HT and norepinephrine transporters but lacks affinity for monoamine receptors[86]. Although duloxetine is a more potent serotonin reuptake inhibitor in comparison with many other antidepressants, duloxetine appears to fail to provide a significant advantage in efficacy over other antidepressants[84].

Duloxetine is one of the only two drugs to have received regulatory approval for the treatment of diabetic peripheral neuropathic pain (DPNP)[87,88]. Clinical trials in patients with DPNP showed that duloxetine treatment produced a modest increase in fasting glucose in short- and long-term studies[25]. In another pooled analysis no statistically significant differences were observed in baseline-to-endpoint changes in both fasting plasma glucose and HbA1c levels in duloxetine-treated patients compared to those treated with placebo[88,89]. Duloxetine was reported to change glucose, but the small change was not considered clinically relevant in a pooled analysis[90]. In addition, there was one case showing that duloxetine was associated with hyperglycaemia in patients with comorbid depression and Parkinson's disease[91].

It remains unclear how duloxetine affected glucose homeostasis. Short-term duloxetine treatment resulted in weight loss, whereas slight weight gain was seen after long-term treatment[25]. Some lipid parameters were also changed[25]. These results suggested that weight change and lipid metabolism were not associated with glycemic changes during duloxetine treatment.

Venlafaxine:

Clinical data showed that venlafaxine did not impact weight gain, did not disrupt lipid milieu and glucose homeostatic dynamics in patients[5,92]. These results were also confirmed in animal studies; venlafaxine did not affect blood glucose levels in non-diabetic normal mice[93]. However, there were three case reports of hypoglycaemia in venlafaxine overdose[26,28].

One article reported a case of hypoglycaemia of 2.7 mmol/l attributed to overdose of venlafaxine and the major active metabolite O-desmethylvenlafaxine in non-diabetic patients with depression[26]. In this case, high levels of insulin and C-peptide were also observed[26]. One other article reported a case of non-diabetic patients with depression who presented hypoglycaemia with high level of venlafaxine in the blood[27]. Blood glucose was normalized after injection of octreotide, but resistant to the administration of large amounts of glucose[27]. These two cases showed that venlafaxine-induced hypoglycaemia was associated high levels of insulin secretion. However, in a recent case report, a non-diabetic patient with depression presented prolonged hypoglycaemia with normal insulin levels in venlafaxine overdose[28]. It seemed that high dose of venlafaxine increased glucose uptake and glucose usage in the peripheral tissues[28]. Although the mechanism underlying the venlafaxine-associated hypoglycaemia remains unknown, the cases described above indicated that potential glucose changes should be considered in patients with diabetes and depression when high dose of venlafaxine is used.

Milnacipran:

Milnacipran exhibited nearly equipotent reuptake inhibition of serotonin and norepinephrine, but has no significant effect on any neurotransmitter receptor[94,95]. Although some evidence revealed that milnacipran is better than TCAs in terms of acceptability and tolerability, there is inadequate evidence to conclude milnacipran is better than other antidepressants in terms of efficacy, acceptability and tolerability in the acute phase treatment of major depression[96]. Data about metabolic effects of milnacipran is lacking. Only two studies showed that treatment with milnacipran significantly improved HbA1c, fasting blood glucose, body mass index, total and low density lipoprotein-cholesterol and serum triglyceride levels in patients with type 2 diabetes and depression, who received metformin for 6 mo[29,30]. These two studies have provided conflicting data concerning effects of milnacipran on fasting blood glucose and HbA1c. In the earlier pilot study, fasting blood glucose and HbA1c were not improved in antidepressant-non-responders, which is in contrast to the later replicated study with a larger cohort[29,30]. The mechanism responsible for

milnacipran on improving blood glucose was not evident from these two studies, further study is need to answer this question.

OTHER NEWER ANTIDEPRESSANTS

Mirtazapine:

Unlike SSRIs, SNRIs and TCAs, mirtazapine has a unique mechanism of antidepressant action, which is classified as a noradrenergic and specific serotonergic antidepressant. Mirtazapine is a potent antagonist of central alpha 2-adrenergic auto receptors and heteroreceptors, and both serotonin 5-HT2 and 5-HT3 receptors[97]. Thus, mirtazapine has some unique therapeutic effects; mirtazapine is likely to have a faster onset of action than SSRIs during the acute-phase treatment[98]. Mirtazapine also has unique adverse profiles; especially, mirtazapine is more likely to cause weight gain[98].

The studies showed that mirtazapine might cause weight gain even for a short period of time (less than six weeks)[99-104]. After treating for 2-6 w, mirtazapine induced weight gain of about 3 kg[99,105]. In one case, mirtazapine induced weight gain of 15.9 kg over 5 mo of treatment[103]. Although weight gain is expected to increase glucose levels in depressive patients, mirtazapine has some opposite effects. After a 6-w treatment period, mirtazapine did not influence the glucose homeostasis[105], even improved glucose tolerance in depressive patients[99,106]. The underlying mechanisms might be associated with a reduction of cortisol secretion and favourable changes self-care behaviours[107,108]. In addition, mirtazapine was reported to enhance the basal β cells replication rate and rescue the norepinephrine-dependent suppression of β cells replication[109].

Maprotiline:

Maprotiline is a tetracyclic antidepressant agent, which acted primarily by blocking reuptake of norepinephrine at nerve endings. Adverse actions of maprotiline are generally similar to those observed in TCAs. Maprotiline has been described to significantly induce weight gain and elevate BMI[110,111]. Treatment of lean patients with maprotiline resulted in an increase of ghrelin and reduction of adiponectin, so maprotiline-induced weight gain might associate with its negative effects on the metabolic variables. Dysglycemia is not usual complication of maprotiline. There were only two case studies showing that maprotiline was associated with hypoglycaemia in patients with comorbid depression and diabetes[31,32]. In one case, maprotiline resulted in hypoglycemia in a patient receiving glyburide and phenformin[31]. A later case report showed that maprotiline caused hypoglycaemia in a patient who treated with insulin[32]. However, no studies indicated that administration of maprotiline caused hypoglycaemia in non-diabetic patients with depression. These results suggest that maprotiline-induced hypoglycaemia is accompanied with use of antidiabetic agents.

Reboxetine:

Reboxetine was the first commercially available selective norepinephrine reuptake inhibitor, which acts by binding to the norepinephrine transporter and blocking reuptake of synaptic norepinephrine in to terminals[112]. Reboxetine appears to have little or no affinity for muscarinic, H1-histaminergic, or adrenergic receptors and for uptake of serotonin and dopamine[113]. Thus, reboxetine exerted less sexual and gastrointestinal side effects compared to other SSRIs. Reboxetine attenuated olanzapine-induced weight gain via suppression of appetite[114,115]. Reboxetine reduced blood triglyceride and leptin levels, and elevated cortisol and dehydroepiandrosterone levels[116]. However, reboxetine did not change cholesterol, glucose, insulin, thyroid-stimulating hormone and prolactin levels[116]. Much less is known about the regulation of blood glucose of reboxetine.

Bupropion:

Bupropion is a norepinephrine-dopamine reuptake inhibitor with minimal direct effects on serotonin, which is a good strategy for patients not responding to SSRIs[117]. Several studies reported weight-loss after bupropion when used as monotherapy or combination therapy[118-120]. Bupropion as monotherapy improved weight changes in obese patients or olanzapine-induced weight gain[118]. A study described that bupropion combination with naltrexone induced weight loss in overweight and obese adults; this effect was associated with controlling eating food cravings[119]. Bupropion plus naltrexone also improved weight changes and glycemic control in overweight/obese patients with type 2 diabetes[120]. The effect of weight-loss is strongly supported by clinical trials, but potential blood glucose effect is poorly understood.

Nefazodone and agomelatine:

Nefazodone is a weaker 5-HT and norepinephrine

reuptake inhibitor, but potently antagonises the action of the 5-HT2 receptor, resulting in greater 5-HT1A binding. Nefazodone has not been described to significantly affect body weight. Only one case report described hypoglycaemia and weight loss in a patients who treated with nefazodone for 8 w[121]. Agomelatine is a novel antidepressant that acts as an agonist on melatonin MT1 and MT2 receptors, and an antagonist on $5-HT_{2B}$ and $5-HT_{2C}$ receptors[122]. Although there are no significant differences in efficacy between agomelatine and other second-generation antidepressants, agomelatine is better tolerated than paroxetine and venlafaxine in terms of overall side effect[122]. Case studies have showed that agomelatine reduced food-intake in night eating syndrome patients, which induced a net loss of weight and normalized levels of blood glucose, total cholesterol and triglycerides[123,124]. Available data about agomelatine on blood glucose are lacking, but agomelatine seems provide an advantage in controlling food craving that might be secondary to control blood glucose.

In this review each individual antidepressant was reviewed according to their effects on glycaemia regulation. However, with respect to dysglycemia, the clinical meaning of this effect is uncertain, and no definitive conclusion could be drawn. Several reasons could be postulated, (1) some studies were short in duration and sample sizes were generally small; (2) most evidence was from case reports, randomized-controlled trials were lacking; (3) especially, some antidepressants exhibited conflicting effects on glucose metabolism; (4) it is difficult to distinguish that glucose regulation following antidepressant therapy is due to a direct effect or secondary effect of well self-care behaviours and (5) the underlying mechanism between antidepressants and glucose regulation remains poorly understood. Therefore, only further research could explore whether and how antidepressants are linked to changes in glucose levels, which might be beneficial to patients with comorbid diabetes and depression.

However, according to published studies, some points could be of concern. Among SSRIs, escitalopram and fluoxetine may have a beneficial effect on glucose control; fluvoxamine and paroxetine may induce hyperglycaemia in some cases; sertraline on metabolic outcomes remain inconclusive, both hyperglycaemia and hypoglycaemia can occur. Among SNRIs, duloxetine may worsen glucose control in patients with comorbid diabetes and depression, but not in non-diabetic patients with depression; taking an overdose of venlafaxine may induce hypoglycaemia; milnacipran may improve metabolic parameters in patients with type 2 diabetes and depression. Mirtazapine may influence glucose homeostasis in mirtazapine-induced weigh gain. Generally, studies have revealed that antidepressants might affect glucose homeostasis in some patients, which should be kept in mind when antidepressants are used in clinical practice, especially in patients with comorbid depression and diabetes.

Conflict of interest

The authors declare that they have no conflict of interest.

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