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Review

Metabolic syndrome and obesity among users of second generation antipsychotics: A global challenge for modern psychopharmacology

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ABSTRACT

Second generation antipsychotics (SGAs), such as clozapine, olanzapine, risperidone and quetiapine, are among the most effective therapies to stabilize symptoms schizophrenia (SZ) spectrum disorders. In fact, clozapine, olanzapine and risperidone have improved the quality of life of billions SZ patients worldwide. Based on the broad spectrum of efficacy and low risk of extrapyramidal symptoms displayed by SGAs, some regulatory agencies approved the use of SGAs in non-schizophrenic adults, children and adolescents suffering from a range of neuropsychiatric disorders. However, increasing number of reports have shown that SGAs are strongly associated with accelerated weight gain, insulin resistance, diabetes, dyslipidemia, and increased cardiovascular risk. These metabolic alterations can develop in as short as six months after the initiation of pharmacotherapy, which is now a controversial fact in public disclosure. Although the percentage of schizophrenic patients, the main target group of SGAs, is estimated in only 1% of the population, during the past ten years there was an exponential increase in the number of SGAs users, including millions of non-SZ patients. The scientific bases of SGAs metabolic side effects are not yet elucidated, but the evidence shows that the activation of transcriptional factor SRBP1c, the D1/D2 dopamine, GABA2 and 5HT neurotransmissions are implicated in the SGAs cardiovascular toxicity. Polypharmacological interventions are either non- or modestly effective in maintaining low cardiovascular risk in SGAs users. In this review we critically discuss the clinical and molecular evidence on metabolic alterations induced by SGAs, the evidence on the efficacy of classical antidiabetic drugs and the emerging concept of antidiabetic polyphenols as potential coadjutants in SGA-induced metabolic disorders.

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1. Introduction

Second-generation antipsychotics (SGAs), clozapine, olanzapine and risperidone, have improved quality of life of billions psychiatric patients worldwide and became essential in the clinical guidelines for treatment of schizophrenia (SZ) [3,44]. Although the primary target of this drugs are SZ patients, estimated in 1% of world population [40,39], leading experts have warned on the exponential increase of the "off-label" applications of SGAs, which include non-SZ adults [75], adolescents and children [86] suffering from a wide range of psychiatric conditions [127]. Intriguingly, several of the increasing off-label indications in non-SZ patients still lack sufficient safety – and efficacy – evidence. This prescription trend might be explained by the unmet need for affordable and efficacious drugs against DSM-IV-TR categorized disorders [33], and by the intensive marketing strategies of the pharmaceutical industry. In fact, US government has fined pharmaceutical companies for the promoting some off-label uses of SGAs [103] because it was considered, not only misleading, but also dangerous for public health [74]. Some SGAs can control positive and negative symptoms of SZ within 6 weeks of use, but they also induce cardiometabolic alterations, which lead to increased morbi-mortality [31], in as short as three months after initiation of the pharmacotherapy [3]. In 2003, the FDA intended to prevent these side effects by requiring all second generation antipsychotic agents to include warning labels regarding the increased risks of diabetes mellitus and severe hyperglycemia [43]. However, recent studies showed that SGAs-induced cardiovascular diseases (CVD) are still responsible for the increased cardiovascular risk of SZ patients [83,72] and for up to 30% of the excess mortality associated with SZ [141]. A recent Meta-analysis revealed that the risk for metabolic syndrome among SZ patients is higher than that of non-SZ individuals and clozapine treatment increases cardiovascular risk of SZ patients [77]. Another Meta-analysis concluded that patients with bipolar treated with antipsychotic display a higher risk of metabolic syndrome than their antipsychotic free counterparts [125].

The group of SGAs includes drugs with different chemical structures, mode of action and risk profile for metabolic side effects, being olanzapine the most toxic drug of this group followed by clozapine, risperidone, quetiapine and aripiprazole [130,31]. Clozapine was launched to market in 1990, with the bizarre retail price of US$8.444 per year treatment, a high risk of accelerated weight gain [23] and warnings of potential agranulocytosis [22]. This astonishing high cost of clozapine included a blood test only performed the manufacturerís personnel [129]. In spite of its cost and serious side effects, the annual sales of clozapine increased up to US$500 million/year in the first ten years, while risperidone reached three times those of clozapine in its first 5 years in the market. Olanzapine, the most unsafe drug (for cardiometabolic side effects), reached around US$ 2.500 million/years in its first ten years in the market and it continues to grow to date [22]. In Chile, according to the official records of the Chilean National Institute of Public Health (ISP), there is a similar trend with increasing annual imports of clozapine and olanzapine during the past 9 years (Fig. 1). Since 2011, the prescription trends in the US are moving toward safer antipsychotics, such as quetiapine, aripiprazole and ziprasidone [67], but the elevated cost of these drugs limits their availability for the majority of SZ patients. For example, in Chile, aripiprazole is not included in the medications that are available through the public health system for SZ patients. Thus, like in the rest of the world, most of SZ patients in Chile continue as a group of high risk for metabolic syndrome (MetS) [72].

The pathophysiology of the SGAs-induced alterations has not been fully elucidated, but increased food intake, weight gain, hyperglycemia, lipid accumulation in adipose cells and liver are hallmarks of this problem [1,11]. The current evidence show that the integration of the appetite regulation signals in the Arcuate Nucleus is impaired by SGAs, such as olanzapine and clozapine, which results in hyperphagia [1]. Clozapine-induced hyperphagia is reversed by i.p. injection of dopamine D1 and D2 antagonists and 5-HT1B, 5-HT2 and 5-HT3 agonists in mice [60] and also by fluoxetine, a serotonin reuptake inhibitor. Unfortunately, the protective effect displayed by fluoxetine had little clinical significance, as it was not reproduced in humans [89]. Prevention strategies based on genomic analyzes are emerging as a possible answer to this problem. For example, the GABA2 receptor polymorphism was suggested as a good predictor of weight gain in SGAs-treated patients [137]. Recent studies have shown that SGAs-induced insulin resistance, weight gain and lipid accumulation are associated with the up regulation of sterol regulatory element-binding protein 1c (SREBP1c) [38,135,53]. This finding has opened new molecular targets for prophylactic drugs. SRBP1c is a master regulator of lipid biosynthesis in liver and fat tissue (Qui et al., 2005) and its inhibition was successful in ameliorating SGAs-induced lipid accumulation cellular and animal models [53]. So far, the life style modifications, nutritional consulting, and polypharmacological interventions have proved limited efficacy against SGAs-induced MetS (Table 1). Our group has received a federal grant from the Chilean government to search for new pharmacological agents against SGAs-induced adipogenesis based on selected molecules derived polyphenols with insulin sensitizing properties [95,100,98,118]. Which is supported by a growing body of evidence, including recent clinical trials [28,101]. Our group and others have demonstrated that specific polyphenols from dietary sources ameliorate insulin resistance [100,98,71,107,64], inflammation [121,107] and obesity [34,108]. Anthocyanins, a family polyphenols, have shown significant clinical effect in improving insulin sensitivity in obese, nondiabetic, insulin-resistant patients [115]. Berberine is also an example of an antidiabetic phytochemical with potential protective effect against lipid accumulation induced by clozapine [53]. The present review analyze the recent progress in understanding the SGAs induced metabolic alterations, and the rational for developing therapeutic agents based on anti-diabetic anti-obesity drugs and dietary polyphenols.

2. Peculiarities of SGAs-induced metabolic syndrome

In general population full-blown type II diabetes and morbid obesity takes up to 5–10 years to unfold [109]. In the case of type 2 diabetes, a pre-diabetic stage characterized by insulin resistance, hyperinsulinemia and progressive pancreatic dysfunction, can asymptomatically develop over several years before diabetes is clinically diagnosed [109]. Conversely, in SAG-treated subjects, the process from low – or completely absent – cardiovascular risk to full-blown diabetes and/or morbid obesity is significantly shorter, ranging from 6 to 12 weeks up to 12 months (Fig. 2) [61]. This prodromal period will depend upon the specific antipsychotic drug used and the individual genetic background. Most of SGA-treated patients will gain and maintain high weight and insulin resistance for long time, even after changes in life style and/or use of anti-diabetic drugs. The burgeoning literature on metabolic issues associated with the use of SGAs [47,130,110,15,3] have increased opportunities for the rational development single-target prophylactic agents, which can protect physical health and improve compliance of patients treated with SGAs [141,130]. A careful selection of the specific SGA is important for risk/benefit evaluation, since clozapine and olanzapine are known to cause the most severe profile of metabolic side effects [110], while quetiapine, aripiprazole and ziprasidone display significantly lower risk of metabolic alterations [72]. The most prevalent manifestations of MetS in clozapine and olanzapine-treated patients are weight

Table 1
Summary of preclinical and clinical studies assessing interventions against SGAs-induced metabolic alterations.

Intervention	SD	N	Dur	PO	SO	Results	MC +/−	Ref.
Metformin 750 mg/day	Double-blind, placebo-controlled	40	3	Changes of weight, BMI, WC, waist-to-hip ratio, fasting glucose, fasting insulin, proportion of patients with >7% weight gain at 3 months, insulin resistance index	Changes in SAPS and SANS scores and adverse effects	Treatment with metformin in patients treated with OLZ decreased body mass index and weight gain, no changes in insulin levels and insulin resistance	Positive	[93]
Metformin 850–1750 mg/day	Double-blind placebo-controlled trial	40	3.5	Body weight gain, HOMA-IR		Metformin decreased HOMA-IR and glucose levels. No changes in weight gain in patients treated with OLZ	Negative	[120]
Metformin 500–850 mg	Randomized, double-Blind, placebo-controlled trial	39	4	Prevention of further weight accumulation from atypical antipsychotics		Metformin ameliorated weight gain, insulin resistance and improved abnormally high glucose levels in children treated with olanzapine, risperidone, or quetiapine	Positive	[30]
Metformin 850–2250 mg/day	Multicentric, double-blind, placebo-controlled trial	80	4	Weight loss (body weight, BMI, WC)	Glucose, insulin, lipids, leptin, cortisol, growth hormone, fibrinogen, c-reactive protein, glycated hemoglobin, and HOMA-IR	Metformin group decreased weight and leptin levels, but did not improve lipid profile and levels of Hb1c in OLZ treated patients	Positive	[13]
Metformin 750 mg/day	Randomized controlled trial	128	24	Changes of weight, BMI, waist circumference, fasting glucose, fasting insulin level, and insulin resistance index	Change in PANSS total scores and adverse effects	Metformin was modestly superior to life style regarding the prevention of weight gain, insulin resistance and increase in BMI. Life style modification-plus-metformin was superior to metformin alone	Positive	[133]
Nizatidine 150 mg b.i.d. or 300 mg b.i.d.	Double-blind placebo-controlled trial	175	4	Weight gain	–	OLZ-Nizatidine patients had less weight gain *versus* the placebo. Nizatidine was well tolerated and is estimated to have a temporary early effect in the low weight gain, but it is diminished after 16 weeks	Negative	[19]
Nizatidine (150 mg b.i.d.)	Double-blind and placebo-controlled	47	2.5	Weight gain	PANSS score, leptin levels and BMI	Decrease in weight gain and leptin levels but below the level for statistical significance.	Negative	[7]
Nizatidine 5–25 mg 15.3 mg/day	Double-blind and placebo-controlled	59	3	Weight gain	Plasma leptin levels, BMI, PANSS scores	Reduction of weight gain and the level of leptin in the nizatidine-OLZ treated group compared with the control group	Positive	[6]
Orlistat	Randomized, double-blind, placebo-controlled trial	71	4	Weight gain		Mild decrease in weight gain in male treated with OLZ and CLO, no effect in women	Positive	[56]
Sibutramine 15 mg/day	Double-blind, Placebo-controlled Trial	37	3	Weight gain	Waist circumference, body mass index, and hemoglobin A1c	Decreased in weight gain, waist circumference, body mass index, and hemoglobin A1c in schizophrenia patients treated with OLZ	Positive	[48]
Ranitidine 600 mg/day	Randomized triple blind controlled trial	52	4	BMI		Ranitidine induced less weight gain in OLZ-treated patients than the control group, but only in the first two months	Negative	[92]
Reboxetine 4 mg/d with betahistine 48 mg/day	Randomized double-blind study	26	1.5	Weight gain		Reboxetin decreased number of patients with >7% weight gain in schizophrenic OLZ-treated. Small number of patients makes challenging to reach decisive conclusions.	Positive	[88]

Drug	Study design	N	Dur	Primary outcomes	Secondary outcomes	Main conclusion	Intervention result	Ref
Reboxetine 4 mg/day	Double-blind placebo-controlled study	60	1.5	Weight gain		Schizophrenic patients treated with OLZ in combination with reboxitine had less weight gain compared to the control group	Positive	[87]
Topiramate 100 mg/d 200 mg/day	Randomized double-blind placebo controlled study	66	3	Weight gain	BMI	Topiramate decreased BMI, weight, and waist circumference. Hip-to-waist ratio did not change in SGAs-treated patients	Positive	[62]
Famotidine 40 mg/day	Double-blind placebo-controlled pilot study	14	1.5	Body weight and BMI		Famotidine did not prevent weight gain in schizophrenic patients treated with OLZ	Positive	[90]
Rosiglitazone 4–8 mg/day	Pilot double-blind, placebo-controlled	30	3	Weight gain	Insulin and the HOMA-IR, lipid profile, fibrinogen and Hb1c levels	Rosiglitazone increased weight and decreased insulin levels and HOMA-IR in OLZ-treated patients	Negative	[12]
Rosiglitazone 4 mg/day	Double Blind, Placebo-controlled Trial	18	2	SG (plasma glucose clearance irrespective of the action of insulin). SI (insulin sensibility)	Serum insulin level and HOMA-IR, LDL, HDL, body weight, body mass index, body fat, waist-hip ratio and waist circumference	Rosiglitazone-treated patients had a reduction in LDL-C, a non-significant improvement in SG and SI. Partial improvement of insulin resistance and hypercholesterolemia in patients treated with clozapine	Positive	[49]
Amantadine 300 mg/day	Double-blind, placebo-controlled	21	3	Body weight and BMI	Glucose, insulin, leptin, prolactin, and lipid levels	Amantadine-treated patients showed less weight gain relative to controls, no changes in the levels of insulin, glucose, leptin, prolactin and lipid levels in patients treated with OLZ	Positive	[41]
Amantadine 100–300 mg/day	Randomized, double-blind	125	6	Body weight and BMI		The OLZ-amantadine treatment was tolerated by patients and achieved a reduction in weight gain compared to placebo-OLZ group	Positive	[32]
Fluoxetine 20 mg/day	Double-blind, placebo-controlled	30	2	Body weight and BMI		Patients treated with OLZ-Fluoxetine showed no significant differences from the control group, so it is concluded that co-administration of these drugs does not reduce weight gain	Negative	[89]
Resveratrol 10 mg/kg/day	Study animals	18	0.6	Non pharmacological therapy		Non pharmacological therapy	Positive	[104]
Green tea and conjugated linoleic acid	Case control	4	6	Weight gain		Resveratrol-plus-olanzapine-group displayed less weight gain than the group treated with olanzapine alone	Positive	[59]
Metformin 300 mg/kg and berberine 380 mg/kg/day	Study animals	48	0.5	Body weight body fat mass, body fat percentage, lean body mass		Green tea decreased the percentage of body fat and increased lean body mass with the use of the tea extract	Positive	[54]
Berberine	Cellular in vitro study			Weight gain and adiposity		Metformin and berberine decreased weight gain and white fat accumulation induced by OLZ in rats. Metformin did not change brown adipose tissue	Positive	[52]

Dur: duration of the study (months), Intervention result: positive (+) and negative (−) N: number of patients, SD: study design, PO: main primary outcomes or biological effects, SO: main secondary outcomes, WC: waist circumference, BMI: body mass index, MC: main conclusion, PANSS: positive and negative syndrome scale, BWG: body weight gain, OLZ: olanzapine, CLO: clozapine.
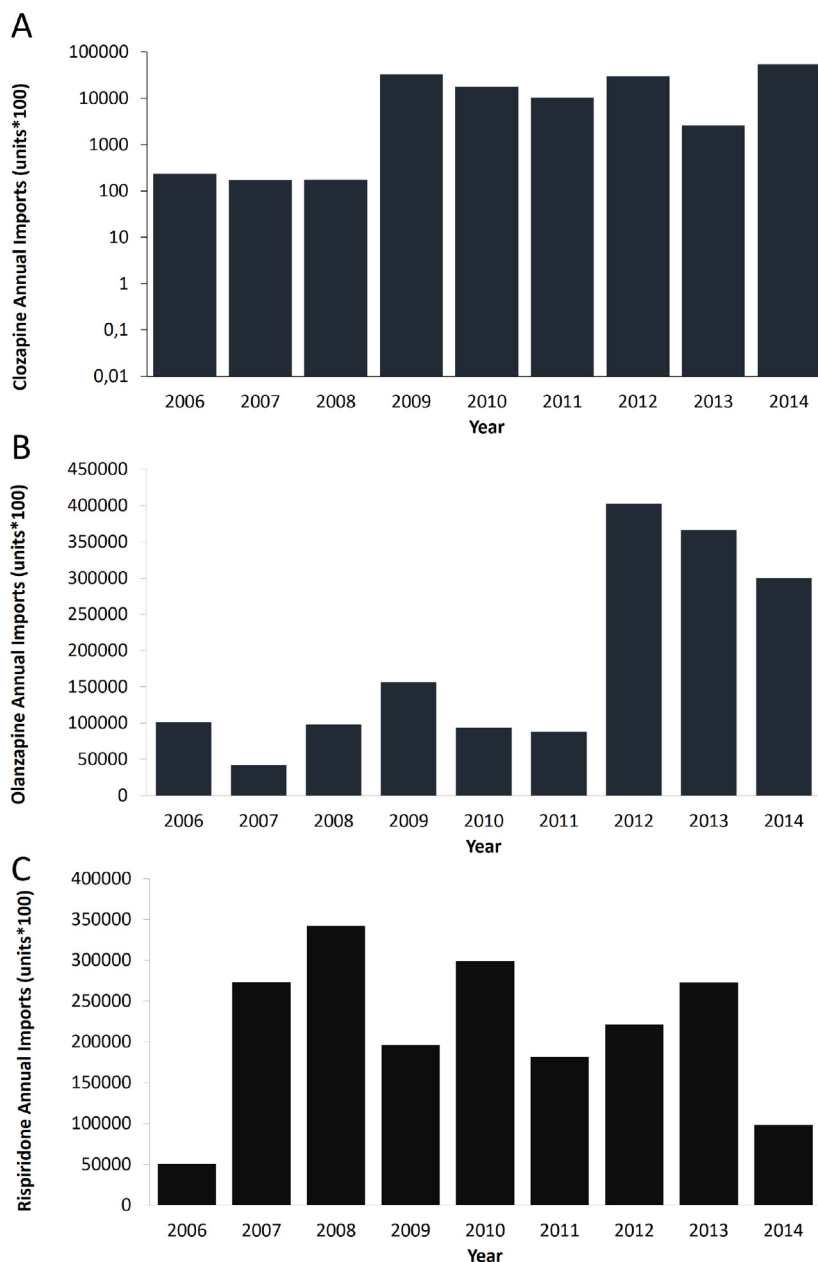
Fig. 1. Annual imports of second generations antipsychotics in Chile.
The graphs shows the annual imports for clozapine (A), olanzapine (B), and risperidone (C) from 2006 to 2014. The data were obtained from official records of The Chilean National Institute of Health (ISP) report N°AO005W0003432.

gain [72,63], hypertriglyceridemia [3], and insulin resistance [66]. There is a positive correlation between the administration of SGAs and hepatic steatosis in – 12–24 h after i.p. injection in rats [55] and the gene expression of profiles follow a biphasic pattern for PPAR controlled genes that leads to rapid accumulation of triglycerides, phospholipids, and cholesterol in the liver [38]. The obesity induced by clozapine is seemingly affected by genetic polymorphsims and it is followed by an increase in plasma leptin of five folds over baseline [4,17,55,112]. Thus, although few studies argue otherwise [45,110], the vast majority of published literature [47,55,82,16], including a recent clinical trial [130], supports the hypothesis that, independent of baseline BMI and the presence/absence of MetS, clozapine and olanzapine induce accelerated obesity, hyperglycemia and hypertriglyceridemia [38]. The current evidence also shows that SGAs-induced MetS is mediated by four biological phenomena: (i) Changes in adipocyte differentia-

tion markers [84], (ii) Induction of lipid biosynthesis/accumulation in liver and fat tissue [60,63,110], (iii) the up-regulation of the sterol regulatory element-binding protein (SREBP) in adipocytes and liver cells [53,136], and (iv) Hyperphagia associated to altered appetite controlling signals regulated by POMC, CART, D2, 5HT2 and H1 [65,46,94] in the hypothalamus and M3 muscarinic receptors in peripheral tissues [94]. Hepatic steatosis [138] is among the most prevalent risk factors found in patients treated with SGAs, especially for those naïve to treatment, in which SGAs cause a more noticeable increase in weight compared with chronically treated patients [132]. The SGAs-induced metabolic disturbances were associated with biphasic patterns of lipid-related genes in the liver and in white adipose tissue depots [55]. In addition to genetic and pharmacological factors, SZ patients are at risk for developing obesity due to behavioral factors including inactive lifestyle, length of the disease [77], poor dietary choices, and smoking [3].
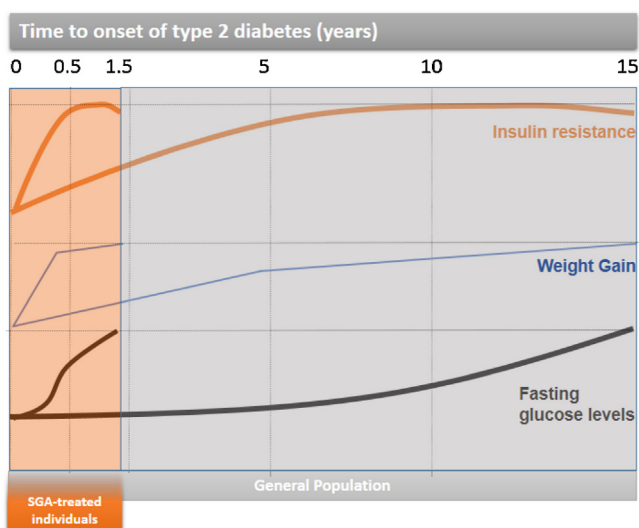
Fig. 2. Schematic representation of the time required for the development of metabolic alterations in SGAs-treated individuals and in regular type 2 diabetes patients.

SAGs-induced MetS can be aggravated by factors like, ethnicity, advanced age, and female sex, Adiponectin is one of the most important adipocytokines, it shows sexual dimorphism, which may explain why the risk of SGA-induced cardiometabolic alterations in females is higher than in males [61]. Polymorphisms in the hormone adiponectin are also associated with SGA-induced cardiometabolic abnormalities [114].

Interestingly, the efficacy of SGA in reducing positive symptoms shows a negative correlation with the appearance of the MetS in drug naive schizophrenia patients [126]. The mechanisms of this correlation are yet to be elucidated, but studies on the role of H1 and 5HT antagonism [114], and expression of leptin and adiponectin [84,130] are providing the first clues to solve this puzzle. Environmental and/or epigenetic factors also contribute to the propensity to develop metabolic syndrome in SGAs-treated patients. For example, the ADRA2A polymorphism is present in European descendants, but not in African descendants. This polymorphism seemingly functions as a risk predictor for clozapine-/olanzpaine-induced weight, because the carriers of the C allele gain more weight compared with the subjects homozygous for the GG allele [112]. Regardless of baseline BMI, ethnicity [77] and initial body fat mass, the advanced age, and female gender are more relevant in the clinical manifestation of SGAs side effects, as the female SGA-treated patients had a higher incidence of diabetes compared with the general population [66].

3. Pathophysiology of SGAs-induced lipid accumulation and weight gain

Cellular and animal studies have established that clozapine increases lipogenesis through the up-regulation of SREBP1c [55,113,136], this transcriptional factor is a major regulator of the lipid biosynthesis in liver and adipose tissue [80]. There are two SREBP isoforms, SREBP1 and SREBP2, encoded by two different genes, SREBP1 has two splice variants, SREBP1a and SREBP1c [80]. SREBP1a is a ubiquitous protein that regulates genes in both cholesterol and fatty acid biosynthesis [111]. While SREBP1c – and its target genes ACL, ACC1, ACC2, FANS, SCD1, GPAT, lipine, adiponectin – are involved in the biosynthesis of triglycerides and in peripheral tissues. The overexpression of SRBP1c can cause pronounced metabolic disturbances [24], as it was demonstrated by the overexpression SREBP1 in rodents that developed hepatic

steatosis and severe insulin resistance [91]. These findings brought the testable hypothesis that SREBP1c inhibitors, like Berberine, can function as protective agents against SGAs-induced lipid accumulation in liver and adipose tissue [53,128,135]. Lipoprotein lipase (LPL) is another key player in of the SGAs-induced alterations of lipid metabolism (Fig. 3). LPL is involved in triglyceride hydrolysis and the transport of free fatty acids [18]. It also mediates the hydrolysis of triglycerides in liver and adipocytes. LPL is inhibited by clozapine in vivo and in vitro [136]. Clozapine-induces elevation of free fatty acids and glucose in serum [1] and hepatic accumulation of lipids in female Sprague–Dawley rats [38]. Hyperphagia is another major contributor to weight gain among SGAs users [1,60]. The evidence suggest that the increase olanzapine-induced hyperphagia might be secondary to the activation of SREBP1c-controlled genes, like PPARγ [37,2,134,117,79], FASN [119,134] and LDLR [134]. We believe that the overexpression of LDLR also results in an augmented capacity of adipocytes to accumulate cholesterol (Fig. 3). Olanzapine decreases the expression of 5-lipoxygenase-activating protein (FLAP) [35]. FLAP is an enzyme involved in the production of leukotriene. Thus, It is not clear how FLAP contributes to SGAs-mediated cardiovascular risk, because leukotriene are known to mediate pathological inflammation in different tissues [35]. Olanzapine also increases levels of adiponectin and leptin, through SREBP1c 1 [134,96,106]. Adiponectin and leptin are associated with appetite control in the arcuate nucleus of the hypothalamus (Fig. 3) [96]. Leptin levels are inversely correlated with appetite [96,139]. However, plasma levels of leptin in obese individuals patients are elevated [96] which led to the concept of central "leptin resistance" [81]. We hypothesized that this phenomena is also present in SGAs-treated patients (Fig. 3), as they also exhibit elevated plasma levels of leptin [63,65,105,68]. Leptin receptors inhibit appetite through the STAT3/PIK3 pathway in POMC neurons [139] of de the arcuate nucleus. During leptin resistance POMC neurons activate the SOCS53 signaling, which results in inhibition of satiety and increased food intake [139,78]. It is not yet clear how POMC and CART signal are impaired by SGAs, however, the hypothesis of multifaceted mechanism triggered by SGAs [21], both at peripheral and hypothalamic levels, seems as an attractive model to explain this puzzle.

4. Prophylactic interventions against SGAs-induced metabolic syndrome

In Table 1, we summarized the results of 20 clinical studies and three preclinical studies, assessing the efficacy of pharmacological interventions (i.e., metformin, nizatadine, orlistat, ranitidine, topiramate, etc.) against SGA-induced metabolic side effects. This summarized evidence shows that one out of five studies with metformin resulted in negative results. The other four positive studies concluded that weight gain, insulin resistance can be efficiently controlled, but lipid profile may even worsen. Metformin reduced body weight in clozapine-treated patients [25], but its beneficial effects disappeared after discontinuing this medication. Orlistat in overweight/obese clozapine-or olanzapine-treated patients failed to prevent obesity and lipid accumulation [56], which suggest that the intestinally absorbed lipids may not be relevant for SGAs-induced obesity. Atomoxetine, a selective norepinepherine reuptake inhibitor with appetite suppressant activity, was not effective in preventing obesity in patients treated with olanzapine and clozapine [9].

Clinical and molecular data supports the hypothesis that SGAs-induced weight gain and hyperglycemia are part of a multifactorial problem, which makes it difficult to tackle with a single-drug therapy [4]. The therapies based on antagonism of hypothalamic dopamine D1/D2 and H1 receptors still awaits for clinical sup-
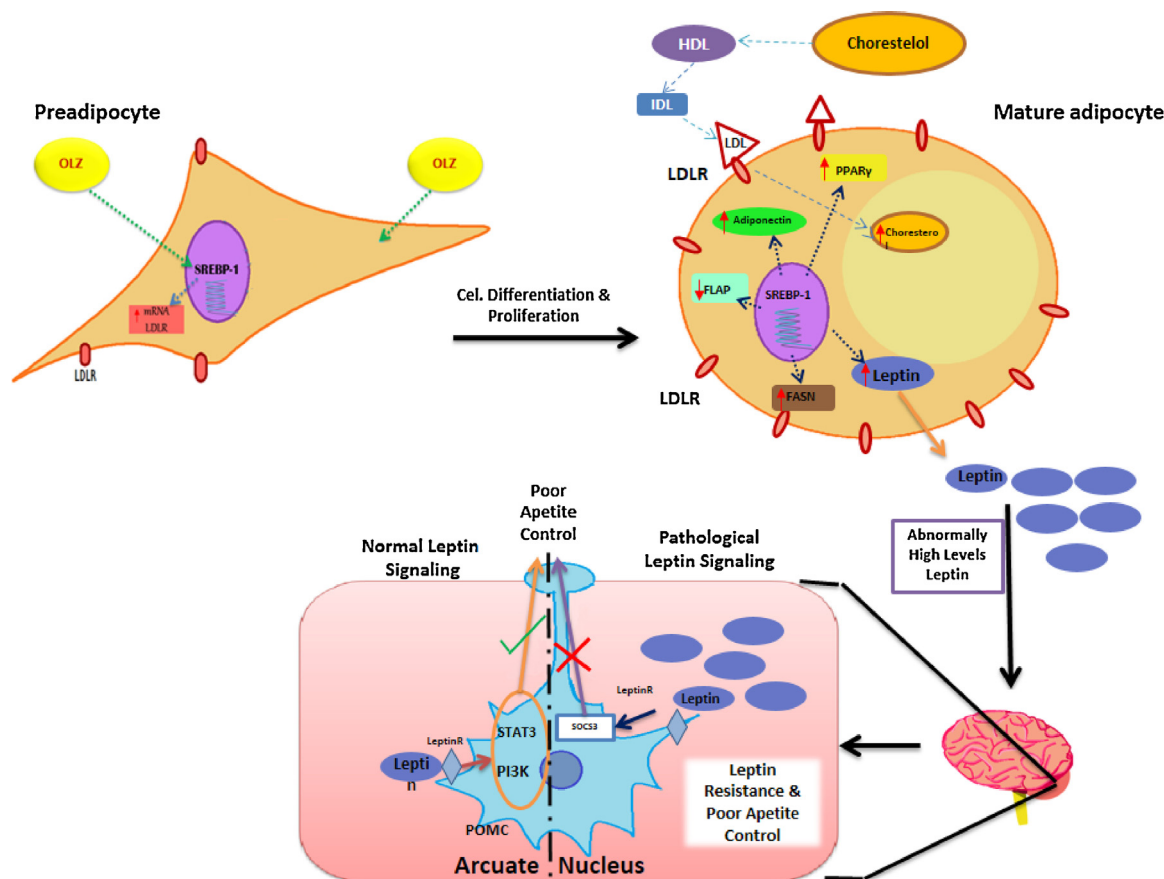
Fig. 3. Metabolic alterations induced by olanzapine in adipose tissue and hypothalamus. Olanzapine promotes differentiation to adipose phenotype in pre-adipocytes and increases expression of SREBP1-controlled gens. Anomalously elevated levels of leptin lead to hyperphagia through "leptin resistance". OLZ: olanzapine.

porting data [46,60]. Respect to the serotoninergic hypothesis, the interventions with fluoxetine also failed. The use of sertraline in clozpaine-induced weight gain resulted in cardiac death [50]. The tetradecylthioacetic acid (TTA), a modified fatty acid, recently showed a minor protective effect against hypertriglyceridemia, but failed to prevent weight gain induced by clozapine in rodents [113]. Berberine, a natural alkaloid, inhibited *in vitro* adipogenesis and SREBP-1 overexpression induced by clozapine and risperidone in 3T3 adipocytes [53]. As shown in Table 1, resveratrol and green tea, showed some efficacy in decreasing weight gain and fat mass accumulation induced by olanzapine in rodents.

5. The emerging concept of antidiabetic polyphenols

Polyphenols are family of polar compounds found in fruits and vegetables, they have been popular for their potent antioxidant effect, but in the past 5 years increasing evidence has shown that, anthocyanins, a specific category of polyphenols, are effective in ameliorating obesity [108,70,57] and insulin resistance [76,42]. In Table 2, we summarized the main clinical and pre-clinical evidence in this area. The mode of action and pharmacokinetic profile of these compounds is not yet fully elucidated and their bioavailability after oral administration is a matter of continuous controversy [71]. However, there is robust evidence on their efficacy in cardiometabolic problems [20,131]. Kurimoto et al. reported that anthocyanins from black soy bean increased insulin sensitivity *via* the activation of AMP-activated protein kinase (AMPK) in skeletal muscle and liver of in type 2 diabetic mice [64]. AMPK, a regulator of glucose and lipid metabolism in liver and muscle cells, is inhibited by olanzapine, which may contribute to the olanzapine-

induced hepatic lipid accumulation [85] Anthocyanins also display insulin-like effects even after intestinal biotransformation [71]. Our laboratory has started a new project funded by the Chilean federal agency CONICYT, to elucidate the effect of polyphenols on SGAs-induced lipid accumulation in liver and adipocytes. We expect that by the end of this program we will have clinical evidence to help SGAs treated patients. We also aim to have a better understanding of the biochemistry and pharmacology of SAGs-induced lipid accumulation and the prophylactic role of specific polyphenols.

We have previously demonstrated that anthocyanins ameliorate signs of diabetes and metabolic syndrome in obese mice fed with a high fat diet have [100,98,71,27]. Delphinidin 3-sambubioside-5-glucoside (D3S5G), an anthocyanin from *Aristotelia chilensis*, is as potent as metformin in decreasing glucose production in liver cells, and it displays insulin-like effect in liver and muscle cells [98]. The anti-diabetic mode of action of anthocyanins have been associated with the transcriptional down-regulation of the enzymes PEPCK and G6P gene in hepatocytes [100,98]. Prevention of adipogenesis is also another reported mechanmis for some anthocyanins from *A. chilensis* [108]. Anthocyanins also induce significant increase in circulating levels of adiponectin in murine models of MetS [124,123]. This is relevant, since adiponectin is reduced in clozapine-treated patients and weight reduction is associated with higher circulating levels of adiponectin. In a recent study Roopchand et al., demonstrated that blueberry anthocyanins are as potent as metformin in correcting hyperglycemia and obesity in obese hyperglyceminc mice [98,100]. Dietary anthocyanins have also proven efficacy in decreasing levels of the inflammatory mediators PAI-1 and retinol binding protein 4 in obesity and type 2 diabetes [121,107]. Recent medical and

Table 2
Clinical trials assessing efficacy of polyphenols in diabetes, obesity and metabolic syndrome.

Polyphenols/dosage	Study design	N (beginning/end)	Duration	Primary outcome	Secundary outcome	Results and comments	Overall conclusion	Ref.
Cinnamon extract/250 mg, twice a day	Randomized double-blind, placebo controlled study	173/137	10 weeks	Fasting serum glucose		Decreased glucose, fasting insulin, LDL and HDL in the supplemented group with cinnamon extract, extract compared to placebo	Positive	[5]
Fresh pomegranate juice/1.5 ml/kg	Randomizedstudy	85	3 h	Fasting serum glucose and insulin		Decreased insulin resistance, FSG and increased B cell function	Positive	[10]
Purified anthocyanin/320 mg/d	Randomized double-blind, placebo-controlled	150/146	24 weeks	Total cholesterol, HDL-cholesterol, LDL-cholesterol and triacylglycerol	Serum inflammatory markers	Anthocyanin mixture reduced the inflammatory response, serum CRP, VCAM-1 and IL-1b in hypercholesterolemic subjects	Positive	[140]
Green tea/250 mg, three times a day	Randomized, controlled trial	60	12 weeks	Body weight, BMI, body composition, resting energy expenditure, and substrate oxidation were measured at baseline	Serum levels of leptin and urine VMA were measured	Reduced body weight of obese individuals	Positive	[8]
Pomegranate juice 50 ml/day	Unspecified	20	15 weeks	serum biochemical parameters		Antioxidant effects in diabetic patients	Negative	[102]
Green tea extract 375 mg (270 mg catechins/day	Randomized, double-blind, placebo-controlled clinical trial	78/100	12 weeks	The body weight (BW), body mass index (BMI) and waist circumflex (WC)	Blood glucose, creatinine, aminotransferases aspartate, aminotransferases alanine, uric acid, and plasma lipoproteins (triglyceride, cholesterol, HDL-cholesterol (HDL) and LDL-cholesterol (LDL)	No significant differences in BW, BMI and WC between the control group and the group treated with GTE. Significant reduction in LDL-cholesterol and triglycerides, increase HDL-cholesterol, adiponectin and ghrelin	Positive	[51]
Raisins (*Vitis vinifera*) 36 g/day	Randomized controlled trial	48	24 weeks	Blood pressure, fasting glucose	HbA1c, lipid peroxidation, high-sensitivity C-reactive protein, antioxidant status, cytokines	Reduced diastolic blood pressure and increased total antioxidant potential type 2 diabetes mellitus	Positive	[58]
Pomegranate juice		14	2 weeks	Total antioxidant capacity (TAC), levels of malondialdehyde, protein carbonyls (CARB) (GSH), catalase activity		Decreased malondialdehyde, protein carbonyls. Increased GSH levels	Positive	[73]
Wine polyphenols 30 g alcohol/day	Randomized clinical trial	67	4 weeks	Fasting plasma glucose and insulin	HOMA-IR, plasma lipoproteins, apolipoproteins, adipokines	Decrease plasmatic insulin, lipoprotein and HOMA-IR, increased HDL, apolipoprotein AI and A-II	Positive	[29]
Resveratrol 150 mg	Double-blind, randomized, placebo-controlled trial	60	15 weeks	Hematological & renal functions test, liver enzyme, glucose and lipid metabolism, and serum cytokines		Decreased aspartate aminotransferase, glucose, alanine aminotransferase, total cholesterol, TNFα cytokeratin and fibroblast growth factor. Elevated adiponectin	Positive	[26]
Green tea (*Camellia sinensis*)	Randomized controlled trial	35	8 weeks	Parameters, of metabolic syndrome		No change in metabolic syndrome features, a decrease in plasma amyloid alpha	Negative	[14]
Whole blueberries 22.5 g, twice a day	Double-blinded, randomized, and placebo-controlled clinical study	32	6 weeks	Insulin sensitivity, inflammatory biomarkers, and adiposity	Body weights	Improved insulin sensitivity with cranberry, no changes in inflammatory biomarkers, adiposity and energy intake	Positive	[116]
Purified anthocyanins 160 mg twice a day	Randomized, placebo-controlled, double-blind trial	58	24 weeks	Serum lipids, fasting plasma glucose, insulin, and glycated hemoglobin	Oxidative stress markers. Plasma concentrations of 8-isoprostaglandin		Decreased LDL cholesterol, triglycerides, apolipoprotein, and apoC-III and increased HDL. Decreased glucose, levels in type 2 diabetes patients.	[69]

nutritional studies suggest that anthocyanins from diverse dietary sources are potent anti-diabetic, anti-obesity and cardioprotective molecules [57,100,99,27,36]. Another fact that makes anthocyanins candidates for preventing clozapine-induced lipogenesis is that they are capable of suppressing the inflammatory response through targeting the phospholipase A2, PI3K/Akt and NF-kappaB pathways, [34]. These pre-clinical findings were corroborated by clinical evidence showing the dietary anthocyanins from blueberries improve insulin resistance in young obese, non-diabetic adults [115]. The clinical efficacy of polyphenols in SGAs-induced MetS has not yet been established, but a recent pre-clinical demonstrated that, resveratrol, a polyphenol found in grapes, decreases olanzapine-induced weight gain [104].

6. Concluding remarks

In Chile, as in the rest of the world, the use of SGAs is increasing, as they provide a powerful therapeutic alternative to control symptoms of SZ patients and non SZ patients. Especially those with severe acute psychotic syndromes. However, given the known cardiometabolic complications, there is a need for affordable prophylactic agents because the newer – and safer – atypical antipsychotics are not yet available to all patients due to their high cost. It is necessary to continue the basic and clinical research on new prophylactic agents, such as D1, H1 ligands, the retinoid ligand AM-80 [97], SREBP1 inhibitors, to further understand their potential for ameliorating SGAs side effects. The current literature suggest that mechanisms of SGAs-induced metabolic syndrome involves at least two separate systems: the peripheral lipid and glucose metabolism, controlled by SREBP1 transcriptional factor, and the alteration of appetite control in the hypothalamus through neurons of the arcuate nucleus. We believe that a better understanding of the antidiabetic effect of specific polyphenols will help us to find new – and affordable – treatments for this medical problem.

Conflict of interest

Authors of this manuscript do not have conflicting interest in regard with the manuscript.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phrs.2015.07.022

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