

# Antipsychotic-Induced Metabolic and Cardiovascular Side Effects in Schizophrenia: A Novel Mechanistic Hypothesis

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**Abstract** The use of antipsychotics is hindered by the frequent occurrence of metabolic and cardiovascular side effects, resulting in worsened quality of life and greater mortality as a result of cardiovascular and cerebrovascular disorders in schizophrenia patients than the comparable general population. The various antipsychotics induce extrapyramidal symptoms, impaired glucose and lipid metabolism, weight gain, hypertension and arrhythmias, with variable frequency. Second-generation antipsychotics appear to have several advantages over first-generation antipsychotics, including a claimed better action on cognitive function and the negative symptoms of schizophrenia, and lower frequency of extrapyramidal side effects; however, their use is associated with a greater frequency of metabolic and cardiovascular disturbances. The mechanisms of these important side effects are not well understood, and generic approaches (psychoeducational programmes and symptomatic therapies) have been proposed to limit their severity. Extensive data from the literature indicate that autonomic nervous system dysfunction—intrinsic to schizophrenia and strongly exacerbated by antipsychotic treatment—is the cause of the pervasive metabolic and vascular dysfunctions associated with schizophrenia. In this article, we marshal further literature data to argue that the metabolic and cardiovascular side effects of antipsychotics are primarily mediated by their ability to block peripheral

dopamine receptors, which physiologically modulate sympathetic activity. We also propose that these effects might be overcome by providing peripheral dopaminergic stimulation.

## 1 Introduction

Compared with first-generation antipsychotics (FGAs), second-generation antipsychotics (SGAs) seem characterized by reduced risk of extrapyramidal motor side effects but high frequency of adverse metabolic events [1]. Insulin resistance, weight gain with abdominal obesity, impaired glucose tolerance, diabetes mellitus, dyslipidaemia, essential hypertension—major diagnostic criteria for metabolic syndrome[2]—all occur frequently in patients treated with SGAs [1]. Metabolic syndrome is a major cardiovascular risk factor in schizophrenia patients, and is associated with greater mortality due to cardiovascular and cerebrovascular diseases than the comparable general population [3]. Furthermore, all antipsychotics (FGAs and SGAs) can cause severe and sometimes fatal cardiac arrhythmias [4].

Although the metabolic derangement and cardiovascular disorders associated with antipsychotic use are well recognized, a comprehensive mechanism able to account for all these effects has not been proposed, so it is time to examine new pathogenetic mechanisms that might account for them. We propose a new pathogenetic mechanism for these effects supported by a MEDLINE search using the search terms metabolic syndrome, insulin resistance, diabetes, dyslipidaemia, hyperglycemia, weight gain, sympathetic, histamine, serotonin, dopamine, triglycerides, cholesterol, hypertension, cardiovascular disorders and sudden cardiac death, cross-referenced with the term schizophrenia. We examined papers published in English

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between 1980 and 2012 and checked references in relevant papers to identify additional studies.

## 2 Schizophrenia as an Independent Risk Factor for Metabolic Syndrome

Impaired glucose metabolism was described in psychiatric patients before antipsychotics were introduced in the 1950s [5]. Although disputed by some authors [6, 7], drug-naïve and first-episode patients with schizophrenia seem to have impaired fasting glucose tolerance, more insulin resistance and higher levels of plasma glucose, insulin and cortisol than healthy control subjects. [8] Moreover, antipsychotic-naïve and antipsychotic-free schizophrenia patients have significantly greater visceral adiposity than age- and sex-matched controls, despite similar subcutaneous adiposity [9–11]. Intra-abdominal adiposity is much more strongly linked to insulin resistance and type 2 diabetes than excess subcutaneous fat [12].

These metabolic disturbances in patients with schizophrenia have been attributed to sedentary lifestyle, poor diet and smoking [1]. However, increased sympathetic-adrenal activity [13], with high plasma levels of catecholamines and cortisol [14], has also been observed in untreated schizophrenia patients. Increased sympathetic-adrenal activity could be a consequence of psychosis-related stress [15], but could also be an effect of nicotine, as these patients are often heavy smokers. Nicotine acts on nicotinic (cholinergic) receptors in sympathetic ganglia, activating postganglionic neurons and stimulating the secretion of catecholamines from their terminals [16]. Smoking is associated with insulin resistance [17], dyslipidaemia [18] and an increased propensity for type 2 diabetes [19, 20] through a body mass index-independent mechanism [21]. Contrary to what one might expect, stopping smoking does not reduce these metabolic abnormalities but, by mechanisms not well understood, is often accompanied by increased weight and a further increase in the risk of diabetes [22, 23].

### 2.1 Metabolic and Cardiovascular Effects of Sympathetic Overactivity

High circulating levels of noradrenaline (norepinephrine), adrenaline (epinephrine) and cortisol oppose the anabolic effects of insulin and can induce metabolic changes. Thus, by activating  $\alpha_2$ -adrenoreceptors, noradrenaline and adrenaline promote the transformation of liver and muscle glycogen to free glucose, enhance glucagon secretion and inhibit insulin release from the pancreatic islets [24], inducing hyperglycaemia; they also act on  $\beta_2$ -adrenoreceptors in muscle and adipose tissue to reduce glucose

uptake and utilization by these tissues, promoting insulin resistance [25]. In addition, noradrenaline and adrenaline stimulate adipose lipolysis, promoting the release of glycerol, free fatty acids, leptin, adiponectin and proinflammatory cytokines into the circulation [26]. The latter three substances are implicated in obesity [27] (see Sect. 3). Increased fatty acid levels contribute to the development of insulin resistance [27] and stimulate the assembly and secretion of very low density and low-density lipoproteins (LDLs) by the liver, so that plasma levels of triglycerides and LDL-cholesterol increase, and high-density lipoprotein (HDL)-cholesterol decreases [28].

Thus, sympathetic overactivity correlates with hypercholesterolaemia and hypertriglyceridaemia. It is noteworthy that serum cholesterol levels are significantly reduced in animals treated with 6-hydroxydopamine, a sympathetic nervous system toxin [29].

Cortisol also increases insulin resistance, further contributing to high levels of circulating glucose and lipids; and in the long term, cortisol promotes abdominal fat accumulation and stimulates the intake of carbohydrates and fat [30].

Finally, excessive sympathetic tone has a major effect on the cardiovascular system: it is implicated in cardiovascular hypertrophy and vulnerability to arrhythmias, and plays a pathogenetic role in essential hypertension by raising cardiac output and heart rate, and increasing peripheral resistance and renin production [31]. Cardiac effects of adrenergic activity are mediated mainly by  $\beta_1$ -receptors, although  $\beta_2$ - and  $\alpha$ -adrenoceptors are also involved.  $\beta$ -Adrenoceptor activation increases both normal (sinoatrial node) and abnormal (Purkinje fibres) pacemaker activity.

## 3 Worsening of Metabolic Syndrome by Antipsychotics

The metabolic syndrome that characterizes many untreated patients diagnosed with schizophrenia can worsen after a few months' treatment with antipsychotics [1, 11, 32]. This happens more frequently with SGAs than FGAs, and with greater probability for some SGAs than others [32, 33]. The prevalence of metabolic syndrome increases with duration of treatment [32].

SGAs are a heterogeneous class of drugs, each agent having differing pharmacological properties and a unique binding profile to multiple receptors, which determine differences in efficacy and side effects [34].

Increased body weight is usually linked to insulin resistance (major cause of metabolic syndrome) [35] and to changes in plasma glucose and lipid levels, but obesity cannot be the causative factor for most cases of diabetes arising during antipsychotic treatment [36]. Dose-

dependent insulin resistance occurs following acute clozapine and olanzapine administration in rats [37], indicating an immediate effect of these agents on metabolic variables. Some [38, 39], but not all [40], studies have found that antipsychotics have a similar short-term effect in humans. In particular, rapid onset of diabetes has been documented after the initiation of antipsychotic therapy, together with rapid disappearance of diabetes after discontinuation [41]—too rapid to be explained by changes in body weight.

Clozapine and olanzapine use appears to be associated with greatest risk of metabolic syndrome; iloperidone, quetiapine, risperidone, paliperidone, sertindole and zotepine are associated with intermediate risk; while amisulpride, aripiprazole, asenapine, lurasidone and ziprasidone are associated with only a small increase in risk [11, 42]. One study found that the increased risk of diabetes was identical in users of olanzapine, quetiapine and risperidone [43]. No antipsychotic is completely free of metabolic side effects [44]; even those usually without such effects may cause them in specific situations. Thus, although aripiprazole does not increase body weight in adults, weight gain has been reported in paediatric patients following aripiprazole administration [45, 46]. Furthermore, long-term side effects tend to come to light only after a drug has been on the market for some time [47], and most data on the side effects of antipsychotics have been obtained from trials on patients with many years of prior drug exposure, and this could lead to the underestimation of side effects in the more recently introduced antipsychotics such as aripiprazole, asenapine, lurasidone and ziprasidone [48]. Finally, metabolic alterations appear to be an intrinsic effect of antipsychotics, since they appear when these drugs are employed to treat diseases other than schizophrenia [49, 50].

#### 4 Previously Proposed Mechanisms for Metabolic Side Effects of Antipsychotics

Despite a large body of research, no specific neurotransmitter or receptor has been identified as the main cause of the metabolic derangement often induced by antipsychotics [51]. Since antipsychotic-induced obesity seems to be related more to increased calorie intake than reduced thermogenesis [52], the antagonistic action of antipsychotics on receptors involved in the control of satiety, feeding and glucose metabolism, and their interactions with orexigenic and anorexigenic peptides have been extensively investigated [53]. Antipsychotic-induced weight gain has been proposed as due to antagonistic effects at, among the others, the histamine H<sub>1</sub> [54, 55], serotonin 5-HT<sub>2C</sub> [56] and dopamine D<sub>2</sub> [57] receptors; while the diabetogenic effect has been correlated with binding affinity to H<sub>1</sub> [55], 5-HT<sub>2C</sub> and muscarinic acetylcholine

receptors [34]. In fact, antagonism at 5-HT<sub>2C</sub> receptors increases insulin resistance and reduces glucose uptake by skeletal muscle, increasing the risk of diabetes [55]. However, antipsychotics such as clozapine, olanzapine, risperidone, sertindole and zotepine have different propensities for inducing metabolic effects, even though they have similar and only moderate binding affinity for 5-HT<sub>2C</sub> receptors; moreover ziprasidone, which has the most potent binding [58], is apparently largely free of metabolic side effects. It therefore appears difficult to reconcile the variable ability of antipsychotics to induce metabolic changes with their binding to the 5-HT<sub>2C</sub> receptor.

The receptor binding profiles involved in dyslipidaemia have not yet been identified [34].

Turning to consider acetylcholine receptors, antagonism at muscarinic M<sub>3</sub> receptors on pancreatic  $\beta$  cells (as shown by olanzapine and clozapine), with consequent suppression of cholinergic-stimulated insulin secretion, has also been suggested as a cause of the metabolic effects of some SGAs [45, 59]. However, when selective M<sub>3</sub> antagonists are used to treat patients with urinary incontinence they have not been associated with increased risk of diabetes. Furthermore, insulin and glucose clearance responses to the oral glucose tolerance test in vagotomized humans do not differ substantially from those of healthy controls [60]. It is likely therefore that M<sub>3</sub> antagonism is only a precipitating factor for diabetes in patients treated with antipsychotics.

Leptin, ghrelin and adiponectin—peptide hormones involved in the regulation of appetite and body weight—might be involved in the metabolic syndrome induced by antipsychotics [61]. Leptin is a cytokine-like molecule produced by subcutaneous adipocytes and actively transported into the hypothalamus where it acts to limit food intake. However, most patients on antipsychotics have increased, not reduced, blood levels of leptin, suggesting that leptin increase is a consequence (not a cause) of increased body weight, or that leptin resistance has developed [61]. Ghrelin is a hunger-inducing hormone produced in the stomach that regulates feeding behaviour through central activity. Plasma levels of ghrelin have been reported increased, unchanged and reduced in various studies on schizophrenia patients treated with antipsychotics [61]. Adiponectin is secreted by adipose tissue and circulating levels correlate inversely with body weight and insulin resistance. As with studies on ghrelin, studies on adiponectin levels in antipsychotic-induced weight gain have produced conflicting results [61]. For more data on these peptides and antipsychotic-induced metabolic side effects see the following review articles [45, 48, 61, 62].

The appearance of metabolic side effects in some but not all patients treated with a given antipsychotic suggests the involvement of genetic factors. Gene polymorphisms may occur at the level of drug transporters, metabolizing

enzymes or the protein targets (receptors) of the drug. Antipsychotic-induced weight gain is associated with a polymorphism of the promoter region of the 5-HT<sub>2C</sub> receptor gene and a functional polymorphism of the leptin gene [63]. Associations of increased risk of metabolic syndrome with polymorphisms of the *MTHFR* gene [64] and the D<sub>2</sub> receptor gene [65] have been suggested in patients receiving SGAs.

From the above survey, it is evident that a convincing account of the mechanisms responsible for the frequent and severe metabolic side effects of SGAs is not available. We suggest that the main mechanism for these effects is deranged autonomic function due first to the ability of these agents to block peripheral dopamine receptors, which increases sympathetic activity (see Sect. 5 for the proposed mechanism); and secondly to the ability of some of these agents to also block peripheral muscarinic receptors, which reduces vagal parasympathetic activity.

## 5 The Missing Piece of the Puzzle: The Peripheral Dopaminergic System

Outside the CNS, dopamine has been traditionally viewed as an inactive precursor of noradrenaline and adrenaline. However, dopamine receptors are widespread peripherally, being present for example in heart, kidneys, adrenal glands, liver, endocrine pancreas and resistance vessels such as renal, coronary, pulmonary, mesenteric and cerebral arteries [66]. D<sub>1</sub> and D<sub>5</sub> (D<sub>1</sub>-like), and D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> (D<sub>2</sub>-like) receptor subtypes have not been extensively investigated in peripheral organs, hence for convenience we apply the D<sub>1</sub>/D<sub>2</sub> classification of Keabian and Calne [67].

Stimulation of D<sub>1</sub> receptors, located postsynaptically in renal, mesenteric and splenic arteries, causes direct vasodilatation; and by reducing vascular resistance reduces blood pressure [68]. D<sub>2</sub> receptors are located presynaptically on postganglionic sympathetic neurons and on adrenal chromaffin cells: their activation inhibits noradrenaline release from nerve endings, and adrenaline secretion from the adrenal medulla [66, 69], resulting in indirect vasodilatation, reduced cardiac contractility and anabolic effects through inhibition of sympathetic tone. These data suggest that the peripheral dopaminergic system is an important modulator of the endocrine and cardiovascular systems [68, 69]. In fact, during intense sympathetic stimulation, endogenous dopamine (in addition to noradrenaline and adrenaline) is secreted and serves to modulate sympathetic discharge [70]. It is not surprising, therefore, that full D<sub>2</sub> receptor agonists have proven effective in reducing blood pressure and plasma glucose and lipids, thereby ameliorating some aspects of metabolic syndrome [68, 71, 72]. Moreover, partial dopamine agonists employed in the treatment of psychosis (e.g.

aripiprazole) do not seem to cause metabolic syndrome [42], probably thanks to their stimulating action on extracerebral presynaptic D<sub>2</sub> receptors.

### 5.1 Metabolic Effects of Peripheral Dopamine D<sub>2</sub> Receptor Blockade

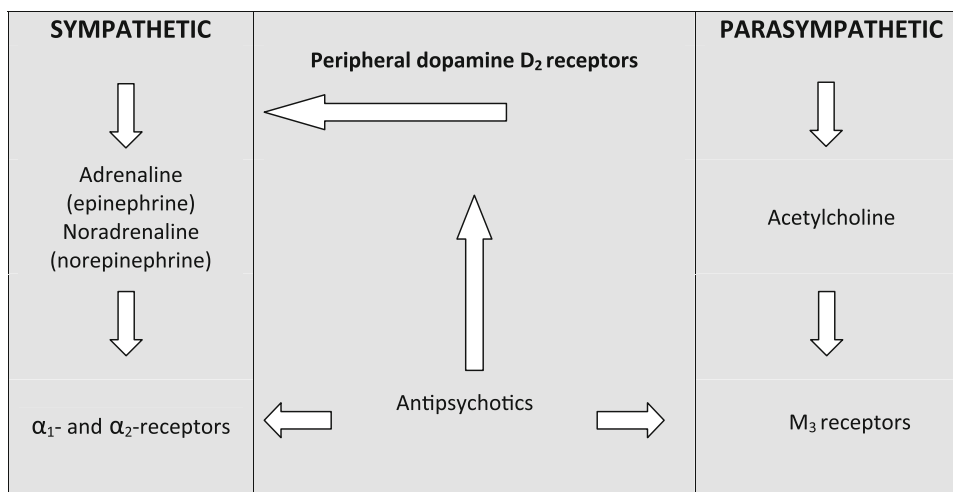
Although the various antipsychotics have differing effects, attributable to differences in their binding to dopamine, serotonin, histamine, glutamate, muscarinic and  $\alpha$ -adrenergic receptors, all effective antipsychotics block D<sub>2</sub> receptors—including peripheral D<sub>2</sub> receptors—with varying potency and dose-dependent effects [34]. Even antipsychotics such as clozapine, generally believed to have very low affinity for D<sub>2</sub> receptors, probably occupy more than 70 % of these receptors, although more loosely than FGAs [73]. When antipsychotics bind to the D<sub>2</sub> receptor they prevent activation by endogenous dopamine, so the modulating effect of dopamine on the sympathetic-adrenal system is inhibited. This effect is illustrated by the peripheral D<sub>2</sub> antagonist domperidone: administration of this agent, which does not cross the blood-brain barrier except in rare cases of blood-brain barrier immaturity or disruption [74], significantly increases the release of both adrenal noradrenaline and adrenaline [75], and reverses the antihypertensive effect of dopaminergic drugs [76].

Thus, we arrive at the central hypothesis of the present paper: chronic D<sub>2</sub> receptor blockade by antipsychotics abolishes peripheral dopaminergic modulation, resulting in chronically increased sympathetic tone, in turn leading to impaired control of glucose and lipid metabolism, chronic increase in blood pressure, and increased propensity for cardiac arrhythmias (Fig. 1).

Two findings provide strong circumstantial support for this sequence of events: First, catecholamine levels are increased in the plasma and cerebrospinal fluid of schizophrenia patients on long-term antipsychotic treatment—and are reduced after these drugs are withdrawn [77, 78]. Second, the hyperglycaemic response to acute administration of high doses of antipsychotics in the mouse is completely blocked by pretreatment with yohimbine (an  $\alpha_2$ -adrenoceptor antagonist), suggesting that the hyperglycaemic effect is due, at least in experimental animals, to increased sympathetic nervous system activity [79].

### 5.2 Cardiovascular Effects of Peripheral D<sub>2</sub> Receptor Blockade

The hypertension sometimes present in patients being treated with antipsychotics [80] can be controlled by  $\beta$ -blockers [81], suggesting that adrenergic hyperactivity is involved. Increased sympathetic tone is known to play a major role in the genesis of essential hypertension [31]. In



**Fig. 1** Schematic outline of proposed effects of antipsychotics on sympathetic and parasympathetic outflow. Antipsychotics block peripheral dopamine  $D_2$ ,  $\alpha$ -adrenergic, and cholinergic  $M_3$  receptors. Physiologically,  $D_2$  receptors modulate the release of catecholamines from sympathetic terminals and the adrenal glands.  $D_2$  receptor blockade causes increased release of catecholamines. If the  $\alpha$ -adrenergic

receptors are not completely occupied by an antipsychotic, sympathetic activity is increased, and would normally be balanced by increased parasympathetic tone. If, however,  $M_3$  receptors are also blocked by the antipsychotic, sympathetic activity is no longer countered by parasympathetic activity so the former exerts its well known clinical effects leading to metabolic syndrome and arrhythmia

this context, it is noteworthy that catecholamine release is increased in isolated cat adrenal glands perfused with antipsychotics, and reduced by apomorphine (dopaminergic agonist), confirming the existence, in adrenal glands, of a dopaminergic system that inhibits catecholamine release and can be inactivated by the administration of antipsychotics, in turn suggesting the adrenal medulla as a possible site of action for the hypertensive response evoked by antipsychotics [82].

Use of both FGAs and SGAs is also associated with a dose-related increased risk of sudden death due to cardiac arrhythmia [4]. Antipsychotics prolong the electrocardiogram QT interval and this has been identified as an important trigger for torsades de pointes, a transient and unpredictable form of polymorphic ventricular tachycardia [83]. The magnitude of the sudden death risk varies between studies—often just case reports—but seems to be at least as high for SGAs as for FGAs [83]. Strikingly, it took around 50 years of use before the US FDA issued its warning (September 2007) regarding the association of haloperidol with QT prolongation and arrhythmias. We suggest that cardiac  $D_2$  receptor blockade by antipsychotics is responsible for the increased sudden deaths due to cardiac arrhythmias in FGA and SGA users. In fact, increased sudden death for this cause has also been reported after intravenous administration of the selective peripheral  $D_2$  antagonist domperidone [84]. Cardiac  $D_2$  receptor blockade by antipsychotics would increase this risk by inhibiting the modulator effect that endogenous dopamine exerts on sympathetic activity. The resulting enhanced stimulation of adrenergic receptors reduces

refractory period duration, and may lead to the initiation of torsades de pointes [85].

### 5.3 Additional Mechanisms

If  $D_2$  receptor blockade by antipsychotics is the main reason why metabolic derangements are common in users of these drugs, then haloperidol and ziprasidone, the most potent  $D_2$  blockers [34], should be most strongly associated with these derangements. This is not the case however since, as noted above, clozapine and olanzapine, followed by quetiapine, appear mainly responsible for these effects [42]. This conflict can be explained by considering that  $D_2$  blockade increases the availability of noradrenaline and adrenaline (sympathetic activity) but these catecholamines can exert their effects only if the following occurs:

- Adrenergic receptors are free. We know, for example, that antipsychotics block the  $\alpha_1$ - and  $\alpha_2$ -adrenoceptors with variable affinity, so the increased availability of an adrenergic neurotransmitter does not produce any metabolic or cardiovascular effect if receptor occupancy is already high and the proportion of receptors remaining active is low. Net adrenergic activity can even be reduced if receptor occupancy by antipsychotics is high. In fact, orthostatic hypotension may occur—instead of hypertension—as a side effect of antipsychotic use, due to  $\alpha_1$ -adrenoceptor antagonism [86].
- Parasympathetic activity does not counteract their actions. Parasympathetic activity opposes sympathetic effects on the pancreatic islets [24] and the

cardiovascular system [87] by acting on cholinergic  $M_3$  receptors. If these receptors are inhibited by antipsychotics, the increased sympathetic activity is no longer counterbalanced by parasympathetic activity and the net result is sympathetic overactivity. For this reason, clozapine, olanzapine and quetiapine (moderate binding at  $D_2$  but potent binding at  $M_3$  receptors) are strong inducers of metabolic side effects, while haloperidol and ziprasidone—potent binding at  $D_2$  but weak at  $M_3$  receptors—are much less so [32, 42].

Antipsychotics also bind to a range of non-dopaminergic targets, such as serotonin and histamine receptors, which also play a role in weight gain and obesity [34], so the ability of each antipsychotic to induce metabolic derangements would be a result of its actions on all the receptor systems involved in the maintenance of metabolic homeostasis.

## 6 Findings in Parkinson's Disease

Our hypothesis that  $D_2$  receptor blockade by antipsychotics is responsible for metabolic syndrome, and ultimately contributes to increased mortality in schizophrenia, is reinforced by observations in Parkinson's disease (PD), an illness in which sympathetic degeneration and dopaminergic treatment produce effects that are opposite to those found in schizophrenia. One neuropathological hallmark of PD is generalized sympathetic denervation, which is known to be present even in patients without clinically evident autonomic failure [88]. Reduced sympathetic activity accounts for the reduced frequencies of hypertension, type 2 diabetes and dyslipidaemia in untreated PD patients [89].

The main aim of pharmacological treatment in PD is to stimulate  $D_2$  receptors, principally in the striatum. Levodopa is still the most effective drug in this respect. However, the quantities of levodopa-derived dopamine present in the periphery (notwithstanding use of a peripheral decarboxylase inhibitor) are sufficient to further reduce sympathetic activity—via actions on peripheral  $D_2$  receptors—further contributing to lowered frequencies of diabetes, hypertension and dyslipidaemia in PD patients taking levodopa [90].

## 7 Overcoming the Metabolic and Cardiovascular Side Effects of Antipsychotics

The arguments presented above make a strong case that the metabolic and cardiovascular side effects of antipsychotics hinge on their action on peripheral (extracerebral) dopaminergic, cholinergic and adrenergic receptors (although a

central component cannot be ruled out). The inhibitory action of these antipsychotics on  $D_2$  receptors plays a major role in this mechanism. It is therefore conceivable that by displacing the antipsychotic from peripheral  $D_2$  receptors by means of a dopaminergic drug, the balance between sympathetic and parasympathetic activity may be restored, at least in part.

The administration of dopamine agonists to patients with psychotic disorders may raise concerns, as the stimulation of cerebral  $D_2$  receptors can exacerbate psychotic symptoms. However, if the dopaminergic medication is unable to cross the blood-brain barrier this risk is very low.

The dopaminergic drug that has these features is levodopa. Levodopa itself is inactive, but is decarboxylated in the body to active dopamine. However, over 90 % of administered levodopa is decarboxylated outside the CNS, and this dopamine does not cross the blood-brain barrier. To overcome this problem when levodopa is administered to parkinsonian patients, it is combined with a peripheral dopa-decarboxylase inhibitor (carbidopa or benserazide) so that more levodopa passes into the brain to increase the amount of dopamine available there. By contrast, when levodopa is used in the absence of a peripheral decarboxylase inhibitor, its central action is minimized in favour of its peripheral action. This property of levodopa is unique, and its use with or without a peripheral decarboxylase inhibitor allows differential targeting of dopamine to the CNS and the periphery. SGAs such as clozapine, olanzapine and quetiapine bind the  $D_2$  receptor more weakly, and have a higher dissociation constant, than dopamine [91]. It is therefore theoretically possible to displace these antipsychotics from peripheral  $D_2$  receptors using relatively low doses of levodopa, so that the probability of exacerbating psychotic symptoms would be low.

In fact, it is possible that very low levels of central levodopa-derived dopamine might mimic the therapeutic effects of partial dopamine agonists thought to act by stimulating presynaptic  $D_2$  receptors. In vitro experiments have shown that it is possible to produce a partial agonistic effect by combining a full direct receptor agonist with a full antagonist [92]. Slightly elevated central dopamine levels might also promote quick dissociation of antipsychotics from  $D_2$  receptors [91], improving their pharmacological profile.

In a review of 30 studies involving more than 700 patients, Jaskiw and Popli reported that administration of high doses of levodopa to patients with schizophrenia caused clinical worsening (measured with various psychiatric rating scales) in 20 % of cases when not associated with antipsychotics, but a significant clinical improvement occurred in 50 % of cases when antipsychotics were also administered. The authors concluded that add-on levodopa may be beneficial in patients already on antipsychotics [93]. It is noteworthy that

the beneficial effects of levodopa prevailed over its negative effects even though high doses of levodopa, associated with a peripheral decarboxylase inhibitor, were given. It is noteworthy, also, that levodopa has proved capable of attenuating peripheral sympathetic activity in experimental animals [94], and has been successfully used (without a decarboxylase inhibitor) to treat congestive heart failure [95].

Levodopa has been widely used (and studied) for the treatment of PD for over 50 years. It may cause nausea when first given due to stimulation of dopaminergic receptors in the area postrema, but this effect usually disappears after a week or two. It is unlikely that this effect will occur when combined with antipsychotic use, first, because of the low doses proposed and, secondly, because antipsychotics have an antagonistic effect on the dopaminergic receptors of the area postrema. The long-term side effects of levodopa treatment in PD ('on-off', psychiatric disturbances) are closely associated with progression of the disease itself [96], and it has been shown that chronic levodopa is not toxic for dopaminergic neurons [97].

## 8 Conclusions

Many cerebral and peripheral factors are involved in the metabolic and cardiovascular side effects of antipsychotics. We propose a new unifying pathogenetic hypothesis for these effects in which autonomic nervous system dysfunction—triggered by the disease and exacerbated by antipsychotic treatment—is at the root of the pervasive metabolic and cardiovascular disorders that characterize patients with schizophrenia. Our suggestion that levodopa may prevent these side effects is both attractive and easily testable.

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