# Zaponex Fact Sheet
# Metabolic side effects

**Important Information**

The information provided in this fact sheet is intended for healthcare professionals, and should not be used as a patient information leaflet.

The information provided in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on information from scientific literature and previous successful experience. Each case should, of course, be considered individually.

**This fact sheet covers the following subjects (CTRL+click to jump to corresponding section)**



## Introduction

The Zaponex SPC (section 4.4) mentions: “Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycaemia, dyslipidaemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific profile.”[1]

Clozapine treatment can be accompanied by a range of the abovementioned metabolic side effects. These symptoms have close overlap with the metabolic syndrome (MetS), of which the major components include (central) obesity, hypertension, dyslipidaemia and glucose intolerance or insulin resistance. MetS is a serious problem, with incidences as high as 33-47% in schizophrenic patients, and up to 69% in chronic patients.[2–6] It contributes to a 5-6 fold increase in the risk of developing type 2 diabetes mellitus (DM) and a 3-6-fold increase in the risk of death from coronary heart disease.[7,8] Though metabolic side effects usually manifest as mild symptoms that gradually build up over many years rather than acutely serious conditions, they can have significant cumulative effects on patient health and self-image.[5,9] MetS is also a frequent cause of poor medicine adherence.[5,6] As such, they form an important but easily overlooked risk of clozapine treatment, and should be carefully monitored and prevented whenever possible.[9]

## General information and background

*Definitions and risk factors*
According to the International Diabetes Federation (IDF), MetS is diagnosed when the patient meets three of the five criteria listed in Table 1.[4]

Table 1. IDF criteria for metabolic syndrome[4,10]

| | Males | Females |
|---|---|---|
| **Waist circumference** | ≥ 94-102 cm* | ≥ 80-88 cm* |
| **Blood pressure** | Systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg | |
| **HDL cholesterol** | < 40 mg/dL (1.03 mmol/L) | < 50 mg/dL (1.29 mmol/L) |
| **Triglycerides** | ≥ 150 mg/dL | |
| **Glucose** | Fasting ≥ 100 mg/dL (≥ 5.6 mmol/L) | |

* numbers depend on ethnicity[10]

Patients with psychotic illness already seem to be at higher risk of MetS than the background population:[4,11–15] at baseline, they show higher frequencies of impaired glucose tolerance, insulin resistance, raised cortisol and adrenocorticotropic hormone (ACTH) levels, and an overactive hypothalamo-pituitary-adrenal axis than controls.[14] Schizophrenic patients are possibly less frequently affected than patients with schizoaffective disorder,[11] but still more than patients with bipolar disorder[4] (although metabolic effects may be more severe in bipolar patients[16]).

The use of antipsychotics (APs) in schizophrenia can significantly add to the baseline risk of MetS (possibly up to threefold[12]), with atypical or second-generation APs (SGAs) believed to pose a higher risk than typical/first-generation APs;[3–5,11,17] however, the differences between these classes are not always clear-cut.[18] AP use exacerbates all features of MetS, but there seems to be a higher risk in patients who are younger,[19,20] male, already overweight or obese at baseline, of non-Caucasian ethnicity,[2,21] and without a family history of DM.[22]

The high risk of developing MetS during the use of clozapine and olanzapine (an SGA structurally related to clozapine) is especially well recognised, with clozapine being directly associated with type 2 DM, weight gain and dyslipidaemia.[1,5,15,17] In one meta-analysis, clozapine caused the most significant alterations in glucose, triglycerides and total cholesterol of all investigated APs; olanzapine only did worse in the areas weight and BMI change.[2] The prevalence of MetS in clozapine users ranges from 25 to 58%;[4,5,10] one meta-analysis found that around 50 percent of 126 clozapine-treated mental patients showed symptoms associated with MetS.[23] A study in 192 schizophrenic patients identified clozapine treatment, pre-existing metabolic disease history and parental history of DM (specifically maternal) as independent risk factors for MetS.[9] Lastly, one review suggested that there is a dose/plasma level-response relationship between clozapine/olanzapine and metabolic complications, something not seen with the other, lower-risk AP drugs.[24,25]

*Mechanisms*
The mechanisms that lead to MetS are incompletely understood, but known to be complex, given the involvement of many processes and the broad variation in presentation. Dysregulation of lipid and carbohydrate metabolism, increases in body weight and adiposity as well as hormonal alterations have been identified as the core processes responsible for most of the symptoms, and are discussed in more detail in later chapters. Although many of the directly underlying molecular and cellular mechanisms

remain elusive, disruption of energy metabolism at the mitochondrial level seems to be a key event.[12]

Scaini et al. found evidence that genes involved in mitochondrial dynamics are downregulated in lymphoid cell lines of psychiatric patients when compared to healthy controls. Conversely, patients with mitochondrial disorders and mitochondrial DNA defects have a higher prevalence of psychiatric symptoms, suggesting that the concurrence of MetS and psychiatric disease may have a partially common origin (see also section *Hyperglycaemia and diabetes*).[12]
In vivo and in vitro studies have shown that the use of SGAs can (further) impair mitochondrial dynamics by changing their structure and function. They can also inhibit both the expression and activity of enzymes in the Krebs cycle and the mitochondrial respiratory chain. Especially drugs with the highest risk of MetS (clozapine and olanzapine) seem to cause the highest decrease in expression and activity of enzymes in the mitochondrial electron transport chain, as well as in mitochondrial oxygen consumption. Prolonged mitochondrial dysfunction can lead to accumulation of oxidative damage in mitochondria, which further impairs their functioning.[12]
These defects in mitochondrial structure and function have been linked to reduced oxidative metabolism and insulin signalling, and increased susceptibility to insulin resistance. Therefore, clozapine's capacity to disrupt mitochondrial energy metabolism may very well be one of the underlying molecular mechanisms through which it (in)directly causes several of the MetS symptoms.[12] However, countless other targets have also been implicated, including genes involved in cell cycle regulation, transcription factors, receptors, signalling proteins and enzymes.[26–28]

The following five sections will focus on five separate aspects of MetS and the role of clozapine therein: Weight gain, Hyperglycaemia and diabetes, Diabetic ketoacidosis, Dyslipidaemia and Cardiovascular disease/mortality.

## Weight gain

The Summary of Product Characteristics (SPC) for Zaponex® mentions the following: "Weight gain has been observed with atypical antipsychotic use, including clozapine. Clinical monitoring of weight is recommended."[1]
Weight gain is listed as a common side effect of clozapine treatment, occurring in 1-10% of users.[1] It may have implications for treatment in terms of reduced compliance and, therefore, increased risk of relapse, as obese patients are 13 times more likely to discontinue their medication because of weight gain than nonobese patients.[6]
Weight gain is also associated with increased risks that can seriously compromise the health of the patient, such as hypertension and dyslipidaemia. In addition, for every 1 kilogram increase in body weight, the risk of cardiovascular disease increases with 3.1%; for every 1 kg/m$^2$ increase in BMI, the risks of heart failure and type 2 DM increase with 5-7 and 8.4% respectively.[2] One meta-analysis found that an increase of 5 kg/m$^2$ in BMI was associated with a 29% higher risk of coronary heart disease.[8]

Weight gain is a well-documented side effect of AP drugs that was already noted shortly after the introduction of chlorpromazine in 1952.[29] It is especially common with SGAs, and said to occur in up to 75% of its users.[1,14,30–32] Especially children seem to be particularly susceptible to AP-induced weight gain (80%).[6] Although several AP drugs have sedative properties that could possibly affect weight gain through a decrease in physical activity, three studies found that weight increase occurred independent of sedation.[14]

Efficacy trials and meta-analyses often show mixed results, but in general, clozapine and olanzapine are considered to be among the APs that cause the most weight gain.[2,5–7,10,14,15,17,25,33–40] The first CATIE study (Clinical Antipsychotic Trials of Intervention Effectiveness) showed a weight gain of 12 kg in one year with clozapine, against 2-3 kg with quetiapine/risperidone, and little to none with aripiprazole, asenapine and ziprasidone.[41] The rate of weight increase is most marked during the first 6 to 12 months (with about 85% of total weight gain in the first year[40]), and usually levels off thereafter, although it may not reach a plateau until after nearly 4 years of clozapine monotherapy.[14,17,37,42,43]

There is evidence suggesting that certain patients may be more genetically predisposed to clozapine-induced weight gain.[44] Patients with a lower BMI or younger age at baseline seem to be at the greatest risk of weight gain from clozapine,[14,39,40,45–47] possibly explaining the increased risk in children and adolescents.[6] Sex differences are somewhat unclear: men seem to be at higher risk of AP-induced MetS,[2] but women are thought to have an increased propensity for clozapine-induced MetS and weight gain, possibly due to a significantly higher risk of central obesity.[15,30,48] Animal studies have confirmed that female rats gain more weight when treated with olanzapine than male rats.[49]

*Adipogenesis*
The process of clozapine-induced weight gain has not been fully elucidated, although research indicates that it is multifactorial, with many neurotransmitters, hormones and genes involved.[44,50] One of the core processes in weight gain and other MetS symptoms is adipogenesis (formation of white adipose or fat tissue).[49,51] Especially abdominal adipogenesis is a significant contributor to the progression of metabolic and cardiovascular disease,[8,10,52] which explains the significance of waist circumference as a predictor of insulin resistance in clozapine patients.[10] In vitro studies suggest that clozapine and many other SGAs are able to stimulate adipogenesis by affecting the expression of many transcription factors (including SREBP-1, INSIG-2 and PPAR-γ, which are further discussed in *Dyslipidaemia*). This enhances lipogenesis (formation of fatty acids and triglycerides), causing preadipocytes to accumulate lipid droplets and stimulate their differentiation into white adipocytes (fat cells). SGAs may also cause hypertrophy of existing adipocytes, and even stimulate skeletal muscle-derived stem cells to differentiate into adipocytes.[5,49,51]

SGAs, especially clozapine, can also inhibit the function of brown adipose tissue (BAT) in rats. These distinct pockets of fat tissue are normally involved in lipid oxidation, whereby excessive energy is released as heat rather than stored (thermogenesis). If this process is disturbed, it could contribute to decreased energy expenditure and increased weight gain. Given that the presence of BAT is limited in humans, the clinical importance of this is unclear, but ex vivo experiments do show that clozapine can shift the development of human white adipocyte stem cells towards an intermediate 'beige' phenotype. Such beige adipocytes have more characteristics of brown adipocytes, but with impaired thermogenesis.[10,49]

*Leptin and adiponectin*
Apart from stimulating adipogenesis, clozapine can affect white adipose tissue's function as an endocrine organ. Adipocytes secrete two hormones, leptin and adiponectin, which are in an inverse relationship: where leptin is secreted in proportion to the body's fat mass, adiponectin release is negatively regulated by (visceral) fat mass.[8,29,49,53–55]

As leptin levels directly reflect fat stores, they can communicate the state of energy reserves to the hypothalamus in the brain, in order to regulate energy intake (through appetite and satiety) and expenditure over the long term. Obese patients may have leptin resistance (a reduced ability of leptin to exert its effect), which may (partially) explain their propensity towards weight gain.[5,8,15,49,52,53,56]

Leptin is also thought to play a role in the body's immune response, as it is considered a proinflammatory cytokine that enhances the release of other cytokines like tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6).[8]
Leptin levels are also positively influenced by sex, as women have higher levels than men, independent of fat mass.[52] Schizophrenic patients have higher plasma levels of leptin at baseline than non-patients, which worsens in both sexes when SGAs (but not first-generation APs) are used for longer periods.[15,52] There is convincing evidence that clozapine is associated with significantly increased levels of leptin (especially in drug-naïve patients), possible leptin resistance and subsequent increases in weight, insulin resistance, triglycerides, LDL, and total cholesterol.[8,49,52,53,56] This is possibly a direct effect;[6,56] however, leptin levels are strongly correlated with adiposity, and association studies suggest that the increased leptin concentrations are probably largely an indirect effect of clozapine use, due to clozapine-induced weight increase and abdominal obesity.[6,8,16,52,53]

Adiponectin, on the other hand, modulates glucose regulation and fatty acid metabolism, and has protective, anti-inflammatory effects. It also improves the differentiation of preadipocytes into adipocytes, a process often impaired in obese patients.[8,15,49] Adiponectin receptors are widely present in brain regions like the cortex, hypothalamus and the pituitary gland, suggesting that it has important central effects as well.[15] The association between low adiponectin and risk of type 2 DM is thought to be stronger than between high leptin and DM risk.
Several factors may influence adiponectin levels, such as sex (men have lower adiponectin levels than women due to the inhibitory effect of androgens), age (adiponectin levels increase over time) and ethnicity (Europeans have higher levels of adiponectin than Chinese and South-Asians).[15] Adiponectin's secretion by mature adipocytes is also negatively affected by (abdominal) obesity, and apparently by clozapine as well.[8,15,29,49,54,55] However, the effect of APs on adiponectin seems much smaller than on leptin; one study found similar adiponectin levels between patients with a mental illness and healthy controls, without significant modification by APs.[16] Clozapine only seems to affect adiponectin levels (modestly) after a few months of use, so just as with leptin, this negative effect seems mostly indirectly mediated via weight gain and glucose dysregulation,[6,15] suggesting that any effect of APs on adiponectin is largely explained by BMI changes.[16]

With increasing body weight and BMI, the leptin/adiponectin ratio rises (though mainly due to increases in leptin).[16] An unfavourably high leptin/adiponectin ratio is often seen in patients with severe mental illness and type 2 DM and obesity, and can worsen with AP use, which has consequences for other components of MetS as well.[8,15,16] See also section *Hyperglycaemia and diabetes* and Figure 1.

*Mechanisms*
In attempts to identify the exact mechanisms by which weight gain processes occur, histaminergic transmission was found to play a significant role, as the extent of histamine $H_1$ receptor antagonism of AP drugs appeared to be the best predictor of the degree of weight gain in clinical studies.[5,7,10,17,57] $H_1$ receptors are found in the hypothalamus and other parts of the central nervous system (CNS) involved in the regulation of appetite and energy expenditure,[58] as $H_1$ signalling normally suppresses appetite and increases lipolysis (the breakdown of fats into fatty acids for fuel).[5,10] Involvement of $H_1$ antagonism is further supported by the fact that betahistine (a $H_1$ receptor agonist) can significantly prevent AP-induced weight gain in rats[49] and in human patients using clozapine/olanzapine (but not other APs).[59]

Many research groups attribute almost equal importance to muscarinic $M_3$ acetylcholine receptors[17,53] and the serotonin receptors 5-$HT_{2A}$ and 5-$HT_{2C}$, which have major roles in the control of food intake

and body weight. A strong affinity for $M_3$ receptors is shared only by clozapine, olanzapine and quetiapine, the APs with the highest capacity for weight gain,[53] and clozapine's potent serotonergic antagonism to 5-$HT_{2C/1A/2A}$ receptors (especially certain polymorphisms of 2A and 2C) has been associated with clozapine-induced weight gain[7,27,60] and MetS.[5,17,49,57,60,61]
Both histamine and serotonin receptors are found in abundance on the major organs involved in glucose and lipid metabolism, i.e. the hypothalamus, adipocytes and hepatocytes, and their blocking could thus play a central role in increased adiposity and the endocrine changes seen in adipose tissues as described above.[49] In addition, the hypothalamus contains high concentrations of dopamine $D_2$ and $D_3$ receptors; dopaminergic antagonism of clozapine is another possible mechanism involved in weight gain, as $D_2$ receptor blockade has a strong effect on feeding behaviour.[5,7,50]
As mentioned above, certain gene polymorphisms can play important roles in weight gain. Some variations in the genes for melanocortin 4 receptor (MC4R), cannabinoid receptor 1 (CNR1), ADRA2A leptin receptor and neuropeptide Y (NPY) receptor have been consistently linked with increased AP-induced weight gain.[27] MC4R is a downstream target of leptin signalling that mediates satiety,[10] while NPY is a orexigenic (hunger-inducing) hormone that is normally inhibited by leptin and insulin.[10,27]

Weight gain can be the result of altered energy homeostasis or increased energy intake, although not many studies have been performed to elucidate how clozapine can actually affect feeding behaviour. De Beaurepaire et al. found that binge eating spectrum disorders were much more prevalent with clozapine and olanzapine use than with other APs. Like weight gain, the occurrence was highest in the beginning, and decreased significantly after 2 years of treatment. Night eating occurred in 30% of clozapine/olanzapine patients, especially in women, with no significant change over time.[62]
Sensations of hunger can be created in the CNS, but peripheral signals from the GI tract are equally important. Garriga et al. suggested that clozapine increases appetite early in treatment, with a specific craving for and intake of "fast-food fats" that predicted significant weight gain in already overweight patients.[38] This effect is attributed to clozapine's inhibition of glucagon-like-peptide 1 (GLP-1) secretion, an endogenous peptide hormone secreted by enteroendocrine L-cells in the gastric mucosa in response to food intake. GLP-1 acts on the GI tract, hypothalamus, pancreas and liver, and is essential for inducing satiety and regulating macronutrient selection, high-sugar food intake as well as glucose levels.[10,60,63,64,64–66] (see also *Hyperglycaemia and diabetes*). Certain genetic variations in GLP-1 signalling are strongly associated with AP-induced weight gain, showing that inhibition of the GLP-1 axis may be a key contributor to the hyperphagic and obesogenic effects of clozapine.[64]

Another important GI tract satiety factor is ghrelin.[15,29,56] This local peptide hormone that is secreted by the stomach is also known as the "hunger hormone", and normally activates the ghrelin receptor (GHSR1a) in the hypothalamus, which causes short-term orexigenic signals. These signals also inhibit the satiety-inducing effects of leptin.[52,67] There are some reports that long-term clozapine use may increase ghrelin levels.[10,52] However, Huang et al. also found evidence that clozapine indirectly enhances ghrelin-mediated hunger signals: activation of the 5-$HT_{2c}$ serotonin receptor can normally reduce ghrelin activity, but as SGAs (and clozapine in particular) block this 5-$HT_{2c}$ pathway, the ghrelin-mediated hunger signals are less inhibited, with an increase in feeding behaviour as result.[67] Certain polymorphisms in the gene for cholecystokinin (CCK), another GI tract satiety factor, also seem to be partially related with clozapine-induced weight gain.[29]

Some researchers have postulated that not clozapine but its main metabolite norclozapine mediates the metabolic dysregulation, possibly due to being a more potent 5-$HT_{2c}$, histaminergic and muscarinic antagonist than clozapine itself.[68,69] Plasma levels of norclozapine indeed show a stronger correlation with increases in weight, blood sugar and triglycerides than clozapine levels.[70] A low norclozapine-to-clozapine ratio may thus attenuate these effects. A Taiwanese research group accomplished this in

schizophrenic patients by using adjunctive fluvoxamine, a potent CYP1A2 inhibitor that decreases the conversion of clozapine into norclozapine.[70,71] Metabolic parameters during the clozapine-fluvoxamine combination were compared to clozapine monotherapy over a 12-week period. They found that compared to clozapine monotherapy, fluvoxamine add-on treatment alleviated body weight gain and significantly limited increases in glucose and triglyceride serum levels, without sacrificing the clinical effect. Adding fluvoxamine to clozapine can increase clozapine levels 2- to 4-fold, and can also be a strategy to reduce clozapine tablet load and improve drug adherence. However, due to the risk of clozapine toxicity, conservative introduction of clozapine and fluvoxamine with low dosages and careful therapeutic drug monitoring of clozapine levels is recommended.[71,72]

*Paradoxical weight loss*

Although clozapine is mostly associated with weight gain, significant weight loss on clozapine has also been reported.[73–82] In 2016, Tungaraza discerned three basic scenarios of clozapine-induced weight loss:[81] 1) clinical response to clozapine led to better motivation to engage in diet and physical activities;[73,77] 2) poor or partial response to clozapine,[80,81] and 3) direct result of taking clozapine.[74–76]

The first scenario, in which patients get better insight into their illness and their psychotic symptoms improve, is of course the preferred and positive one. Patients who already had (gross) overweight before initiation of clozapine ended with a healthier weight, especially because of clozapine's effect in reducing negative symptoms; they had increased levels of motivation, improved initiative and an ability to engage more fully in goal-directed physical activity, enabling them to better adhere to a diet and exercise regimen.[73,77]

The second scenario links with the relationship between clozapine-induced weight gain and treatment response; weight loss early in clozapine treatment could be a prognostic factor for poor treatment response. Thomas et al. presented a case series of patients who had poor response to clozapine treatment and also lost varying amounts of weight during therapy. Strikingly, all 5 patients showed clinical deterioration only after an initial response to clozapine.[80] In another case report, a partial response to clozapine led the patient to act more strongly on their psychotic beliefs and restrict food intake.[81] Mechanistically, this could be explained because both clinical response and food intake may be regulated through serotonin receptors $5HT_{2A}$ and $5HT_{2C}$,[80,81] and possibly through histamine $H_1$, muscarinic $M_3$ and dopamine $D_2$ receptor involvement as well.[2]

In the third scenario, due to lack of an obvious other reason, clozapine was assumed to be the cause of weight loss.[74–76] Poor efficacy could be excluded since patients were discharged while still using clozapine.[81] Differing neuroreceptor affinities of clozapine, individual genetic variations of receptors or clozapine-induced obsessive-compulsive symptoms (compulsive exercise and dieting or obsessing with food) have been postulated as possible mechanisms,[75,78,83] although one case described fluoxetine addition early during titration, which has decreased weight as a known side effect.[74]

There could also be a fourth scenario: weight loss due to clozapine-related adverse events. For instance, one patient lost 30 kg of fat and muscle (approximately one third of body weight) over 6 months due to severe and constant hypotension-induced dizziness, which caused prolonged caloric restriction and reduced physical activity. Treatment of hypotension with fludrocortisone made the weight go slowly up again.[82] In another case, dysphagia became significant 4 weeks after clozapine initiation, but the patient had already started to lose weight since week 1, finally ending up with a 20% weight loss by week 10 (starting from a healthy BMI).[78] Finally, a 30-year-old female complained of nausea after taking clozapine, which started within 2 weeks after initiation. Strikingly, her appetite was otherwise good and food intake was normal. Nonetheless, she suffered a weight loss of 13 kg (25%) in 7 months.[79]

*Patient management*

Apart from physical risks, weight gain increases the social stigma associated with mental illness, which is often a reason for compliance issues. Given these risks and psychological impact, it is important that patients are carefully informed about this side effect when clozapine treatment is initiated.
Monitoring of body weight, BMI and waist circumference (at the level of the umbilicus) should be part of each patient's baseline screening, and also performed regularly after starting clozapine.[5,17,40,60,84]
Most guidelines strongly recommend to determine weight, BMI and waist circumference at baseline, after 1, 3 and 6 months of clozapine use, and annually thereafter.[85–89] Both the American Diabetes Association and American Psychiatric Association advise an additional measurement at 2 months after the start of AP treatment.[90] These measurements can be done concurrently with the periodic blood tests for neutrophils and WBCs that are mandatory for clozapine users in the UK.[4]

Psychiatrists, other physicians, nurses, etc., can educate patients and their carers about healthy lifestyle and should use effective behavioural interventions to motivate patients to make the necessary changes, including smoking cessation, adoption of a healthy diet and regular physical exercise.[7,17,43]
Some patients may also benefit from psychoeducation or cognitive behavioural therapy to change lifestyle habits, e.g. by entering an intervention programme.[5,40,91]
Though often effective, it should be noted that the success of such interventions can be limited in some populations,[17] e.g. mental patients with limited insight, or who have increased appetite due to clozapine.[64] Also, glucose dysregulation and weight gain may not always be successfully reversed with lifestyle changes.[92,93]

Patients should be carefully monitored to verify whether the lifestyle changes are effective. If weight gain becomes problematic, switching to drugs with better metabolic profiles may be indicated. Aripiprazole, paliperidone, amisulpride, brexpiprazole, ziprasidone, asenapine, cariprazine and lurasidone all have neutral profiles and, in some cases, even improve the metabolic parameters. However, use of these drugs may be limited in the treatment-resistant patient population, due to lack of efficacy or association with extrapyramidal side effects.[2,5,40,64,94]

*Pharmaceutical treatment*

When lifestyle interventions are insufficient, there are several therapeutic agents that may be trialled in an attempt to prevent weight gain or effectuate weight loss.
As mentioned above, clozapine plays a role in the inhibition of the hormone GLP-1, an important satiety factor that regulates energy intake by delaying gastric emptying and promoting satiety.[95]
**Metformin** is an anti-diabetic drug that suppresses hepatic gluconeogenesis and increases peripheral insulin sensitivity, and there is also evidence that it increases GLP-1 production, which promotes insulin secretion and satiety. The latter effects could account for metformin's direct and indirect effects on weight loss.[60,96,97] In a large meta-analysis of 34 randomised clinical trials (including more than 8000 patients without psychiatric illness), metformin was found to be effective in reducing body weight in overweight and obese people without concurrent diabetes.[98]
Metformin also shows promise as a weight loss agent in patients on long-term clozapine therapy. Four placebo-controlled studies showed significant reductions in fasting plasma glucose and BMI, and positive effects on body weight, waist circumference, blood insulin and blood lipids.[17,99–101] Some beneficial increases in HDL cholesterol and decreases in triglyceride and leptin levels have also been seen,[99–101] with the latter likely to be a direct effect of metformin rather than an indirect consequence of weight loss.[99]

A review and meta-analysis found that metformin is superior to placebo in clozapine patients, in terms of weight loss (3.12 kg) and BMI reduction (1.18 kg/m$^2$), enough to be clinically meaningful (>2.3 kg

loss).[96] However, the positive effects on body weight had disappeared 6 months after discontinuation, so treatment adherence is important.[101] Metformin can also help to prevent clozapine-induced weight gain: among 90 patients who were initiated on clozapine, the group using metformin only gained an average of 1.32% of body weight over 12 months, versus 5.95% in the placebo group.[102]

In general, metformin is well-tolerated in clozapine-treated patients,[99,100,103] although it can increase the risk of vitamin B12 malabsorption during long-term use, so routine B12 measurement may need to be considered.[40,104] There has been one report of pancreatitis associated with metformin used for management of clozapine-related weight gain, but the symptoms resolved after reducing the high dose of metformin from 3000 mg daily to 500 mg.[105] Typical side effects of metformin include gastrointestinal symptoms, which can be lessened with slower titration, dose decreases or by using extended release formulations.[40,99]
Metformin may thus be worth adding to the treatment regimen of obese clozapine patients.[96,106] There is, however, evidence that metformin is more effective in preventing weight gain at the start of AP use than losing weight later in treatment; an explanation could be that patients become less sensitive to the metformin-induced insulin secretion over time. It is therefore recommended to initiate metformin early on, preferably as soon as there is evidence of AP-induced weight gain, rather than waiting until substantial weight has already been gained.[40,97,102]

Although the endogenous hormone GLP-1 suppresses appetite and normalises hyperglycaemia, its effect is only short-term as it is degraded rapidly in the blood. Synthetic homologues to GLP-1 called **GLP-1 receptor agonists** (GLP-1RAs) have a longer duration of action, and promote the direct stimulation of GLP-1 signalling (and possibly also increase leptin concentrations).[64]
Liraglutide is a GLP-1RA specifically indicated for weight management. In a Danish randomised double-blind clinical trial, subcutaneously injected liraglutide significantly decreased body weight (average 5.3 kg) and waist circumference (4.1 cm) as compared to placebo in patients with schizophrenia spectrum disorders treated with clozapine or olanzapine. Significant improvements in glucose tolerance, systolic blood pressure and LDL levels were also seen,[10,64,107] although higher dosages of liraglutide (3 mg/day) seem to be needed to achieve weight loss than for improving glycaemic control (1.8 mg/day).[64] On the other hand, weight loss may be more permanent than with metformin: one year after a 16-week course of liraglutide, most MetS parameters had returned to normal again, yet body weight, though increased, remained significantly reduced from baseline.[108]
Another injectable GLP-1RA, exenatide, is indicated for treatment of type 2 DM, and is also a promising therapeutic agent for weight loss in non-diabetic clozapine-treated people with obesity.[10,64–66,95] In a randomised, controlled, open-label, 24-week pilot trial, Siskind et al. found that 6 out of 14 clozapine patients on exenatide (43%) achieved >5% weight loss, against 1 out of 14 patients receiving usual weight loss care (7%; P = .029). The mean weight loss with exenatide was also higher than with usual care (-5.29 vs -1.12 kg; P = .015), as was BMI reduction (-1.78 vs -0.39 kg/$m^2$; P = .019). The authors also noted significant improvements in other MetS markers with exenatide, such as reduced fasting glucose and glycated haemoglobin, but not in lipid levels.[66]

In a review of 3 studies, Siskind et al. found that compared to placebo or usual care, 37% of all AP users on either liraglutide or exenatide achieved a >5% weight loss (against 11% of controls), and 19% lost >7% (against 6% of controls). Specifically, clozapine patients on a GLP-1RA lost an additional 4.90 kg of body weight compared to controls,[95] significantly more than with metformin (mean 3.1 kg).[96] One case study even reported that exenatide in combination with metformin caused a morbidly obese clozapine patient to lose almost 42 kg; since weight losses with metformin are usually more modest, exenatide was believed to be the cause.[65] The decrease may even be greater in non-diabetic than in diabetic patients.[64]

In Siskind's review, the effects of GLP-1RAs on weight, BMI and glucose levels were stronger in patients on clozapine and olanzapine than in users of other APs, which supports the hypothesis that the disruption of GLP-1 signalling is a major factor in clozapine/olanzapine-associated weight gain and hyperglycaemia.[64,95] The GLP1-RA group also had a significantly greater reduction in visceral fat, which is advantageous as this is an independent risk factor for cardiovascular disease, diabetes and death. The study group did report significantly more nausea than the controls (54 vs. 28%), but it did not affect weight loss.[95]

As mentioned before, disruption of $H_1$ receptor signalling seems to be one of the most important pathways of clozapine-induced weight gain, so a histaminergic agonist like **betahistine** may be a particular helpful adjunctive treatment. A double-blind placebo-controlled study in a subset of 26 patients treated with olanzapine or clozapine found that betahistine was significantly better than placebo in preventing increases in weight (3.1 kg less weight gain), BMI and waist circumference. Betahistine did not significantly improve appetite or glucose-lipid measures, and there were no significant differences in side effects or psychopathology changes between betahistine- and placebo-treated patients.[59,109] In a single-case report, clozapine initiation caused a marked increase in appetite and weight, which were both remedied by betahistine. When betahistine had to be temporarily reduced due to malaise and rhinorrhoea, appetite and weight increased again, although not to their previous values.[58] Betahistine does not seem to have clinically significant interactions with clozapine, and it may also help with clozapine-associated sedation, which is also thought to be mediated by $H_1$-antagonism.[58,109]

**Orlistat** is a lipase inhibitor indicated for weight loss in overweight adults in combination with a hypocaloric diet. It has shown some success in clozapine- and olanzapine-treated men (but not women), as well as some desirable alterations in other metabolic parameters.[110,111] However, it seems more effective in preventing weight gain than promoting weight loss, so it should be initiated early in clozapine treatment. Sustained therapy may be required to achieve reduction of cardiovascular risk, and side effects (mainly gastrointestinal) may affect compliance.[5,17]

Adding a less obesogenic AP to clozapine therapy can sometimes be helpful. In several cases, substituting a part of the clozapine dose for **ziprasidone** was well tolerated and effective in weight loss,[112] and in another, adding it to the existing clozapine dose eventually worked as well.[113] **Aripiprazole** may improve psychiatric symptoms and reduce metabolic risk factors when combined with clozapine.[86,114] Some studies demonstrated improvement in positive and negative symptoms,[115,116] and in a large, nationwide Finnish cohort study, the combination was associated with a 14-23% lower risk of rehospitalisation as compared to clozapine monotherapy.[117] The addition of aripiprazole (which only very rarely causes weight gain) allows for a lower clozapine dose, thereby attenuating its effect on weight without losing clinical effect.[118] Diabetes, hyperglycaemia and a few cases of diabetic ketoacidosis have been reported with aripiprazole, though.[119–122]

Anticonvulsants can be used in similar ways. **Topiramate** can reduce appetite and body weight in clozapine-treated patients by inhibiting glutamate signalling.[5,123–125] Since it also serves as a mood stabiliser, it may have a place in the treatment and prophylaxis of clozapine-induced seizures,[126] and to augment clozapine's effect in case of suboptimal response.[127] The same goes for **lamotrigine**, which possesses mood-stabilizing and acute antidepressant properties, and has been shown to have a beneficial additive antipsychotic effect when added to clozapine therapy for schizophrenia. In addition, lamotrigine is not sedative and does not cause weight gain.[126]

Lastly, clozapine-associated weight gain can sometimes be alleviated by adding the noradrenalin reuptake inhibitors **atomoxetine**[128] and **reboxetine**,[5] since noradrenalin signalling seems to be able to suppress hunger.[5,128] Atomoxetine is indicated for ADHD,[129] and reboxetine for major depression,[130] so in some patients, these drugs may be helpful in treating these conditions as well as weight gain.

## Hyperglycaemia and diabetes

The Zaponex SPC (sections 4.4 and 4.8) states: "Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. A mechanism for this possible association has not yet been determined." Also, "although most patients had risk factors for non-insulin-dependent diabetes mellitus, hyperglycaemia has also been documented in patients with no known risk factors."[1]

Many studies have confirmed that AP use, especially SGAs, significantly adds to the risk of type 2 DM in schizophrenia patients.[25,34,131–134] One long-term retrospective study found that 18.4% of schizophrenic patients treated with SGAs were diagnosed with DM, against 6.6% of the general hospital population.[135] Most publications found that the risk of developing DM and increased fasting glucose levels appears to be higher with clozapine (and olanzapine a close second) than with most other SGAs,[2,5,10,25,127,134,136–141] with as many as one-third of clozapine patients having developed DM after 5 years of treatment.[127] In a 21-year naturalistic study of 96 clozapine-treated patients in the USA, 42.7% was diagnosed with diabetes (n=41) during the study period, compared to a nationwide prevalence of 13.7% in a similar age group: a threefold-increased risk.[43]

*Risk factors*
Although diabetes is strongly linked to clozapine use in particular, schizophrenia in itself seems to be already associated with relatively high rates of insulin resistance and type 2 DM,[142,143] twice that of the general population.[134] This observation predates the discovery of effective APs,[144–146] and suggests that genetic risk factors (i.e. susceptibility genes) for schizophrenia and diabetes may overlap[57] (as already discussed in *General information and background*).

In a genome-wide association study with 58 pre-treatment, first-episode psychotic patients and matched controls, insulin resistance was significantly associated with the polygenetic risk score for schizophrenia, hinting at a partially common origin for both disorders.[147] Another association study identified 29 genes that are associated with both comorbid schizophrenia and type 2 DM, and several of these genes have been implicated in the biological processes relevant to both disorders[148] (e.g. several genes that regulate glycolysis[14]).
Certain metabolic defects, like lack of Insulin-Like Growth Factor-1 (IGF-1), phospholipid dysregulation and altered signalling of Protein Kinase B (PKB, also known as AKT1) have been associated with psychiatric illness like schizophrenia as well.[14,57,149] PKB is a signal transducer important in metabolic regulation, cell survival, motility, transcription and cell-cycle progression, and is often disrupted in diabetes.[57,149]

The strongest predictors of type 2 DM in people with psychosis are a body mass index of at least 40 and treated hypercholesterolaemia, followed by a body mass index between 35 and 39.9, a family history of diabetes and treated hypertension.[134,150] Family history, especially in the paternal line, increases the diabetes risk about four-fold and confirms the significant genetic component in the development of the condition.[134] This also applies to race, judging by the observation that the

prevalence of diabetes in African-Americans, Mexicans, Hispanic, Asians, East Indians and Native Americans is twice that of (non-Hispanic) whites.[149]
Abnormal birth weight, especially low birth weight, is another risk factor, suggesting a strong influence of prenatal factors in both schizophrenic patients and the general population as well; one hypothesis is that growth problems during intrauterine development may epigenetically prepare the foetus for a postnatal life of food scarcity, thus favouring energy conservation and storage. When these individuals are subsequently born in an environment where nutrition is sufficient, obesity, diabetes and hypertension often ensue. Although family history and abnormal birth weight are independent risk factors for diabetes development, their risks seem to be additive.[134]
Lastly, schizophrenia patients often have lifestyle habits that place them at risk of developing diabetes, for instance poor-quality diet, exhibiting low physical activity, smoking, alcohol abuse, reduced capacity for self-care and being overweight.[14,151,152]

There may be additional diabetes risks in clozapine patients: an Icelandic study found a sex difference where male and female patients are respectively 2.3 and 4.4 times more likely to develop type 2 DM than controls.[94] Older age, higher baseline levels of glycolated haemoglobin ($HbA_{1C}$) and longer clozapine treatment duration are also associated with development of new-onset glucose intolerance in clozapine patients.[153]

*Glucose intolerance and insulin resistance*
As stated before, weight gain is thought to be an important indicator for the risk of hypertension, cardiovascular disease and type 2 DM. However, the mechanisms by which AP use leads to diabetes seem to be largely independent of weight gain, as glucose disturbances in clozapine use often occur long before weight changes.[5,64,64]
In an eight-year cohort study in patients treated with clozapine, MetS and most metabolic parameters were related to weight gain, but glucose dysregulation was associated with treatment duration, independent of weight gain.[154] In another study, clozapine was a weight-independent predictor of post-challenge insulin secretion in non-diabetics, particularly in those with normal glucose tolerance before clozapine initiation.[155] Since 25% of patients develop hyperglycaemia without weight gain, it can be considered a contributing factor, but not a decisive one.[5,10]
Interestingly, patients without a family history of DM[22] and with normal glucose tolerance before clozapine initiation[155] seem to be at increased risk of glucose dysregulation and development of diabetes, and weight gain is not a reliable predictor.[154,155] This should be taken into account when arranging glucose monitoring, as clinicians may intuitively be more concerned about patients with pre-existing risk factors and significant weight gain.

Many animal studies have confirmed the effects of SGAs on increased food intake and weight gain, as well as the clozapine-induced glucose dysregulation that can occur independently.[63,156–160] In-vitro and animal studies have also shown that olanzapine, clozapine and norclozapine were able to disrupt insulin's downstream signalling cascade, which causes peripheral insulin resistance. As a result, both insulin-induced and insulin-independent transport of glucose into adipocytes (for storage as triglycerides) are reduced in dose-dependent ways (an effect not seen with first generation AP), and pancreatic β-cells enhance their insulin secretion to compensate.[5,10,49] Insulin resistance also impairs myocytes and hepatocytes in their ability to take up glucose from the blood; this process is worsened by increasing levels of free fatty acids, another hallmark of type 2 DM[5] (see also section *Dyslipidaemia*). Chronic hyperglycaemia can lead to oxidative stress and vascular damage in the renal glomerulus and retinae, as well as arteries in the brain, heart and lower limbs; areas commonly affected by diabetic complications.[10]
Hyperinsulinaemia is seen in 30-60% of patients using clozapine or olanzapine, but clozapine's role in

this is somewhat controversial, since the increased insulin secretion seen with hyperglycaemia can simply be the body's way of compensating for the increasing clozapine-induced insulin resistance. However, several in-vitro studies have confirmed that clozapine and olanzapine also increase basal insulin secretion, whereas haloperidol, ziprasidone or aripiprazole do not (see also 'Role of GLP-1' below). In any case, both prolonged hyperglycaemia and hyperinsulinaemia cause (further) deterioration of pancreatic β-cell function, creating a progressively worsening cycle of events that can develop into type 2 DM, and can be additionally burdened by weight gain[5] (see also Figure 1).

*Role of leptin and adiponectin*

One theory states that insulin resistance is not associated with absolute weight gain per se, but with changes in visceral adiposity.[57] As described in the section *Weight gain*, clozapine promotes the increase of (visceral) adipose tissue and influences the way in which it acts as an endocrine organ, through altered release of leptin and adiponectin. Abdominal obesity and waist circumference are strongly linked to insulin resistance and glucose dysregulation, processes that also strongly affect the genesis of other MetS components such as dyslipidaemia and cardiovascular disease.[8,10]

The proinflammatory hormone leptin is released in proportion to fat reserves, which is further enhanced by both insulin and increasing adiposity.[8,15,52] High levels of leptin in patients promote the release of the adipocyte-derived cytokines resistin, TNF-α and IL-6. Especially the latter two are strongly associated with increased insulin resistance, hyperinsulinaemia, type 2 DM and MetS.[8,10] As mentioned before, it is hypothesised that MetS patients have leptin resistance and that chronically elevated leptin levels further exacerbate insulin resistance and hyperinsulinaemia by lowering the responsiveness of pancreatic β-cells. Worsening of insulin resistance and increasing insulin levels further contribute to both adiposity and increased leptin levels, thus forcing insulin and leptin into a diabetogenic feedback loop[8] (see Figure 1).

Conversely, adipocyte-derived adiponectin has an inverse relationship with fat reserves.[8,29,49,54,55] Receptors for this hormone are found on liver, muscle, heart, adipose and pancreas tissue,[15] as adiponectin signalling has antidiabetic properties: it sensitises several tissues to the effect of insulin, which decreases triglycerides and increases fatty acid oxidation in the liver and muscles, increases skeletal muscle lactate production and cellular glucose uptake, and reduces hepatic gluconeogenesis.[8,10,15] Not surprisingly, adiponectin release and the expression of its receptor are downregulated in obesity (whether aggravated by clozapine or not), which exacerbate insulin resistance, DM and MetS.[8,10,15,29,49,54,55] In fact, as mentioned before, low levels of adiponectin are stronger markers for the risk of type 2 DM than high leptin levels. Furthermore, adiponectin protects against inflammation and oxidative stress by having the opposite effect of leptin, i.e. it inhibits production of (adipocyte-derived) cytokines, and also limits the differentiation of monocytes into macrophages and harmful foam cells.[8,16]

The net effect of increased fat mass and a high leptin/adiponectin ratio is the increase in neutrophilic, monocytic and macrophagic infiltrations in adipose tissue, as well as increased release of pro-inflammatory cytokines. This creates a low-grade chronic pro-inflammatory state with the decreased insulin sensitivity often seen in obese and/or diabetic patients.[5,8,10,16,49] (See Figure 1)

The leptin/adiponectin ratio is positively correlated with increased body weight, BMI and waist circumference, as well as lipolysis and levels of cholesterol, triglycerides, LDL and insulin.[10,15] This ratio is more strongly associated with the risk of type 2 DM and MetS than leptin and adiponectin levels separately, so much that it can be used as an index for insulin resistance[8,15,161] and as a measure of efficacy for antidiabetic medicine.[8] A ratio below 1 is suggested to be normal; between 1 and 2 signifies moderate metabolic abnormality, and over 2 means severe cardiometabolic risk. A value of 1.88 has been proposed as cut-off for increased risk of early obesity-related metabolic disturbances.[15]

Patients with severe mental illness have higher ratios than healthy controls, which is worsened by the use of SGAs, including clozapine, which seem to (indirectly) enhance the pro-inflammatory cytokine release from white adipose tissue in a myriad of ways.[8,15,16,49] Schizophrenic patients (with or without MetS) treated with clozapine and olanzapine indeed have significantly higher plasma levels of IL-6, IL-10 and TNF-α than controls (as do MetS patients compared to non-MetS controls).[162] Both animal and human in vivo studies support this as a central process in the aetiology of insulin resistance, metabolic dysfunction and atherosclerosis (see also *Cardiovascular disease and mortality*).[8,15,16,49]

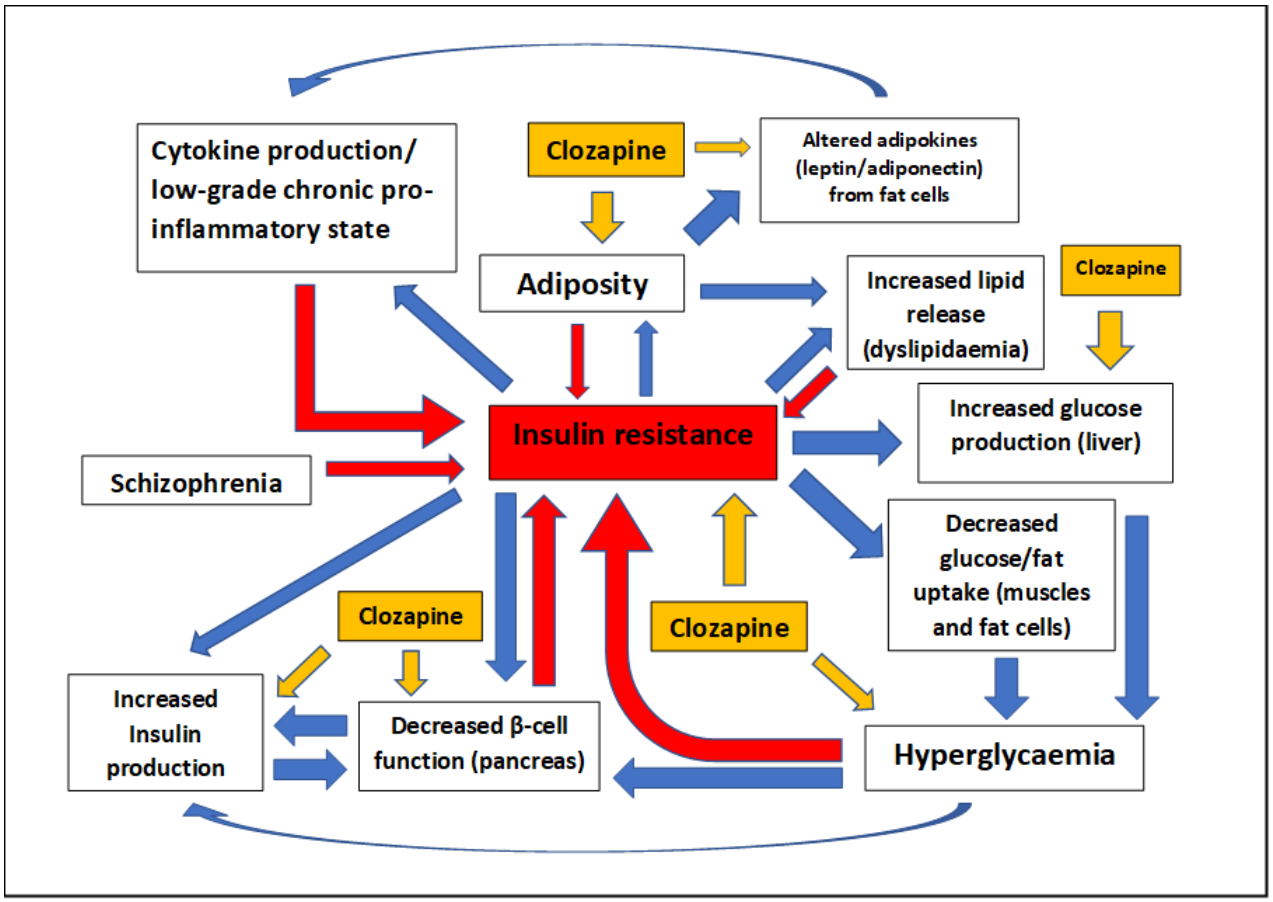


Figure 1: The diabetogenic feedback loop. In this simplified schematic, insulin resistance (red box) is represented as the central process in MetS, which has complex interconnections with the other components and processes (displayed by white boxes). Blue arrows indicate how processes affect one another; red arrows specifically indicate worsening of insulin resistance; the yellow clozapine boxes and arrows indicate where clozapine can negatively influence the MetS process.

*Role of GLP-1*

As mentioned in *Weight gain*, several studies suggest that many effects of clozapine on body weight and glucose homeostasis are mediated through GLP-1, an important satiety and glucose regulator released from the stomach in response to food:[63–66]

1) Clozapine (and olanzapine) inhibits secretion of GLP-1.[63,157] Peripherally, GLP-1 acts on the pancreas, where it stimulates β-cells to secrete insulin and inhibits glucagon secretion from α-cells.[5,10,60,63,64] GLP-1 thus prevents glucagon from converting glycogen into free glucose in the liver.

2) GLP-1 also exerts direct effects on the liver to reduce glucose production.[64,163,164] By inhibiting GLP-1 secretion, clozapine thus has a twofold effect that increases hepatic glucose output.[64]

Because clozapine prevents GLP-1 from promoting insulin release, clozapine should theoretically decrease insulin secretion. However, as already discussed in 'Glucose intolerance and insulin resistance', these levels are paradoxically increased in clozapine users as well. This is thought to be an effect of the clozapine-induced increase in glucose levels; this hyperglycaemic state associated with increased levels of insulin has the hallmarks of insulin resistance, but probably reflects a more elaborate derangement of glucose homeostasis that can exacerbate into true insulin resistance.[64,156,158,159]
Studies have shown that treatment with GLP-1RAs such as exenatide and liraglutide caused significant weight loss and improvements in fasting glucose in clozapine patients.[10,95] Two-thirds of clozapine patients had a fully normalised glucose tolerance after 16 weeks on liraglutide or exenatide, against less than a quarter who received placebo.[95,107] Another study showed that after discontinuing liraglutide, glucose returned to its previous levels within a year (weight increase was also observed, but not to baseline).[108] These data strongly suggest that clozapine-induced GLP-1 hyposecretion and associated defects in glucose homeostasis are significant causative pathways in the diabetogenic effect of clozapine.[64]

*Mechanisms*
Proposed molecular mechanisms for clozapine-induced diabetes include antagonism for many receptors involved with hyperglycaemia, and for which clozapine has high affinity: $M_{1/2/3}$, $D_{2/3}$, 5-$HT_{2A/2C/1A}$, $H_1$ and $\alpha_{1/2}$-adrenoceptor.[57] It is thus not surprising that these receptor types are all found on pancreatic β-cells.[5,10,49,165,166] However, it should be born in mind that clozapine's receptor actions and interactions are very complex, can be both direct and indirect, and also depend on the location of the receptor. This can make clozapine's effects broad in action, and often seemingly contradictory.[5]

For example, GLP-1 release from intestinal L-cells is stimulated by muscarinic neurotransmission,[167,168] so its inhibition by clozapine may be due to clozapine's antagonism of $M_1$ and $M_2$ receptors.[64,166]. Activation of the $M_3$ receptor (which is also implicated in weight gain[53]) augments the release of insulin in pancreatic β-cells,[5,10,57,169,170] stimulates glycogen synthesis in the liver[5] and is involved in glucose homeostasis and insulin release in the hypothalamus. APs with the highest risk of weight gain and metabolic dysregulation (clozapine, olanzapine and, to a lesser extent, quetiapine) were found to have the highest affinity for the $M_3$ receptor.[5,53,169,170] Clozapine antagonism of $M_3$ receptors may disrupt several post-receptor signals, including glucose transporter proteins that arrange cellular glucose uptake (e.g. GLUT-4).[57,149] There are also indications that olanzapine (and perhaps also the structurally similar clozapine) can alter the density of $M_3$ receptors in the hypothalamus and brain stem, areas involved in glucose homeostasis and insulin secretion.[170]

Dopamine and serotonin antagonists are known to increase insulin secretion from β-cells, which could partially explain the insulin hypersecretion seen with clozapine. Furthermore, clozapine-induced $H_1$ antagonism in the hypothalamus is believed to increase signalling of 5' AMP-activated protein kinase (AMPK), a downstream signalling protein. Hypothalamic AMPK restores low glucose levels by increasing appetite and enhancing hepatic gluconeogenesis and glycogenolysis via the sympathetic nervous system (increasing (nor)adrenalin levels), a process that can be overstimulated by clozapine (possibly by countering the anorexic effects of leptin). In skeletal muscle however, AMPK has the opposite effect: it mediates the effect of insulin (enhanced by adiponectin[10]) by activating GLUT-4 to promote glucose uptake into cells and increasing fatty acid oxidation. In a reversal of the effect in the hypothalamus, clozapine antagonism of $H_1$ (and possibly 5-$HT_{2A}$) disrupts the working of AMPK in muscle tissue.[5,10]
Interestingly, $H_1$, $D_2$ and $M_3$ antagonism were also mentioned as hypothesised mechanisms for clozapine-induced weight gain. Betahistine, the $H_1$- agonist that is effective in preventing $H_1$-mediated

weight gain, can also partially reverse hypothalamic AMPK activation (and thus ameliorate hyperglycaemia).[5] This overlap strengthens the hypothesis that although clozapine-induced weight gain and diabetes are largely independent processes, they may have a partially shared aetiology.

*Pre-existing diabetes and possible exacerbation by clozapine*
The Zaponex SPC (section 4.4) states: "Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control."[1]
DM is not a contraindication for clozapine therapy, so in principle, patients with pre-existing diabetes can start clozapine at the consultant's discretion. Although such patients may not be at the highest risk of metabolic side effects, clozapine may lead to further impaired glucose tolerance and/or exacerbation of diabetes.[1,131,153]
Information is limited, as neither the Maudsley Guidelines nor the Clozapine Handbook mention anything on this specific group, possibly because they are already on increased glucose monitoring. It is advised to follow at least the recommended monitoring frequency of fasting glucose levels for new clozapine patients, as described below in 'Patient management', and extended where necessary.

Koller et al. conducted a descriptive epidemiologic study of spontaneous adverse event reports of hyperglycaemia occurring in clozapine-treated patients. In total, 384 reports were identified. Of these, new-onset diabetes was diagnosed definitively in 242 patients, and 54 patients had exacerbation of pre-existing disease. Out of 384 patients, glycaemic control improved in 26 cases after clozapine was discontinued or reduced.[131] A naturalistic study by Henderson et al. identified 5 patients with pre-existing diabetes prior to clozapine initiation. Of these 5 patients, 2 were treated with insulin and 3 with an oral hypoglycaemic agent. Both of the insulin-treated patients required an almost twofold increase in their insulin requirements after initiation of clozapine. Two of the three patients treated with oral agents went on to require insulin after clozapine initiation.[42]

As for single case reports, Patel et al. noted a serious exacerbation of a patient's type 2 DM into diabetic ketoacidosis (DKA) within one month after starting clozapine, so their recommendation is to perform daily capillary blood glucose tests during the first month of treatment.[171] Popli et al. reported two patients with pre-existing diabetes that worsened within 2 weeks after starting clozapine; both improved after their oral hypoglycaemic drug was replaced with insulin. One patient discontinued clozapine due to lack of efficacy, and was able to switch back to the oral agent.[21]

Porras-Segovia et al. described a case of exacerbation of metformin-controlled diabetes in a male patient. Rapid-onset insulin-dependent hyperglycaemia occurred twice, each time within days after starting clozapine, thereby all but excluding possible confounders such as increased appetite, weight gain and long-term insulin resistance. There was a linear relation between clozapine dose and glycaemic levels during the first two months.[172] Following the Maudsley Prescribing Guidelines' recommendations for treatment of AP-related diabetes,[127] clozapine was re-introduced with baseline and follow-up monitoring of glucose levels and $HbA_{1C}$ values, slower titration and full control of glycaemic levels before every dose increase of clozapine. Insulin and long-acting exenatide (weekly injection) were added to his existing metformin, leading to a successful rechallenge.[172]
By contrast, Chathoth et al. described a patient on oral antidiabetic medications and insulin who experienced severe loss of glucose control starting 3-4 days after clozapine initiation. There was again a clear relationship between clozapine dose and the severity of hyperglycaemia, which could not be treated by increasing insulin to three high-dose injections daily, nor by direct insulin infusion. The hyperglycaemia was only resolved five days after discontinuing clozapine.[173]

*Patient management*
The Zaponex SPC (section 4.4) states: "Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug."[1]

As the last two case reports from the previous section described, glucose deregulation can be fast, within a few days after starting clozapine, and often shows a linear dose-response relation. The patient described by Chathoth et al. experienced a relatively uncommon insulin resistance; as the authors comment in their own literature review, a diabetic patient's response to clozapine initiation may lie anywhere in the continuum, from no worsening at all to ketoacidosis (see also *Diabetic ketoacidosis*).[173] Most cases resolve upon clozapine discontinuation.[10].
Therefore, we advise to carefully monitor for any changes in glucose levels in new clozapine patients. Frequent fasting blood glucose measurements should be performed, preferably concurrent with mandatory testing for neutrophils and WBCs.[4] As with weight gain, the recommendation is at baseline, after 1, 3 and 6 months of clozapine use, and yearly afterwards.[85–89] In patients with pre-existing DM prior to clozapine, it may be appropriate to do more frequent measurements, up to daily capillary blood glucose tests during the first month of treatment as suggested by Patel et al.[171] The monitoring for glucose dysregulation may be extended with (but not replaced by[89]) recurrent measurement of $HbA_{1C}$, as there is evidence that this parameter has additional value for identifying pre-diabetes.[7,155]
If changes occur, antidiabetic medication may be adjusted. If the diabetes cannot be sufficiently controlled, clozapine withdrawal and switching to a drug with a lower diabetes risk may need to be considered.[1,10,127]

*Pharmaceutical treatment*
Most therapeutic agents that help with weight loss also have beneficial effects on glucose dysregulation. **Metformin**, which is specifically indicated for non-insulin dependent DM, has been shown to be effective in reducing body weight as well as improving pre-existing metabolic abnormalities.[99,101] It activates AMPK and GLUT proteins in peripheral tissues, thereby reducing fasting glucose and insulin levels via a decrease in glucose production by the liver, increased glucose uptake by muscles, and an increase in peripheral insulin sensitivity; it possibly enhances secretion of GLP-1 as well, which in turn stimulates insulin and inhibits glucagon release.[5,60,96,99–101,125,174] Because metformin does not stimulate insulin secretion strongly, there is little risk of hypoglycaemia (as seen with sulphonylureas and insulin).[174] In a review, metformin significantly improved three of the five components of metabolic syndrome: waist circumference, fasting glucose and triglycerides.[96]
During a six-month trial, the effects appeared as early as week 2 and were sustained for as long as 24 weeks,[101] although most of the beneficial changes (except for fasting glucose) seemed to occur in the first 3 months of treatment.[96] Effective decreases in fasting plasma glucose, insulin and other metabolic markers were observed to the extent that about half of the patients who had a diagnosis of MetS at baseline no longer met those criteria after 12 weeks of treatment.[101]

As discussed above, disruption of GLP-1 signalling appears to be an important step in clozapine-related weight gain and hyperglycaemia, explaining why **GLP-1RAs** such as exenatide and liraglutide may be even more effective as treatment than metformin. They stimulate insulin secretion and decrease glucagon secretion, and have been shown to cause substantial improvements in glucose tolerance in clozapine patients.[10,95,107] They also carry little risk of hypoglycaemia because the GLP-1 pathway

becomes inhibited when glucose levels drop below 4–5 mM.[64]
In one study, exenatide caused a significant improvement in fasting glucose (-0.34 vs 0.39 mmol/L; P = .036) and glycated haemoglobin levels (-0.21% vs 0.03%; P = .004) as compared to usual diabetic care.[66] Liraglutide at higher dosages helps to reduce weight,[5,64] with nausea and vomiting as the most frequently seen side effects.[64]
In a review of three studies, treatment with either liraglutide or exenatide in AP users for an average of 16 months significantly lowered fasting glucose levels and $HbA_{1C}$ as compared to controls. Of the AP users with impaired fasting glucose at baseline, 68% had a normalised fasting plasma glucose at the end of the trials, against 24% of controls.[95] For liraglutide treatment in clozapine/olanzapine patients, these proportions were 64 and 16% respectively.[107] As with metformin, sustained treatment seems important, as most MetS parameters except body weight had returned to baseline one year after stopping liraglutide.[108]

## Diabetic ketoacidosis

The Zaponex SPC (section 4.4) states: "Cases of severe hyperglycaemia with ketoacidosis or hyperosmolar coma have been reported very rarely in patients with no prior history of hyperglycaemia, some of which have been fatal."[1]

Diabetes can exacerbate to hyperglycaemic emergencies, with DKA as one of its most serious complications. Although AP-induced DKAs are rare, they are a cause for concern since they have a mortality rate of 0.44%,[89] and a case-fatality of 13-31%, much higher than the case-fatality in the general population (4%).[57,89] By comparison: the mortality rate of agranulocytosis has dropped to 0.01% due to mandatory blood monitoring.[1] The lack of a screening protocol for DKA is thought to be the reason for these high rates.[89]

*Incidences and clinical course*
AP-induced diabetes can go unnoticed for years, and DKA is often the first apparent sign.[57,175] In a 7-year retrospective study, Henderson et al. found that the risk of diabetes presenting as DKA was tenfold higher in AP-treated schizophrenic patients than in the general population (1.493 versus 0.14 per 1,000 patient years), and 7.5-fold higher than in the general hospital population (1.493 vs 0.198).[135] Not surprisingly, among AP users with pre-existing diabetes, the risk of DKA was 30 times higher than in the general population.[176]
In another study in 725,000 patients, Lipscombe et al. found a comparable incidence of 1-2 acute hyperglycaemic emergencies per 1,000 person-years among non-diabetic, new AP users. They noted that the incidence was approximately 1 per 1,000 person-years in the age group of 18-65 years, and closer to 2 per 1,000 in elderly patients. Age thus seems to be a risk factor for DKA in non-diabetic AP users. In the patients with pre-existing diabetes, the incidence of hyperglycaemic emergencies was almost tenfold higher (about 12 per 1,000 person years); however, in this group, younger rather than older age seems to be a risk factor, as DKA occurred about 30 times more frequently in patients aged 18-65, and 8 times more in patients over 65 than in age-matched non-diabetic controls.[176]

Like with DM, drug-induced-DKA is more common with SGAs than with first-generation APs, and clozapine and olanzapine in monotherapy are most frequently associated with it; other APs only seem to pose a bigger risk when used in combinations.[57,176] Henderson et al. found that in 7 years, 2.2% of clozapine users had experienced a DKA, against 0.8% of olanzapine users, 0.2% of risperidone users, and none of the ziprasidone or quetiapine users.[135] Among patients with clozapine-associated diabetes, DKA occurrences of up to 20% have been reported (versus 2.35% in the general diabetic

population), although this may be at least partially explained by clinical expectations and detection through mandatory blood monitoring during clozapine use.[131] Cohen et al. reviewed several studies, and estimated the annual incidence of clozapine-induced DKA to be in the 0.12%-0.31% range, much higher than the general population incidence of 0.04% in the United States and 0.01% in Denmark. However, the authors noted that these data may be biased by underreporting of (non-fatal) cases, and the few small studies that have been done often differed widely in design, length and execution.[89]

*Mechanisms and risk factors*
In an extensive review, Vuk et al. confirmed that in the majority of cases, AP-induced DKA is the first clinical presentation of newly diagnosed diabetes.[57,175] The authors concluded however that both conditions have a different set of risk factors: where AP-induced (worsening of) DM is more common in patients with pre-existing diabetes, non-Caucasian ethnicity, family history of DM and baseline obesity, DKA patients are predominantly younger, male, and less likely to be overweight or obese at baseline.[57] One study showed that diabetes presenting as DKA indeed occurs on average between ages 38-42; patients are more likely to be African-American, and both the pre-onset dose and treatment duration of clozapine are significantly lower and shorter (61.5% occurring within 3 months) than for diabetes.[149] However, the dose-response relationship between clozapine and DKA doesn't seem to be particularly strong, with incidences reported on dosages ranging from 150 to 500 mg/day.[177]

Use of antidiabetic medication, and, surprisingly, a family history of DM, are both negatively associated with risk of DKA.[149] The first finding is not unexpected, as poorly controlled DM causes prolonged glucotoxicity towards pancreatic cells, which increases the risk of hyperglycaemic exacerbation when clozapine is started.[90] Family history of DM as a protective factor underlines the finding that DKA can occur independently of the presence of (risk factors for) diabetes, and that both clozapine-associated conditions may have different aetiologies. This would explain the somewhat atypical presentation of DKA during AP use, a condition that is normally caused by absolute insulin deficiency and therefore strongly associated with type 1 DM, whereas AP-induced DM closely resembles an aggravated case of type 2 DM.[57,149,178]

Another feature that DKA shares with DM is that although significant weight gain is an important hallmark (seen in appr. 50% of patients), it is by no means essential, as the occurrence of DKA is most frequent in the first 3-6 months, often before any significant changes in body weight are seen.[57,176,177] Again, these are hallmarks of type 1 DM, which also occurs independently of body weight. As discussed in *Hyperglycaemia and diabetes*, this suggests that apart from the indirect clozapine-induced (and weight gain-mediated) insulin resistance, clozapine also has direct effects on pancreatic β-cell secretion of insulin and its cellular targets, which can disrupt glucose homeostasis much faster and more severely (see also Figure 1). The capacity of clozapine to peripherally block the insulin-mediated activation of AMPK and GLUT-4 might explain these acute forms of insulin resistance.[149] A possible mechanism for these processes is the blocking of $H_1$, $M_3$ and serotonin 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors, which are abundantly found on pancreatic β-cells.[57,90]
All this illustrates the complex effects of APs in general, and clozapine in particular on glucose homeostasis; they may indirectly cause diabetes and hyperglycaemic crises via weight gain-induced insulin resistance, but also directly via various degrees of cellular signal disruption.[57,149,176]

*Patient management and pharmaceutical treatment*
As with diabetes, an important step in the prevention of ketoacidosis is to carefully monitor clozapine-treated patients as described in *Hyperglycaemia and diabetes*, preferably by monitoring fasting glucose levels at baseline, in month 1, 3 and 6 of treatment, and then annually, to ensure that glucose

deregulation is detected early, and specific precautions can be taken swiftly.[57,89]

Effects of a DKA can be mild, with normalisation of glucose levels within 10 days after clozapine discontinuation; however, in some cases the effect was so significant that normalisation took 2 years, and sometimes (temporary) insulin therapy was necessary to gain back glycaemic control.[57,90,149,178] Acute cases of DKA can sometimes be treated conservatively, with symptomatic treatment (rehydration, electrolyte replacement) and dietary control. In most instances however, discontinuation of clozapine, hospitalisation and standard therapy are necessary for a full recovery.[175,177] Standard therapy consists of acute glycaemic control in the form of insulin[175,177] (first intravenous, later subcutaneous, with a combination of the long acting analogue and ultra-short acting forms before meals).[57] In severe cases, continuous insulin infusion may be inevitable,[90] with concomitant administration of glucose when plasma levels fall below 300 mg/dL (16.7 mmol/L).[175] The patient should also be monitored for associated problems such as acute pancreatitis and infection. [175]

After recovery, patients are often placed on AP drugs with a lower capacity for causing hyperglycaemia. However, due to lack of effect from other drugs, clozapine is sometimes reconsidered. Before a retrial with clozapine, it is important to consult with a diabetologist first, and do a thorough risk/benefit analysis, taking in account the previous clinical response to clozapine and possible efficacy of alternative APs; these should be weighed against the risks of recurring DKA, the burden and risks of antidiabetic treatment (e.g. daily insulin injections or antidiabetic medications, ketoacidosis, hypoglycaemia and other complications) as well as the possibility of non-compliance.[175] It should be kept in mind that reintroduction of clozapine often causes clinical DKA to re-appear much faster than during initial presentation, within hours or days, and disappear again after stopping clozapine.[57,90,149,178] Given the treatment-resistant nature of schizophrenia in many clozapine patients, rechallenge with clozapine is often attempted, with add-on treatment of hypoglycaemic agents (saxagliptin, metformin) and insulin to prevent reoccurrence of the DKA.[90,149,175,178] Based on glycaemic values, insulin and oral hypoglycaemics may eventually be decreased or discontinued altogether.[175]

## Dyslipidaemia

The Zaponex SPC mentions: “Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics including clozapine. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine is recommended”.[1]

Dyslipidaemia, usually manifested as increased serum triglycerides and total cholesterol levels with low HDL cholesterol levels, is another prominent metabolic side effect of SGAs in general, and clozapine in particular. These changes are most unfavourable since they are among the most important factors in the aetiology of cardiovascular disease, especially coronary artery disease.[2,5,10,84,94,179] Hypertriglyceridaemia accompanies the development of type 2 DM (causing fasting glucose levels to rise with 1 mmol/L on average), and for every 1 mmol/L increase in serum triglyceride level, there is a corresponding 32–76% increased risk of cardiovascular disease.[2]

*Clinical course and risk factors*
The onset of dyslipidaemia can often be seen within 2 to 6 weeks after clozapine initiation.[2,10,84] Triglyceride levels may increase by up to 33.8 - 48.1%,[180] and are often more strongly affected than cholesterol levels.[94] These changes cause endothelial injury through accumulation of excessive lipids, which is followed by infiltration of monocytes and T-cells, and the proliferation of smooth muscle cells and macrophages that form the fibrous plaques characteristic of atherosclerosis.[10] (see also

*Cardiovascular disease and mortality*)
As with glucose dysregulation, AP-induced dyslipidaemia is complicated by the fact that schizophrenic patients often have lifestyles (unhealthy weight, poor dietary habits and lack of exercise) that already increase their baseline risk.[166,181] Nevertheless, clozapine, olanzapine and (to a lesser degree) quetiapine are generally considered to cause the most profound lipid changes, while first-generation APs and the SGAs ziprasidone, risperidone and aripiprazole pose a lower risk.[2,34,53,182,183] Male gender is an additional risk factor in clozapine users, as men have a significantly higher prevalence of hypertriglyceridaemia than women (56.94 vs. 29.79%). The protective effect of oestrogens and a lower prevalence of central obesity in women have been suggested as possible reasons for this.[48]

*Mechanisms*
Like with hyperglycaemia, atherogenic lipid ratios seem to be already enhanced in schizophrenic patients, and may be worsened by AP use.[16] The association between clozapine and dyslipidaemia can be partially explained by clozapine-induced weight gain;[154,166] alterations in triglyceride levels and enhanced cholesterol are clearly linked to adiposity,[5,10,53] and may be more strongly mediated by norclozapine than clozapine.[69,166] In addition, increased leptin and decreased adiponectin secretion (frequently seen in clozapine-associated MetS) are associated with higher levels of blood triglycerides, LDL and total cholesterol, and decreased fatty acid metabolism in muscles.[15,16,53]
Weight increase and glucose dysregulation also worsen dyslipidaemia. Free fatty acids (FFAs) are normally taken up from plasma by hepatocytes, myocytes and adipocytes, after which they are either metabolised or stored as triglycerides. Normal insulin signalling and glucose uptake decrease the activity of lipoprotein lipase; with clozapine-induced insulin resistance and glucose intolerance, there is increased lipogenesis and fat accumulation in the liver, increased production of VLDLs and FFAs, and less sequestering of FFAs from the blood into adipocytes.[2,5,84,90] When FFAs increase in the blood beyond the point where the peripheral cells can either metabolise or store them, they decrease the sensitivity of hepatocytes and skeletal muscles to insulin; this leads to enhanced glucose production and reduced uptake, thereby further exacerbating the diabetogenic feedback loop[5] (see also *Hyperglycaemia and diabetes* and Figure 1).

Since many of these processes occur over longer periods, they cannot readily explain the fast onset of dyslipidaemia that is often seen within a few weeks after starting clozapine. In parallel to glucose dysregulation, there are also indications for a direct and faster effect of SGAs on lipid regulation that is independent of weight gain, as dyslipidaemia often starts to develop before any meaningful weight increase has taken place. [7,10,56,184–187]
Extreme cases are sometimes seen in DKA, where spiking levels of plasma triglycerides (>22 mmol/L) can occur very quickly.[90] As already detailed in *Hyperglycaemia and diabetes* and *Diabetic ketoacidosis*, direct toxic effects of clozapine on GLUT-4 transporters and pancreatic β-cells, which negatively impact insulin secretion and glucose uptake, are believed to be responsible for this.[5,57,90,149] GLUT-4 activation and subsequent glucose uptake by liver and skeletal muscle may be mediated by AMPK: as explained before, SGAs and clozapine activate the AMPK pathway in the hypothalamus, causing increased hepatic glucose output. However, the effect is reversed in peripheral organs: clozapine inhibits AMPK signalling in liver and muscles, which increases gluconeogenesis and lipogenesis, and decreases glucose uptake and fatty acid oxidation.[5]
Many of the abovementioned clozapine-associated processes are thought to be mediated via antagonism of $D_2$, $H_1$ and 5-$HT_{2C}$ receptors, the same ones associated with weight gain and diabetes, so this might again explain the overlap between the various metabolic symptoms.[57,84,90,188]

Other proposed targets of clozapine include the inhibition of peroxisome proliferator-activated receptors (PPARs) which regulate transcription of proteins involved in lipid and carbohydrate

metabolism,[5,84,166] e.g. adiponectin.[10] The antidiabetic agents glimepiride and rosiglitazone, as well as the lipid-lowering drug fenofibrate are all PPAR agonists that can significantly reverse clozapine-induced increases in triglycerides.[166] In contrast to inhibitive effects, sterol-regulatory element-binding protein 1c (SREBP-1c), an important protein involved in the regulation of lipid and cholesterol biosynthesis, shows hepatic overexpression in clozapine patients, which is associated with lipid accumulation and liver steatosis. Clozapine-induced changes in 5-$HT_2$ and $H_1$ signalling and subsequent inhibition of peripheral AMPK signalling appear to be responsible for this overexpression.[5]
In rats, treatment with clozapine or risperidone enhanced de novo hepatic lipogenesis and cholesterogenesis via alterations in expression of several genes, including Insulin-induced gene 2 (*INSIG-2*), progesterone receptor membrane component 1 (*PGRMC1*), SREBP transcription factors and liver X receptors.[84,189] In schizophrenic patients, several polymorphisms of *INSIG-2* have also been linked to clozapine-associated weight gain and obesity,[190] whereas mutations found in the genes for the leptin receptor, adiponectin (*ADIPOQ*) and Fat mass and obesity-associated protein (*FTO*) were significantly associated with clozapine-induced dyslipidaemia.[191]
Lastly, recent in-vitro research indicates that clozapine-induced reduction of reabsorption of L-carnitine, a compound that plays a crucial role in fatty acid oxidation in mitochondria, may contribute to lipid dysregulation in the liver.[192]

*Dyslipidaemia and clozapine efficacy*
A fairly consistent finding in association studies is that the most efficacious APs like clozapine and olanzapine tend to cause the most significant degrees of metabolic dysregulation, and this is certainly true with regards to dyslipidaemia. For example, in clozapine users, increases in (mainly) serum triglycerides and (to a lesser extent) cholesterol are strongly correlated with the decrease in the subject's Positive and Negative Syndrome Scale (PANSS) score, independent of weight gain.[10,180,188] This association was not seen with quetiapine or risperidone,[188] and may seem simply coincidence; an indirect result of clozapine's broad action on the many (sub)types of receptors mentioned before, which can be expected to produce both desired and undesired effects.[2] However, there could be a more direct relation, judging by the observation that the use of atorvastatin, which decreased serum triglycerides and cholesterol levels, sometimes caused a concurrent relapse in schizophrenic symptoms. [180,188] No worsening of psychopathology was seen with orlistat, which only induced weight loss in clozapine or olanzapine-treated patients.[193] When statin treatment was discontinued, lipids increased again, and so did clozapine's antipsychotic effects.[180,188]

There is some evidence that cholesterol may increase central serotonin receptor function, possibly through a membrane effect in neuronal and glial cells, and that low serum cholesterol levels might thus contribute to treatment resistance in patients with schizophrenia.[180,194] It has therefore been postulated that the clozapine-induced increase in blood lipids in itself may already have an antipsychotic effect,[180] although it is unlikely that clozapine causes changes in brain lipid levels.[10] Furthermore, dyslipidaemia may also be instrumental in potentiating AP drug effects by altering the pharmacokinetics, tissue distribution and pharmacological activity of lipophilic drugs like clozapine. In vitro studies have shown that clozapine redistributed from albumin and glycoproteins into the blood's lipoprotein fractions (especially VLDL) when serum triglycerides rise, which may also increase the unbound and pharmacologically active fraction of clozapine. It has been hypothesised that this creates a 'physiologic clozapine depot' that possibly enables a more consistent release of free clozapine, and facilitates its transport over the blood-brain barrier.[10,95,180,188] Whether dyslipidaemia is essential for clozapine's potent antipsychotic effect remains to be seen though, since the negative influence of lipid-lowering interventions on clozapine's efficacy has not been a consistent finding.[95,188]

*Patient management and pharmaceutical treatment*
Just as with weight gain and blood sugar, adequate monitoring is advised to detect and treat any significant changes in lipid metabolism during clozapine use. The American Diabetes Association and American Psychiatric Association recommend monitoring of plasma glucose and lipids every three months during the first year, followed by annual monitoring of fasting plasma glucose or $HbA_{1c}$, with lipid monitoring to occur at least every 5 years.[90] For convenience, fasting lipid profile measurements can be included during the monitoring of fasting glucose levels at baseline, 1, 3 and 6 months, and annually thereafter, as recommended in *Hyperglycaemia and diabetes*, to be done concurrently with neutrophil/WBC counts.[4,85–89]

As described in *Diabetic ketoacidosis*, acute cases of severe hypertriglyceridaemia and acidosis can sometimes occur within the context of DKA, and should be discerned from other causes, such as acute pancreatitis or hyperviscosity syndrome. They are usually responsive to insulin infusion, since acute insulin resistance seems to be the direct cause of these symptoms.[90]
Many patients are undertreated for dyslipidaemia associated with clozapine,[5] even though lipid-reducing agents such as fenofibrate, some antidiabetics (e.g. glimepiride and rosiglitazone) and statins (e.g. **rosuvastatin** and **simvastatin**) are often helpful.[90,166] As mentioned, **fenofibrate, glimepiride** and **rosiglitazone** are PPAR agonists that reduce the VLDL and LDL levels in the blood, and thereby triglyceride and cholesterol levels.[10,166] Statins are blockers of the enzyme HMG-CoA reductase, and reduce the formation and release of cholesterol by the liver,[10,94] and triglyceride levels to a lesser extent.[10] They are recommended in patients with high levels of HDL (>4.90 mmol/L) without type 2 DM and (a high risk of) atherosclerotic cardiovascular disease.[94]
Lastly, in overweight patients with type 2 DM, the anti-diabetic drug **metformin** can also help with dyslipidaemia: it activates hepatic AMPK and inhibits SREBP, which reduce hepatic steatosis and glucose production, and stimulates fatty acid oxidation.[5] There is also some evidence that sustained use of the weight management and anti-diabetic drug **liraglutide** may help lower lipids and LDL cholesterol.[95,107,108]
However, it should be born in mind that decreased clinical response, cognitive impairment and memory loss have been reported with use of some statins like atorvastatin and simvastatin, possibly due to reasons discussed above.[95,180,188,194] These effects have been mostly documented in isolated case reports, but a relationship has never been clearly demonstrated in clinical trials.[188,194]

## Cardiovascular disease and mortality

The Zaponex SPC (section 4.4) mentions: “There have been post-marketing reports of myocardial infarction, including fatal cases. Causality assessment was difficult in the majority of these cases because of serious pre-existing cardiac disease and plausible alternative causes. (…) As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation.”[1]

Schizophrenia patients generally die between 10 and 28 years earlier than people in the general population,[43,94,95,195–201] and their all-cause mortality is 3.5 times higher than in the background population.[201] In naturalistic studies that covered two decades, the all-cause mortality risk was 30% in SGA users,[197] and 22% in clozapine users.[43] Most of this excess mortality affects male patients, and seems to be primarily due to cardiovascular deaths (specifically from coronary artery disease) and diabetes.[8,17,43,95,197,202,203] Cardiovascular disease has a standardised mortality ratio (SMR) of 3.5, meaning it affects schizophrenics 3.5 times more often than the general population.[201] This is followed by cancer (lung cancer has an SMR of 2.4), non-HIV infection (the SMR of pneumonia and influenza is

7.0) and respiratory conditions (COPD has an SMR of 9.9).[201] Schizophrenic patients also have a relative risk of 1.71 for stroke as compared to the reference group.[6]

*Mechanisms*
As with all other facets of MetS, the relation between clozapine and cardiovascular disease is not a straightforward one. Although there are no clear indications that clozapine has a direct effect on the onset of cardiovascular disease,[43] an in vitro study showed that clozapine, when incubated with aortic strips, could deregulate the production of nitrous oxide from the endothelium. This induces oxidative stress and prevents the aorta from relaxing completely, which could possibly initiate vascular events that lead to cardiovascular complications.[204]

Most effects of clozapine on cardiovascular disease are thought to be indirect, and weight increase appears to be an important intermediate step. As discussed in *Weight gain* and *Hyperglycaemia and diabetes*, clozapine promotes (abdominal) obesity, which increases leptin levels and inhibits adiponectin release. High leptin levels are a risk factor for cardiovascular disease, as they are associated with the release of pro-inflammatory cytokines from adipose tissue, which in turn is linked to insulin resistance and atherosclerosis (see Figure 1): the latter causes a dysfunction of vascular endothelial cells, with subsequent loss of vasodilatory, antithrombotic and antiatherogenic properties.[8,15,49] This may be further aggravated by oxidative stress from chronic hyperglycaemia.[10]
By contrast, adiponectin decreases the release of several pro-inflammatory cytokines, which has vasoprotective effects: it protects endothelial cells against oxidative stress-induced apoptosis and molecular adhesion, improves their nitric oxide secretion, and inhibits smooth muscle cell proliferation.[8,15] High levels of adiponectin therefore decrease the risk of coronary artery disease, myocardial infarction and other cardiovascular events.[8,15,16]

A high leptin/adiponectin ratio is not only a biomarker for MetS and insulin resistance, but also for cardiometabolic risk, with levels above 0.61 suggestive of MetS in schizophrenic patients.[15] The arteries of patients with severe coronary artery disease, abdominal obesity and a high leptin/adiponectin ratio were found to have a decreased vascular response to acetylcholine, as well as increased vasoconstriction to adipocyte-derived angiotensin II (Ang II). Ang II is also strongly suggested to contribute to insulin resistance in endothelial cells.[8,10] Insulin normally enhances production of nitric oxide secretion for vascular relaxation. Decreased endothelial insulin sensitivity and compensatory hyperinsulinaemia are thought to directly and indirectly contribute to hypertension, a complication seen in 85% of MetS patients, and a significant number of clozapine patients as well.[10]

Atherosclerosis, venous thromboembolism (VTE) and stroke are frequent causes of cardiovascular death, and VTE is a class effect of (mainly second-generation) APs. Clozapine has the highest odds ratio for pulmonary embolisms of all APs (1.46 compared to non-AP users),[17] possibly due to increased platelet adhesion/aggregation via activation of the serotonin 5-$HT_{2A}$ receptor,[205] but also via indirectly increasing VTE risk factors such as obesity, hypercholesterolaemia and reduced activity.[206]

Furthermore, clozapine use is strongly associated with autonomic dysregulation, probably via antagonism of adrenergic and cholinergic receptors, increased sympathetic activity, vagal inhibition and alterations in levels of (nor)adrenalin.[10,17,203,207] These changes may precipitate many interrelated cardiovascular side effects such as ventricular arrhythmias, QT interval prolongation, decreased heart rate variability, orthostatic hypotension, paradoxical hypertension and sustained tachycardia.[17,203,207]
Chronically increased resting heart rates (>75 bpm) are believed to be particularly detrimental to patient health, as they are associated with cardiomyopathy and fatal myocardial infarction,[17] possibly through increased oscillatory shear stress, cardiac work and oxygen consumption, leading to coronary

atherosclerosis and myocardial ischaemia.[208] Prolonged heart rates >80 bpm were found to increase both the risks of cardiovascular disease (by 30%) and non-cardiovascular disease excluding stroke (by 57%) as compared to heart rates <60 bpm.[17]

Clozapine-induced cardiovascular side effects such as arrhythmias, blood pressure abnormalities and tachycardia can possibly exacerbate into severe cardiac pathophysiology like heart failure, ventricular hypertrophy, myocardial infarction, cardiomyopathy and sudden cardiac death.[17,203] Clozapine use has indeed been found to significantly increase the risk of sudden cardiac death (3.8 times more than in non-clozapine use),[209] which can have a multitude of underlying causes: QT interval prolongation and Torsade de Points due to potassium channel blocking, malignant arrhythmias, and coronary artery disease.[17] Additional potential causes are myocarditis,[17,203,210,211] myocardial infarction,[17] cardiomyopathy[17] and pulmonary embolisms.[212] However, these associations were often found in small studies that did not always correct for confounders like mental disease severity, lifestyle or co-morbidities.[17]

*Risk factors*
In a naturalistic study, Nemani et al. estimated that clozapine users (mean age at start: 36.4 years) had a 29% chance to experience cardiovascular events over a 21-year period, and a 10% mortality rate for cardiovascular disease.[43] An older and shorter (10 year) study by Henderson et al. found a comparable 9% cardiovascular mortality risk (although mean age at the start was 36.5, so the effect of age was less well studied).[213] By comparison, the 30-year prevalence of cardiovascular events in normal patients aged 20-29 is 2.5-5.0% for women and men respectively.[43] Even though there is no reliable comparison between clozapine patients and the general population of similar age groups, the former is implied to be at considerable higher risk. Caucasian patients are apparently more frequently affected than other ethnicities.[197] Nemani's study also showed that, as expected, the highest risk for cardiovascular morbidity and mortality manifested during the first decade, through increased BMI, weight and triglycerides. Weight gain was especially marked in the first three months, before increasing at a slower rate in the remainder of the first year and levelling off in the second decade, which coincided with a significant decrease in metabolic risk markers (significant attenuation of increases in cholesterol, triglycerides and weight) and a corresponding decrease in cardiovascular events and deaths during the second decade.[43]

The abovementioned mechanisms and the well-documented effects on weight gain, glucose dysregulation and lipid homeostasis make that clozapine has one of the highest risks of cardiovascular problems.[197] But despite this, clozapine has not been found to cause substantially more (cardiovascular) mortality than other APs in population studies.[2,43,197] One explanation for this paradoxical discrepancy lies in the many confounding factors that complicate the clozapine-cardiovascular events relationship.

As mentioned before, schizophrenia patients often have lifestyle habits that already exacerbate their baseline risks of developing MetS, VTE and cardio/cerebrovascular disease independently from AP use: they are more likely to be overweight (often with central obesity and accompanying glucose intolerance/insulin resistance[25]); they often smoke and exhibit alcohol/substance abuse, low physical activity, unhealthy eating habits and poor self-care. Additionally, they usually have low education and employment levels (which limit the chances for improvement), and their cardio-metabolic risk factors are often underdiagnosed and undertreated.[14,17,25,151,152,195–197,214] Due to these background risks, the additional risks that come from AP and clozapine treatment are difficult to quantify. For example, myocardial infarction is mentioned in the Zaponex SPC, but the frequency cannot be estimated.[1]

Of the lifestyle factors, cigarette smoking in particular seems to be most detrimental for cardiovascular health, increasing cardiovascular death risk by 86% over 20 years.[197] Schizophrenic patients (especially males) smoke 2-3 times more often than the general population, are 3 times more likely to have ever smoked in their lifetime, and 2-6 times more likely to be heavy smokers[215] (although there are substantial international differences in smoking prevalence due to social and economic factors[17,216]). However, it has been suggested that clozapine may have a protective effect here,[17,43] since one Sri Lankan study showed that clozapine users smoked considerably less (18%) than non-clozapine AP users (38-48%).[216] Clozapine's superior therapeutic effect, its ability to improve abnormal sensory processing, coping skills and cognitive impairments, as well as its serotonergic antagonism which may reduce nicotine craving have all been speculated as possible reasons.[17,216]
Furthermore, a 2-year association study showed that unhealthy lifestyle markers such as poorer dietary quality and cardiorespiratory fitness, higher BMI, waist circumference and $HbA_{1c}$ levels and lower HDL levels were primarily associated with negative symptoms in schizophrenia spectrum disorders.[198] One review found that apathy and anhedonia, common occurrences in schizophrenia, specifically lead to limited physical activity, which, combined with high sugar and fat intake, result in MetS.[25] Better cognitive functioning and employment were associated with better cardiorespiratory fitness. Reduction of negative symptoms can improve sedentary lifestyles, and may therefore be a good strategy to manage cardiovascular morbidity and mortality in patients.[25,198]

*Cardiovascular risks versus benefits of clozapine*
So paradoxically, clozapine use has one of the worst metabolic outcomes, but also carries the lowest risk for all-cause mortality of all AP drugs,[2,10,202] partially due to having one of the lowest cardiovascular mortality rates.[2,200,217] Apart from lifestyle factors that substantially exaggerate clozapine's perceived risk, it would stand to reason that it also offers ample protective effects.

That said, several claims have been made that clozapine's lower mortality could be due to confounding by indication: given its serious side effect profile, clinicians may be selective in prescribing clozapine to the healthiest patients only, and not to patients who already have significant cardiovascular comorbidities. However, in a large Dutch cohort study with more than 78,000 AP users, there was evidence to the contrary: clozapine users had more cardiovascular or diabetic comorbidities at the start than users of other drugs, and cardiovascular or antidiabetic drugs were prescribed earlier and more often in the clozapine group than in the olanzapine group. This doesn't exclude the possibility though that some countries with low clozapine prescription rates (e.g. Canada) indeed preserve clozapine for their low-risk patients.[199]

Other claims are made that clozapine's beneficial effects on mortality may not be "true" effects, but largely secondary to 1) the mandatory medical monitoring[199,200] (especially of neutrophils and WBCs), or 2) its anti-suicide effect.[200,212] Concerning the first, the increased clinical contact in clozapine use might positively influence lifestyle, and cause metabolic disturbances to be diagnosed and treated better, earlier and more often than in users of other APs.[199,200] As for the second, clozapine may reduce overall mortality primarily by reducing the number of suicides rather than the natural deaths.[200,212]

These theories have already been disproven to some extent in a few large cohort studies, such as an 11-year study where the reduction in completed suicides was certainly found to play a substantial part in clozapine's lowest risk of all-cause death, but a significant reduction in death from ischaemic heart disease was also a major factor.[218] It is true that compared to olanzapine users (a drug with a largely similar MetS profile), clozapine users had a higher prescription rate of anti-diabetic drugs, beta-blockers and lipid-modifying agents, so some of the clozapine benefits may indeed stem from better treatment of MetS.[199] However, a 5-year British cohort study among 14,754 seriously mentally ill

patients found that clozapine's positive effect on mortality remained significant and robust even after adjusting for a range of potential confounders, including contact with specialist mental health services, disease severity, other AP use, other mental and physical health issues and use of alcohol or other drugs. The authors did not control for some adverse lifestyle choices (such as smoking, poor diet, inactivity), so there was a chance that increased clinical contact with clozapine users positively affected their lifestyle choices.[200]
What was especially remarkable was that although clozapine patients had 9 out of 15 characteristics that were significantly associated with increased mortality risk, clozapine still substantially reduced the risk of both natural and unnatural death. This further ruled out the possibility that the lower mortality rate in clozapine users could be almost entirely explained by the reduction in suicides.[200]

Even though the cardiovascular death risk among clozapine users (exacerbated by adverse lifestyle habits) is a substantial 9-10%,[43,213] most studies still could not find an increased risk of cardiovascular deaths with clozapine use when compared to other APs.[2,43,197,200] This observation is not new,[43,197,217] and suggests the possibility that clozapine may protect against cardiovascular mortality relative to other AP drugs.[218] Proposed reasons for this comparable or decreased cardiovascular risk despite clozapine's higher metabolic risk include the improvements in mental state caused by clozapine that lead to better self-care, decreases in smoking behaviour, and increased engagement with health care services by patients.[2,197] This does not preclude the possibility that clozapine is associated with a higher risk of certain causes of death (e.g. respiratory, metabolic and haematologic mortality), but these are speculated to be outweighed by reduced risks of death from other causes.[200]

*Patient management and pharmaceutical treatment*
Given the high mortality rate associated with cardiovascular side effects, it is important to perform regular extensive health checks in clozapine-treated patients, which should include examinations for cardiovascular disease. At least annual physical checks are recommended for patients with psychosis or schizophrenia, with referrals for diagnosis of cardiovascular disease and its risk factors, and treatment offered accordingly.[17,195]

Early detection of cardiac abnormalities is not only crucial for preventing fatalities, but will also reduce the eventual costs of health care in the long run.[203] Echocardiography is often employed to detect heart enlargement and left ventricular hypertrophy/dysfunction, which can confirm a diagnosis of cardiomyopathy, but the technique is usually not cost-effective enough for periodic screenings. It is therefore highly recommended to do a baseline echo prior to clozapine treatment, to exclude pre-existing conditions and enable better comparisons with ad hoc imaging studies done later in treatment.[17]
In lieu of echocardiograms, ECGs are practical diagnostic tools to detect abnormalities in heart rhythm or other cardiac parameters. During the first four weeks of clozapine therapy, weekly ECGs and monitoring of vital signs are advised; since ECGs lack sensitivity to detect myocarditis, these should be coupled with weekly C-reactive protein (C-RP) and troponin (I or T) assays which can pick up any early inflammation and/or myocardial damage, especially myocarditis (which typically occurs during the first month) and cardiomyopathy. These tests can be done concurrently with the mandatory weekly bloods, and any sufficiently abnormal results (especially with symptoms like fever) should be a reason for follow-up with echocardiography.[203] See ZTAS Fact Sheet 'Myocarditis and cardiomyopathy' for more detailed information.

People at high risk of cardiovascular disease are often put on antiplatelet anticoagulants such as aspirin or clopidogrel, but these are also associated with increased bleeding. **Selective serotonin reuptake inhibitors** (SSRIs) may be suitable alternatives, since platelets rely on serotonin reuptake for

aggregation as they cannot synthesise it themselves. This class of drugs inhibits platelet aggregation and vasoconstriction, which may help prevent (severe) coronary heart disease and ischaemic strokes without increasing bleeding risk. They could be helpful in patients who also need antidepressant therapy for (residual) negative symptoms of schizophrenia, since they have previously shown promising results in major depressive disorder.[25]
Due to clozapine's risk of thrombotic events, a risk assessment for VTE is recommended, and patients should be informed to seek medical care in case of early symptoms. Prophylactic anticoagulants should be considered in high-risk patients.[17,206,219,220]

Due to the dangers of prolonged tachycardia, monthly or at least 6-monthly heart rate monitoring is advised during stable clozapine therapy.[17] In the first year, heart rate is preferably measured concurrently with the mandatory blood monitoring, i.e. weekly during the first 4 months, and then fortnightly during the remaining 8 months. In case of tachycardia or a prolonged pulse of >80 bpm, a reduction in heart rate via the use of beta-blockers or nondihydropyridine calcium channel blockers (e.g. verapamil and diltiazem) demonstrably lowers the mortality from myocardial infarction and heart failure. In theory, these drugs should lower the incidence of cardiomyopathy and cardiovascular mortality as well, but due to the risk of orthostatic hypotension, their use is best discussed with a cardiologist beforehand.[17] Please see ZTAS Fact sheet 'Tachycardia' for more information.

Orthostatic hypotension is defined as a sustained reduction in systolic blood pressure of at least 20 mmHg, or in diastolic blood pressure of 10 mmHg within 3 min of standing. It is often encountered in elderly patients with co-morbidities, usually in the beginning of clozapine treatment (especially with fast dose increments during titration) or with treatment of tachycardia (as described above). Although usually transient and innocent, it can lead to dizziness, falls and injury, and in the general population, orthostatic hypotension is associated with (but not always causally related to) increased risks of all-cause death (50%), coronary heart disease-related events (41%), heart failure (125%) and stroke (64%). When persistent during clozapine treatment, dose decreases are often helpful, and treatment in patients with ischaemic heart disease, heart failure, cardiac arrhythmias, tachycardia or hypertension should be tailored as to not exacerbate hypotension. If the event still does not abate, increasing intravascular volume with fludrocortisone or desmopressin can be considered.[17]

## Metabolic symptoms and clozapine efficacy

A recurrent observation is that the most efficacious APs like clozapine and olanzapine tend to cause the most significant degrees of metabolic dysregulation. This is evidenced by the fact that improvements in total psychiatric symptom severity are strongly correlated with increases in weight, BMI, total cholesterol and LDL cholesterol concentrations, and decreases in HDL cholesterol concentrations (although this association is most strongly explained by changes in blood lipids).[14,15,29,59,95,172,188] However, the suggestion that metabolic symptoms are inherent to a drug's antipsychotic effect and thus unavoidable (and perhaps even instrumental) has been disproven in several publications. As described in previous sections, factors like weight gain, hyperglycaemia and DKA can be (partially) prevented with treatment, with no apparent loss of antipsychotic efficacy.[59,95,172] Clozapine-associated dyslipidaemia could also be (partially) treated without a corresponding loss in clinical response, although literature has reported conflicting results in this area.[95,188]

The controversy about the severity of metabolic symptoms being proportional to an AP's effectiveness prompted Pillinger et al. to explore an alternative hypothesis, namely that metabolic dysregulation is relatively equal among the AP drugs, but that compliance issues may explain the perceived

differences: less effective APs may only seem to cause less metabolic side effects because patients do not take them as diligently as the effective drugs. However, comparisons between the oral and long-acting injectable formulations of aripiprazole showed that both caused similar alterations in glucose and lipids, so compliance issues alone cannot explain such differences.[2] Not only do APs differ genuinely and markedly in their degree of metabolic dysregulation, some drugs can even improve certain metabolic parameters: e.g. lurasidone, cariprazine and aripiprazole/brexpiprazole were shown to have a favourable effect on levels of glucose, LDL cholesterol and HDL cholesterol respectively when compared to placebo.[2,15]

MetS shows a highly interindividual variability, as male gender, non-white ethnicity and increased baseline body weight seem to be independent risk factors for development of AP-induced MetS. This reflects its complex and multifactorial aetiology, where choice of AP drug can interact with certain patient characteristics.[2] Several gene polymorphisms with strong MetS associations have already been mentioned in previous sections, including the genes for INSIG-2, FTO, leptin and the leptin receptor[15] which are involved in weight and/or lipid regulation. Other genetic associations include genes involved in cholesterol metabolism (such as *SREBF2*), the folate cycle (*MTHFR*), regulation of neurotransmitter signalling (*COMT*), but also the dopamine receptor $D_2$, serotonin 5-$HT_{2A/2C}$ and alpha-2A adrenergic (ADRA2A) receptors.[5,6,15]

As explained in *Dyslipidaemia*, one explanation for the differences in efficacy and metabolic dysregulation between AP drugs seems to be that the most efficacious drugs tend to have the broadest and most complex pharmacodynamics. Clozapine is the most atypical of the SGAs, as it targets many different receptors and neural pathways which produces its strong antipsychotic effect. However, it also acts on many central and peripheral off-target pathways in the hypothalamus, liver, pancreatic β-cells, adipose tissue and skeletal muscle, thereby disrupting the regulation of glucose and lipid metabolism by these organs.
The section *Weight gain* ('Paradoxical weight loss') revealed that clozapine's therapeutic effect is indeed exerted via antagonism of many different types of receptors. These include mainly dopamine $D_2$, serotonin 5-$HT_{2A}$, histamine $H_1$, and also muscarinic $M_3$, the same mechanisms also implicated in many facets of metabolic dysregulation; in fact, a drug's effect on serotonin, histamine and muscarinic activity, as well as on peripheral dopamine receptors (e.g. antagonism or partial agonism) may largely predict how it will affect glucose and lipid levels.[2,5] Clozapine's main metabolite norclozapine may play a special role here, as it has a stronger affinity for several types of receptors than its parent compound, and may thus be responsible for many of clozapine's metabolic effects; however, norclozapine is also believed to improve antipsychotic efficacy, and have beneficial effects on cognition (such as improved working memory performance).[69]
On a subcellular level, clozapine's disruption of cellular energy homeostasis via alteration of glucose and mitochondrial regulation may be among the many processes that cause both its therapeutic and metabolic effects (see *General information and background* and *Hyperglycaemia and diabetes*).[221]

Furthermore, the raised leptin plasma levels that accompany AP treatment and increases in fat mass are known to contribute to the pro-inflammatory state and insulin resistance seen in type 2 DM,[8] but are also hypothesised to mediate clinical improvement (especially in negative symptoms): leptin receptors are found throughout several regions of the central nervous system (CNS), and in leptin-deficient adults, leptin administration can activate several areas in the brain that are defective in schizophrenia.[14,29]
The same was found for several other components in the gut-brain signalling axis, like adiponectin, ghrelin, cholecystokinin (CCK), neuropeptide Y (NPY), GLP-1, orexin-A and insulin: AP-induced changes in these hormones negatively influence energy balance, appetite and food intake, but they may also

act in the CNS and positively affect synaptic plasticity, cognition, and symptomatology. Although the GLP-1 agonist exenatide did not show improvement in cognition or psychosocial function in patients, some promising results in psychopathological improvement were seen when CCK, NPY and orexin-A receptors were therapeutically targeted. This again emphasises the complex array of actions of clozapine, some of which are desired while others are not.[29]

## Management

*Patient care*

Considering the severity of the syndromes that can result from clozapine-induced metabolic side effects, it is important to carefully monitor the patients for weight gain and other parameters associated with MetS.[4] Since the symptoms of MetS largely occur co-dependently, an integrative approach to monitoring and patient management is recommended. Where the previous sections aimed to provide management options for each symptom separately, this section is specifically about interventions meant to deal with MetS as a whole.

As weight increase, glycaemic dysregulation and dyslipidaemia can have negative consequences for the health and self-image of the patient during long-term clozapine treatment, dietary intervention, physical exercise and psychoeducation should be the first-line basis of treatment.[5] Specifically tailored health programmes have been proven successful in helping to improve diet, increase exercise, promote weight loss and quit smoking,[7,17,43] possibly in combination with psychological interventions such as cognitive behavioural therapy, which help to change notions towards food habits and promote healthy behaviour.[5,40,91]

Such interventions alone are often insufficient or difficult to maintain in patients with limited insight into their pathology. Since clozapine is also known to be able to increase hunger, pharmacological assistance may be needed.[17,60,64] See section *Pharmaceutical treatment of metabolic side effects of clozapine* below.

Lastly, nicotine replacement therapy, varenicline and bupropion can help with smoking cessation, although caregivers should be aware that since smoking significantly lowers clozapine plasma levels, smoking cessation usually requires a clozapine dose decrease.[222] See ZTAS Fact Sheet 'Clozapine metabolism and plasma level monitoring' for more information.

*Monitoring metabolic side effects*

Fortunately, many clinicians seem to be aware of the dangers of clozapine-induced MetS, and routine screening for MetS symptoms occurs more frequently in patients on clozapine than on other AP drugs.[4]

As per most guidelines, in patients taking SGAs, personal and family history of obesity, diabetes, dyslipidaemia, hypertension and cardiovascular disease should be recorded, and they should receive appropriate baseline screening and ongoing monitoring of weight and height (BMI), waist circumference (at the level of the umbilicus), blood pressure, fasting plasma glucose and fasting lipid profile.[17,84–89]

If these parameters, coupled with age and smoking status, indicate high risk, clozapine prescription may need to be reconsidered. In absence of viable alternatives, lifestyle/pharmacological interventions and referral to a specialist may have to be initiated immediately.[17]

Table 2 shows suggestions for routine monitoring of metabolic side effects in adult patients. These

recommendations are an assemblage of recommendations by The Maudsley Prescribing Guidelines,[85] the Clozapine Handbook[86] and various other publications on this subject.[87–89]

Table 2. Monitoring protocol for patients with normal baseline values at start of an episode of care.

| | Baseline | 1 month | 3 months | 6 months | at least annually |
|---|---|---|---|---|---|
| Personal/family history | ✓ | | | | |
| Blood pressure | ✓ | ✓ | ✓ | ✓ | ✓ |
| Weight, BMI, waist | ✓ | ✓ | ✓ | ✓ | ✓ |
| Fasting plasma glucose | ✓ | ✓ | ✓ | ✓ | ✓ |
| Fasting lipid profile | ✓ | ✓ | ✓ | ✓ | ✓ |
| Lifestyle advice | ✓ | ✓ | ✓ | ✓ | ✓ |

It is strongly recommended to perform these tests (especially the haematological ones) when the patient comes over for the mandatory periodic full blood counts that check the neutrophil counts and WBCs.[4] In case of abnormal findings, monitoring frequency may need to be increased.[161] As mentioned in *Hyperglycaemia and diabetes*, fasting glucose measurement can be expanded (but not replaced) by measurement of $HbA_{1C}$, a parameter that may have additional value for identifying pre-diabetes.[7,89,155] After the first year of clozapine use, routine annual checks may eventually suffice for most patients, but more frequent monitoring is recommended in high-risk patients. Intervention should not be regarded as a substitute for monitoring.[17]

*What to do in case of abnormal test results*
The Zaponex SPC (sections 4.4 and 4.8) states: "When follow-up data were available, discontinuation of clozapine resulted mostly in resolution of the impaired glucose tolerance, and reinstitution of clozapine resulted in its reoccurrence. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycaemia has failed." "Glucose levels normalised in most patients after discontinuation of clozapine and in a few cases hyperglycaemia recurred when treatment was reinitiated."[1]

The general advice for patients who develop severe hyperglycaemia or dyslipidaemia while on SGAs is to first attempt to implement (additional) lifestyle changes as described above in 'Patient care'. If these are insufficient or unattainable, health care professionals may consider using adjunctive pharmacological interventions to combat metabolic side effects (see *Pharmaceutical treatment of metabolic side effects of clozapine* below).[7,64] Many interventions aimed at weight loss, such as metformin or orlistat, have broad actions and target other symptoms of MetS like hyperglycaemia and dyslipidaemia as well.[17] If a metabolic or cardiovascular disease is diagnosed, the patients should be referred to a specialist in diabetology, endocrinology and/or cardiology or to other services to receive appropriate care.[7]

In case of uncontrollable hyperglycaemia, obesity or dyslipidaemia where all management approaches have been unsuccessful, switching to an SGA that has not been associated with significant weight gain, diabetes or lipid alterations may need to be considered.[7,64,223] However, when an effective response on clozapine is finally achieved, a switch from a beneficial AP regimen is usually considered a last resort effort,[224,225] so the decision should take the entire psychiatric and physical condition of the patient into consideration, as well as the pharmacological profiles of current and proposed drugs.[7]

Drugs like aripiprazole, amisulpride, paliperidone, brexpiprazole, ziprasidone, cariprazine, asenapine and lurasidone have neutral metabolic profiles, and, in some cases, even improve the metabolic parameters.[2,5,40,94] Especially switching to aripiprazole, lurasidone or ziprasidone significantly reduced weight and improved cardiometabolic outcomes.[40,226]
However, it should be born in mind that many clozapine patients are treatment-resistant or -intolerant: they have either not responded well to other APs in the past or suffered untreatable extrapyramidal side effects, so other drugs may have substantial less clinical effect.[2,40,64,94,224,225]

## Pharmaceutical treatment of metabolic side effects of clozapine

Various drugs have been described to reduce metabolic side effects induced by APs. Although studies have shown some promising possibilities, the evidence remains somewhat limited,[227,228] and more than a third of patients may not benefit from such therapies.[5] One reason for the latter finding may be a suboptimal dose or plasma concentration of the treating drugs. Secondly, some aspects of MetS may be sensitive to high (nor)clozapine levels, so therapeutic drug monitoring of both clozapine and the treatment drugs may have important benefits.[5,40] A third proposed reason is that such interventions are most effective when initiated in patients who are new on APs; many of them start much later in treatment, when MetS symptoms have already appeared, and as a result, patients rarely return to their pre-treatment values.[40] Below is an overview of the medication that acts on various facets of MetS, and may reverse or mitigate exacerbation of disease.

*Metformin*
Although not included in official guidelines, there is ample evidence to support the use of the anti-diabetic drug metformin to treat AP-induced weight gain.[97] For clozapine-treated patients, metformin has been reported to be safe and effective in the control of MetS, due to its broad array of actions on AMPK and GLP-1 that ameliorate obesity, hyperglycaemia and dyslipidaemia.[5,10,60,96,125] There have been several double-blind, placebo-controlled studies as well as meta-analyses and reviews on the use of metformin and clozapine, and although there are a few inconsistencies in some of the parameters studied, metformin generally had a positive effect on weight and BMI reduction, waist circumference, blood glucose/insulin and blood lipids,[5,96,99–101,229] with average weight losses around 2.9-3.1 kg.[96,125] Some studies reported favourable effects on both triglycerides and cholesterol (total and HDL cholesterol), although these findings as well as effects on blood pressure are somewhat inconsistent.[99–101] A review or a few small studies showed that 16 weeks of metformin treatment was also effective in weight loss in children, although the use is considered off-label, and the evidence is less robust than in adults.[97,230]
Dosages around 3000 mg/day were considered appropriate in adults, and 1000 mg/day in adolescents,[98] although dosages as low as 750 mg/day already had beneficial effects on metabolic profiles in schizophrenic patients.[103] The most frequently reported side effects are gastrointestinal symptoms such as upset stomach and nausea,[100] and vitamin B12 deficiency during long-term use.[104]

In studies with patients using SGAs (including clozapine), the beneficial effects of metformin on weight loss seem to be similar or somewhat less robust than intensive lifestyle interventions, but metformin is superior in managing glucose dysregulation. Adding metformin as adjunctive therapy to lifestyle changes such as healthier diet and increased exercise gave the best results for all parameters.[17,40,97,100,101,103,229]

One trial found the prevalence of MetS significantly decreasing in the metformin group throughout the first 16 weeks of a 24-week study period, but also noted that the weight returned to baseline again

after metformin was stopped. So although the effects of metformin can last for up to ten years, sustained use of metformin is important.[97,101]
There is also growing evidence that metformin may be more helpful in preventing weight increase than causing weight loss; its effects in long-term users seem much smaller than in new ones, possibly because the former group already has significant insulin resistance. This would make a strong argument to initiate metformin early in AP therapy, as soon as patients are starting to show signs of increased weight or glucose levels, and not delay until significant weight gain or glucose dysregulation has already occurred.[40,60,97,102]

*Glucagon-like-peptide-1 receptor-agonists (GLP-1RAs): liraglutide and exenatide*
Due to their direct stimulation of GLP-1 receptors, GLP-1RAs have effects similar to metformin on body weight and blood glucose. They may also help restore pancreatic β-cells mass and functionality, and improve cardiovascular risk markers, including blood pressure and lipid profiles.[95]
Effectivity and tolerability of GLP-1RAs exenatide and liraglutide in AP users (average duration of 16 months) were confirmed in three systematic reviews and meta-analyses, which demonstrated favourable outcomes on body weight, BMI, fasting glucose, waist circumference and BMI.[10,95] A weight loss of 5% or more was seen in 37% of all AP users on either liraglutide or exenatide (only 11% of patients on usual care managed this), and 19% of patients achieved a weight loss of 7% or more (against 6% on usual care). Clozapine patients on a GLP-1RA lost an average of 4.90 kg of body weight more than controls, and 64% had a normalised fasting plasma glucose after treatment (against 16% on usual care). $HbA_{1C}$ levels were also significantly lowered.[95,107]

Liraglutide is specifically indicated for weight management; it significantly decreased body weight (average loss 5.3 kg) and waist circumference (4.1 cm) as compared to placebo in patients with schizophrenia spectrum disorders treated with clozapine or olanzapine, together with substantial improvements in glucose tolerance, systolic blood pressure and LDL levels.[10,107] Weight loss remained significant even one year after stopping.[108] Exenatide, indicated for treatment of type 2 DM, caused a higher mean change in weight (-5.29 kg) and fasting glucose (-0.34 mmol/L) than traditional weight loss strategies (-1.12 kg and +0.39 mmol/l), and 6 out of 14 exenatide patients achieved weight losses of >5% (against 1 in 14 patients with usual care).[66,95]
Nausea and vomiting seem to be the most commonly encountered and dose-related side effect of GLP-1RAs, which typically resolve within 4-8 weeks.[64,65,95] With relatively few included patients, further studies are required before making routine use recommendations for these GLP1-RAs.[66,95]

Other GLP-1RAs like semaglutide also show significant weight loss in obese patients with once-weekly injections, combined with intense behavioural therapy and diet. Whether this drug is also as effective in clozapine patients still needs to be investigated though.[231]

Since inhibition of GLP-1 by clozapine is believed to be of major importance in the aetiology of MetS, GLP-1RAs are possibly even more effective than metformin in improving body weight and hyperglycaemia.[10,65,95,96,107] Their complementary actions could possibly reinforce each other's effect, as seen in one case where an obese clozapine patient lost 42 kg of his 187 kg body weight while on both metformin and exenatide.[65] Both drugs had been given at the start of clozapine initiation, so a lack of AP-induced insulin resistance may have been instrumental in the success of this treatment. The safety of this combination should first be investigated before any formal recommendations can be made, though.

*Statins, PPAR-agonists and fenofibrate*
Statins are effective in reducing total and LDL-cholesterol, and (to a lesser extent) triglycerides. They

inhibit HMG-CoA reductase and thereby limit the biosynthesis of cholesterol.[232] However, as a class effect, they can also raise blood glucose,[232] and may increase the risk of developing diabetes. The clinical benefits of improving cardiovascular health in clozapine patients should therefore be weighed against the increased occurrence of type 2 DM.[10]
PPAR agonists (e.g. glimepiride, rosiglitazone and fenofibrate) are also effective against clozapine-induced dyslipidaemia and atherosclerosis as they improve HDL, LDL and triglycerides[10,166] by eliminating atherogenic triglyceride-rich particles from plasma (fenofibrate)[233] or increasing the transcription of genes involved in fatty acid uptake and oxidation (rosiglitazone and glimepiride).[166]

*Orlistat*
Orlistat, a lipase inhibitor, in combination with a reduced fat diet, may be effective in reducing weight and preventing weight gain in clozapine- and olanzapine-treated men, but not women.[5,110,111,229] It does not affect the CNS, but may cause diarrhoea, bloating and cramps.[5] As with metformin, it seems more effective in early clozapine treatment than later on, and therapy may need to be sustained for the best effect.[5,17]

*Aripiprazole/ziprasidone*
Aripiprazole is sometimes also used to augment clozapine efficacy, allowing the clozapine dose to be lowered.[118] In several clinical trials, aripiprazole addition reduced weight, waist circumference, or low-density lipoprotein (LDL) cholesterol, and improved glucose response.[114,118,229,234] However, other side effects, such as akathisia or increased psychotic symptoms, are repeatedly reported.[114,235] In addition, note that in post marketing evaluation and in several case reports, aripiprazole has also been implicated to cause hyperglycaemia and diabetic ketoacidosis.[119–122]
Limited evidence exists for weight loss after adding ziprasidone to clozapine, or substituting part of the clozapine dose for it.[112,113]

*Topiramate/lamotrigine*
In literature, topiramate in combination with clozapine is mainly used to augment efficacy, but it also reduced body weight in clozapine-treated patients.[123–125] Topiramate reduces glutamatergic activity in the hypothalamus, which causes weight loss through decreased appetite.[5] A study in olanzapine-treated patients also demonstrated reduced glucose, total cholesterol, LDL cholesterol and blood pressure.[236]
Studies generally show that topiramate is well-tolerated in patients treated with clozapine, paraesthesia being the most common side effect.[123,124] Its anticonvulsive properties also make it a suitable addition in clozapine patients with a lowered seizure threshold.[126] Note, however, that worsening of psychosis has also been reported after the addition of topiramate.[237,238]

Lamotrigine is another possible addition to clozapine due to its mood-stabilising and antidepressant properties without causing weight gain[126], which may allow for the clozapine dose to be lowered and metabolic symptoms to be ameliorated.

*Betahistine*
A double-blind placebo-controlled study in patients being treated with olanzapine or clozapine (n = 26) found that betahistine was significantly better than placebo in preventing increases in weight (3.1 kg less weight gain than placebo), BMI, and waist circumference. Betahistine did not significantly improve appetite or glucose-lipid measures and there were no significant differences in side-effects or psychopathology changes in the betahistine- versus placebo-treated patients.[59]

*Atomoxetine/reboxetine*

Negative symptoms in chronic schizophrenia are associated with decreased noradrenergic stimulation, which is known to lead to inhibition of dopamine signalling in the prefrontal cortex. The noradrenalin reuptake inhibitor atomoxetine, indicated for treating ADHD, can therefore be used to treat residual negative symptoms and enhance cognition. Atomoxetine is also known to very commonly cause loss of appetite.[129] The same was found for another noradrenalin reuptake inhibitor, the antidepressant reboxetine,[5] indicated for depressive illness and major depression.[130] Augmentation of clozapine with atomoxetine or reboxetine could therefore have additional clinical effect and promote weight loss/prevent weight gain as well,[5,128] although one study found that atomoxetine did not offer additional benefit for weight loss over structured group support and exercise programmes.[239]

*SSRIs*

Patients with an increased risk of cardiovascular disease may benefit from the use of SSRIs, as they can prevent thrombus formation and vasoconstriction, which help prevent (severe) coronary heart disease and ischaemic strokes. They are preferred over anticoagulants such as aspirin or clopidogrel (which may increase the risk of bleeding) and may also help with residual negative symptoms.[25]

Especially fluvoxamine addition to clozapine can have several advantages; apart from reduced clotting and providing additional antidepressant effect,[25] it inhibits clozapine metabolism, which can be used to reduce clozapine tablet load and improve the clozapine/norclozapine ratio. This can have several favourable metabolic effects, such as improving body weight and limiting hyperglycaemia and dyslipidaemia, thus ameliorating clozapine-induced MetS. Care should be taken though to prevent clozapine from going into toxic ranges.[71,72]

The antithrombotic capacities of different SSRIs can vary significantly though, since different drugs have different additional pathways in which they can decrease platelet aggregation. Some SSRIs, such as escitalopram, sertraline, citalopram and paroxetine, may therefore be more effective than others (e.g. fluoxetine), and the protective effect can even differ between genders, age groups and therapeutic indications. Additionally, while some SSRIs like fluvoxamine may have beneficial effects on body weight and levels of insulin, glucose and triglycerides, others ended up worsening them, depending on confounders. As a result, SSRIs have unique metabolic risks and cardiovascular benefits depending on sex, age, therapeutic indication and concomitant use of other APs, and should be used with caution.[25]

**Advice for daily practice**

- The Metabolic Syndrome (MetS) is a collection of symptoms characterised by obesity, diabetes, dyslipidaemia and hypertension, and associated with increased (cardiovascular) mortality.
- Patients with schizophrenia already have a higher baseline risk of MetS that can be exacerbated by antipsychotic use.
- Family history of diabetes mellitus and weight gain are poor predictors for developing glucose dysregulation and diabetes mellitus.
- Clozapine is among the antipsychotics with the highest potency to cause weight gain, hyperglycaemia, diabetes and dyslipidaemia. Although very rare, clozapine can also cause diabetic ketoacidosis, which can be fatal.
- Clozapine can exacerbate the diabetogenic feedback loop through (abdominal) weight gain, glucose dysregulation, insulin resistance, altered leptin/adiponectin signalling, dyslipidaemia, deteriorated β-cell function and pro-inflammatory cytokine release (see Figure 1).
- Monitor weight, BMI, waist, plasma glucose and lipid profile (see table 2).
- Promoting lifestyle changes by providing advice on diet and exercise prior and during clozapine treatment may help.
- When metabolic side effects develop, switching to an antipsychotic with a lower metabolic risk is usually effective, but it may be undesirable for mental health.
- Metformin and GLP-1 receptor agonists are probably the best studied pharmacological treatments of clozapine-induced metabolic side effects, and appear effective and safe.
- Pharmacological treatment seems more effective at preventing MetS symptoms than treating existing ones, so early initiation is recommended.

## References


1. Leyden Delta B.V. *Zaponex® Summary of Product Characteristics* (23-Jun-2020). www.ztas.co.uk.
2. Pillinger, T. *et al.* Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry* **7**, 64–77 (2020).
3. Cocoman, A. M. & Gallagher, D. A Retrospective Chart Review of Screening on the Prevalence of Metabolic Syndrome (MetS) in an Irish Community Mental Health Service. *Issues Ment Health Nurs* **40**, 895–901 (2019).
4. Lydon, A. *et al.* Routine screening and rates of metabolic syndrome in patients treated with clozapine and long-acting injectable antipsychotic medications: a cross-sectional study. *Ir. j. psychol. Med.* **30**, 1–9 (2020).
5. Carli, M. *et al.* Atypical Antipsychotics and Metabolic Syndrome: From Molecular Mechanisms to Clinical Differences. *Pharmaceuticals (Basel)* **14** (2021).
6. Dayabandara, M., Hanwella, R., Ratnatunga, S., Seneviratne, S., Suraweera, C. & Silva, V. A. de. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. *Neuropsychiatr Dis Treat* **13**, 2231–2241 (2017).
7. Hert, M. de, Detraux, J., van Winkel, R., Yu, W. & Correll, C. U. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol* **8**, 114–126 (2011).
8. Lopez-Jaramillo, P. *et al.* The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. *Horm Mol Biol Clin Investig* **18**, 37–45 (2014).
9. Zeng, Y. *et al.* Parental history of diabetes mellitus has additive risk of metabolic syndrome in patients treated with clozapine. *Asian Journal of Psychiatry* **50**, 101939 (2020).
10. Yuen, J. W. Y., Kim, D. D., Procyshyn, R. M., Panenka, W. J., Honer, W. G. & Barr, A. M. A Focused Review of the Metabolic Side-Effects of Clozapine. *Front Endocrinol (Lausanne)* **12**, 609240 (2021).
11. Ventriglio, A. *et al.* Metabolic Syndrome in Psychotic Disorder Patients Treated With Oral and Long-Acting Injected Antipsychotics. *Front Psychiatry* **9**, 744 (2018).
12. Scaini, G., Quevedo, J., Velligan, D., Roberts, D. L., Raventos, H. & Walss-Bass, C. Second generation antipsychotic-induced mitochondrial alterations: Implications for increased risk of metabolic syndrome in patients with schizophrenia. *Eur Neuropsychopharmacol* (2018).
13. McEvoy, J. P. *et al.* Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophrenia Research* **80**, 19–32 (2005).
14. Sharma, E., Rao, N. P. & Venkatasubramanian, G. Association between antipsychotic-induced metabolic side-effects and clinical improvement: A review on the Evidence for “metabolic threshold”. *Asian Journal of Psychiatry* **8**, 12–21 (2014).
15. Chen, C. Y.-A., Goh, K. K., Chen, C.-H. & Lu, M.-L. The Role of Adiponectin in the Pathogenesis of Metabolic Disturbances in Patients With Schizophrenia. *Front Psychiatry* **11**, 605124 (2020).
16. Reponen, E. J. *et al.* Adiponectin Is Related to Cardiovascular Risk in Severe Mental Illness Independent of Antipsychotic Treatment. *Front Psychiatry* **12**, 623192 (2021).
17. Ronaldson, K. J. Cardiovascular Disease in Clozapine-Treated Patients: Evidence, Mechanisms and Management. *CNS Drugs* (2017).
18. Rojo, L. E. *et al.* Metabolic syndrome and obesity among users of second generation antipsychotics: A global challenge for modern psychopharmacology. *Pharmacol Res* (2015).

19. Hammerman, A., Dreiher, J., Klang, S. H., Munitz, H., Cohen, A. D. & Goldfracht, M. Antipsychotics and diabetes: an age-related association. *Ann Pharmacother* **42**, 1316–1322 (2008).
20. Albert, S. G., Grossberg, G. T., Thaipisuttikul, P. J., Scouby, J. & Green, E. Atypical antipsychotics and the risk of diabetes in an elderly population in long-term care: a retrospective nursing home chart review study. *J Am Med Dir Assoc* **10**, 115–119 (2009).
21. Popli, A. P., Konicki, P. E., Jurjus, G. J., Fuller, M. A. & Jaskiw, G. E. Clozapine and Associated Diabetes Mellitus. *J. Clin. Psychiatry* **58**, 108–111 (1997).
22. Foley, D. L. *et al.* Effect of age, family history of diabetes, and antipsychotic drug treatment on risk of diabetes in people with psychosis: a population-based cross-sectional study. *The Lancet Psychiatry* **2**, 1092–1098 (2015).
23. Mitchell, A. J., Vancampfort, D., Sweers, K., van Winkel, R., Yu, W. & Hert, M. de. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. *Schizophr Bull* **39**, 306–318 (2013).
24. Simon, V., van Winkel, R. & Hert, M. de. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. *J Clin Psychiatry* **70**, 1041–1050 (2009).
25. Bellon, A. & Nguyen, K. Selective serotonin reuptake inhibitors and risk reduction for cardiovascular disease in patients with schizophrenia: A controversial but promising approach. *World J Psychiatry* **11**, 316–324 (2021).
26. Sárvári, A. K., Veréb, Z., Uray, I. P., Fésüs, L. & Balajthy, Z. Atypical antipsychotics induce both proinflammatory and adipogenic gene expression in human adipocytes in vitro. *Biochemical and Biophysical Research Communications* **450**, 1383–1389 (2014).
27. Shams, T. A. & Muller, D. J. Antipsychotic induced weight gain: genetics, epigenetics, and biomarkers reviewed. *Curr Psychiatry Rep* **16**, 473 (2014).
28. Smith, G. C., McEwen, H., Steinberg, J. D. & Shepherd, P. R. The activation of the Akt/PKB signalling pathway in the brains of clozapine-exposed rats is linked to hyperinsulinemia and not a direct drug effect. *Psychopharmacology* **231**, 4553–4560 (2014).
29. Garcia-Rizo, C. Antipsychotic-Induced Weight Gain and Clinical Improvement: A Psychiatric Paradox. *Front Psychiatry* **11**, 560006 (2020).
30. Covell, N. H., Weissman, E. M. & Essock, S. M. Weight gain with clozapine compared to first generation antipsychotic medications. *Schizophr Bull* **30**, 229–240 (2004).
31. Gentile, S. Long-term treatment with atypical antipsychotics and the risk of weight gain. A literature analysis. *Drug Saf* **29**, 303–319 (2006).
32. Leucht, S. *et al.* Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* (2013).
33. Allison, D. B. *et al.* Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* **156**, 1686–1696 (1999).
34. Newcomer, J. W. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* **19 Suppl 1**, 1–93 (2005).
35. Leucht, S., Corves, C., Arbter, D., Engel, R. R., Li, C. & Davis, J. M. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* **373**, 31–41 (2009).
36. Rummel-Kluge, C. *et al.* Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr. Res.* **123**, 225–233 (2010).
37. Bushe, C. J., Slooff, C. J., Haddad, P. M. & Karagianis, J. L. Weight change from 3-year observational data: findings from the worldwide schizophrenia outpatient health outcomes database. *J Clin Psychiatry* **73**, e749-55 (2012).
38. Garriga, M. *et al.* Food craving and consumption evolution in patients starting treatment with clozapine. *Psychopharmacology (Berl)* (2019).

39. Bak, M., Drukker, M., Campforts, B., Cortenraad, S., Vandenberk, E. & Viechtbauer, W. S2. ANTIPSYCHOTICS RESULT IN WEIGHT GAIN BUT THE SEVERITY OF WEIGHT GAIN DIFFERS BETWEEN ANTIPSYCHOTICS. *Schizophr Bull* **46**, S30 (2020).
40. Hendrick, V., Dasher, R., Gitlin, M. & Parsi, M. Minimizing weight gain for patients taking antipsychotic medications: The potential role for early use of metformin. *Ann Clin Psychiatry* **29**, 120–124 (2017).
41. Lieberman, J. A. *et al.* Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N. Engl. J. Med.* **353**, 1209–1223 (2005).
42. Henderson, D. C. *et al.* Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study. *Am J Psychiatry* **157**, 975–981 (2000).
43. Nemani, K. L. *et al.* Clozapine, Diabetes Mellitus, Cardiovascular Risk and Mortality: Results of a 21-year Naturalistic Study in Patients with Schizophrenia and Schizoaffective Disorder. *Clin Schizophr Relat Psychoses* (2017).
44. Lett, T. A. P., Wallace, T. J. M., Chowdhury, N. I., Tiwari, A. K., Kennedy, J. L. & Muller, D. J. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. *Mol Psychiatry* **17**, 242–266 (2012).
45. Cortes, B., Becker, J., Mories Alvarez, M. T., Marcos, A. I. S. & Molina, V. Contribution of baseline body mass index and leptin serum level to the prediction of early weight gain with atypical antipsychotics in schizophrenia. *Psychiatry Clin Neurosci* **68**, 127–132 (2014).
46. Kang, S. H., Lee, J.-I., Han, H. R., Soh, M. & Hong, J. P. Polymorphisms of the leptin and HTR2C genes and clozapine-induced weight change and baseline BMI in patients with chronic schizophrenia. *Psychiatr Genet* **24**, 249–256 (2014).
47. Lau, S. L. *et al.* Predicting Weight Gain in Patients Treated With Clozapine. *Journal of Clinical Psychopharmacology* **36**, 120–124 (2016).
48. Martini, F. *et al.* M202. SEX-RELATED DIFFERENCES IN CLOZAPINE SIDE EFFECTS IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA. *Schizophr Bull* **46**, S213 (2020).
49. Ferreira, V., Grajales, D. & Valverde, Á. M. Adipose tissue as a target for second-generation (atypical) antipsychotics: A molecular view. *Biochim Biophys Acta Mol Cell Biol Lipids* **1865**, 158534 (2020).
50. Teff, K. L. & Kim, S. F. Atypical antipsychotics and the neural regulation of food intake and peripheral metabolism. *Physiol. Behav.* **104**, 590–598 (2011).
51. Cottingham, C. M., Patrick, T., Richards, M. A. & Blackburn, K. D. Tricyclic antipsychotics promote adipogenic gene expression to potentiate preadipocyte differentiation in vitro. *Hum Cell* **33**, 502–511 (2020).
52. Sentissi, O., Epelbaum, J., Olie, J.-P. & Poirier, M.-F. Leptin and ghrelin levels in patients with schizophrenia during different antipsychotics treatment: a review. *Schizophr Bull* **34**, 1189–1199 (2008).
53. Potvin, S., Zhornitsky, S. & Stip, E. Antipsychotic-induced changes in blood levels of leptin in schizophrenia: a meta-analysis. *Can J Psychiatry* **60**, S26-34 (2015).
54. Bartoli, F., Crocamo, C., Clerici, M. & Carra, G. Second-generation antipsychotics and adiponectin levels in schizophrenia: A comparative meta-analysis. *Eur Neuropsychopharmacol* **25**, 1767–1774 (2015).
55. Bartoli, F., Lax, A., Crocamo, C., Clerici, M. & Carrà, G. Plasma adiponectin levels in schizophrenia and role of second-generation antipsychotics: A meta-analysis. *Psychoneuroendocrinology* **56**, 179–189 (2015).
56. Lu, M.-L. *et al.* Differential effects of olanzapine and clozapine on plasma levels of adipocytokines and total ghrelin. *Prog Neuropsychopharmacol Biol Psychiatry* (2014).

57. Vuk, A., Kuzman, M. R., Baretic, M. & Osvatic, M. M. Diabetic ketoacidosis associated with antipsychotic drugs: case reports and a review of literature. *Psychiatr Danub* **29**, 121–135 (2017).
58. Suhas, S., Shivani, S., Singh, G. K. & Venkatasubramanian, G. Festina Lente: Betahistine for Clozapine-Associated Weight Gain. *J Clin Psychopharmacol* **41**, 332–333 (2021).
59. Smith, R. C. *et al.* Betahistine effects on weight-related measures in patients treated with antipsychotic medications: a double-blind placebo-controlled study. *Psychopharmacology (Berl)* **235**, 3545–3558 (2018).
60. Siskind, D. *et al.* CoMET: a protocol for a randomised controlled trial of co-commencement of METformin as an adjunctive treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia newly commenced on clozapine. *BMJ Open* **8**, e021000 (2018).
61. Puangpetch, A., Unaharassamee, W., Jiratjintana, N., Koomdee, N. & Sukasem, C. Genetic polymorphisms of HTR2C, LEP and LEPR on metabolic syndromes in patients treated with atypical antipsychotic drugs. *J Pharm Pharmacol* (2018).
62. Beaurepaire, R. de. Binge Eating Disorders in Antipsychotic-Treated Patients With Schizophrenia: Prevalence, Antipsychotic Specificities, and Changes Over Time. *J Clin Psychopharmacol* **41**, 114–120 (2021).
63. Smith, G. C., Vickers, M. H. & Shepherd, P. R. Olanzapine effects on body composition, food preference, glucose metabolism and insulin sensitivity in the rat. *Arch Physiol Biochem* **117**, 241–249 (2011).
64. Mayfield, K. *et al.* Glucagon-like peptide-1 agonists combating clozapine-associated obesity and diabetes. *Journal of Psychopharmacology* **30**, 227–236 (2016).
65. Siskind, D., Wysoczanski, D., Russell, A. & Ashford, M. Weight loss associated with exenatide in an obese man with diabetes commenced on clozapine. *Aust N Z J Psychiatry* **50**, 702–703 (2016).
66. Siskind, D. J. *et al.* Treatment of clozapine-associated obesity and diabetes with exenatide in adults with schizophrenia: A randomized controlled trial (CODEX). *Diabetes Obes Metab* (2017).
67. Huang, X.-F., Weston-Green, K. & Yu, Y. Decreased 5-HT2cR and GHSR1a interaction in antipsychotic drug-induced obesity. *Obes Rev* (2017).
68. Mel, V. N. de, Korman, N., McArdle, P. & Siskind, D. J. Weight gain correlated with decrease in clozapine/N-desmethyl-clozapine ratio in a man with treatment-refractory schizophrenia. *Australas Psychiatry* **26**, 558–559 (2018).
69. Smith, R. L., Wollmann, B. M., Kyllesø, L., Tran, T. T. A., Tveito, M. & Molden, E. Effect of Valproic Acid on the Metabolic Spectrum of Clozapine in Patients With Schizophrenia. *J Clin Psychopharmacol* **42**, 43–50 (2022).
70. Lu, M.-L., Lane, H.-Y., Lin, S.-K., Chen, K.-P. & Chang, W.-H. Adjunctive fluvoxamine inhibits clozapine-related weight gain and metabolic disturbances. *J Clin Psychiatry* **65**, 766–771 (2004).
71. Lu, M.-L., Chen, T.-T., Kuo, P.-H., Hsu, C.-C. & Chen, C.-H. Effects of adjunctive fluvoxamine on metabolic parameters and psychopathology in clozapine-treated patients with schizophrenia: A 12-week, randomized, double-blind, placebo-controlled study. *Schizophr Res* (2017).
72. van Wigard MEH, Gool AR & Schulte PFJ. Additie van fluvoxamine aan clozapine: theorie en praktijk. *Tijdschr Psychiatr* **55**, 113–121 (2013).
73. Appiani, F., Carroll, B. T., Muñoz, C. & Trecco, J. Clozapine-induced weight loss? *Ann Clin Psychiatry* **23**, 225 (2011).
74. Das, S., Manjunatha, N. & Thirthali, J. Clozapine-induced Weight Loss and Stuttering in a Patient with Schizophrenia. *Indian J Psychol Med* **40**, 385–387 (2018).
75. Gelegen V, C. S. T. Clozapine-associated weight loss: a case report. *Bulletin of Clinical Psychopharmacology* **23**, S214 (2013).
76. Hanwella, R., Silva, V. de, Wijeratne, C., Ketharanathan, T. & Silva, J. de. Clozapine-associated weight loss. *J. Psychopharmacol. (Oxford)* **24**, 1127–1129 (2010).

77. Lally, J. & McDonald, C. Dramatic weight loss associated with commencing clozapine. *Case Reports* **2011**, bcr0920114790 (2011).
78. Osman, M. & Devadas, V. Clozapine-induced dysphagia with secondary substantial weight loss. *BMJ Case Reports* **2016**, bcr2016216445 (2016).
79. Singh, H. & Haumik, U. B. Weight loss associated with clozapine: Mechanism and review of literature. *Minerva Psichiatrica* **59**, 160–162 (2018).
80. Thomas, N., Ravan, J. R., Jebaraj, P. & Braganza, D. Clozapine producing weight loss: a case series with possible clinical implications - a hypothesis. *J Postgrad Med* **55**, 317 (2009).
81. Tungaraza, T. E. Significant weight loss following clozapine use, how is it possible? A case report and review of published cases and literature relevant to the subject. *Therapeutic Advances in Psychopharmacology* **6**, 335–342 (2016).
82. Webster, A. & Ingram, L. A weight off the mind: Clozapine and profound weight loss. *Australian & New Zealand Journal of Psychiatry* **47**, 1212–1213 (2013).
83. Baker, R. W., Chengappa, K. N., Baird, J. W., Steingard, S., Christ, M. A. & Schooler, N. R. Emergence of obsessive compulsive symptoms during treatment with clozapine. *J Clin Psychiatry* **53**, 439–442 (1992).
84. Kumar, M. & Sidana, A. Clozapine-induced Acute Hypertriglyceridemia. *Indian Journal of Psychological Medicine* **39**, 682–684 (2017).
85. Taylor, D., Paton, C. & Kapur, S. *The Maudsley Prescribing Guidelines in Psychiatry. 12th Edition* (Wiley Blackwell, UK, 2015).
86. Bleakley, S. & Taylor, D. *Clozapine handbook* (Lloyd-Reinhold Communicat, [S.l.], 2013).
87. Hert, M. de *et al.* Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation. *Br J Psychiatry* **199**, 99–105 (2011).
88. Clozapine Plus Werkgroep. Guideline for the use of clozapine. http://www.clozapinepluswerkgroep.nl. 2013.
89. Cohen, D., Bogers, J. P. A. M., van Dijk, D., Bakker, B. & Schulte, P. F. J. Beyond White Blood Cell Monitoring. *J. Clin. Psychiatry* **73**, 1307–1312 (2012).
90. Hepburn, K. & Brzozowska, M. M. Diabetic ketoacidosis and severe hypertriglyceridaemia as a consequence of an atypical antipsychotic agent. *BMJ Case Reports* **2016**, bcr2016215413 (2016).
91. Khazaal, Y. *et al.* Cognitive behavioural therapy for weight gain associated with antipsychotic drugs. *Schizophr. Res.* **91**, 169–177 (2007).
92. Gill, J. M. R. & Cooper, A. R. Physical activity and prevention of type 2 diabetes mellitus. *Sports Med* **38**, 807–824 (2008).
93. Max Marshall *et al.* The HELPER programme: HEalthy Living and Prevention of Early Relapse – three exploratory randomised controlled trials of phase-specific interventions in first-episode psychosis. Programme Grants for Applied Research, No. 3.2. *NIHR Journals Library* (2015).
94. Ingimarsson, O., MacCabe, J. H., Haraldsson, M., Jonsdottir, H. & Sigurdsson, E. Risk of diabetes and dyslipidemia during clozapine and other antipsychotic drug treatment of schizophrenia in Iceland. *Nord J Psychiatry* **71**, 496–502 (2017).
95. Siskind, D. *et al.* Glucagon-like peptide-1 receptor-agonists for antipsychotic-associated cardio-metabolic risk factors: a systematic review and individual participant data meta-analysis. *Diabetes Obes Metab* (2018).
96. Siskind, D. J., Leung, J., Russell, A. W., Wysoczanski, D. & Kisely, S. Metformin for Clozapine Associated Obesity: A Systematic Review and Meta-Analysis. *PLoS ONE* **11**, e0156208 (2016).
97. Silva, V. A. de, Suraweera, C., Ratnatunga, S. S., Dayabandara, M., Wanniarachchi, N. & Hanwella, R. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. *BMC Psychiatry* **16**, 341 (2016).

98. Hui, F., Zhang, Y., Ren, T., Li, X., Zhao, M. & Zhao, Q. Role of metformin in overweight and obese people without diabetes: a systematic review and network meta-analysis. *Eur J Clin Pharmacol* **75**, 437–450 (2019).
99. Carrizo, E. *et al.* Extended release metformin for metabolic control assistance during prolonged clozapine administration: a 14 week, double-blind, parallel group, placebo-controlled study. *Schizophr. Res.* **113**, 19–26 (2009).
100. Hebrani, P. *et al.* Double-blind, randomized, clinical trial of metformin as add-on treatment with clozapine in treatment of schizophrenia disorder. *J Res Med Sci* **20**, 364–371 (2015).
101. Chen, C.-H. *et al.* Effects of adjunctive metformin on metabolic traits in nondiabetic clozapine-treated patients with schizophrenia and the effect of metformin discontinuation on body weight: a 24-week, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* **74**, e424-30 (2013).
102. Spokes, J. *et al.* Metformin reduces 12-month change in body weight among people newly commenced on clozapine: a retrospective naturalistic cohort study. *Ther Adv Psychopharmacol* **11**, 20451253211000609 (2021).
103. Wu, R.-R. *et al.* Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA* **299**, 185–193 (2008).
104. Jager, J. de *et al.* Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ* **340**, c2181 (2010).
105. McFadden, M., Gordon, A., Leong, G., Ward, D. & Scott, J. G. Pancreatitis associated with metformin used for management of clozapine-related weight gain. *Australian & New Zealand Journal of Psychiatry* **50**, 701–702 (2016).
106. Flanagan, R. J., Lally, J., Gee, S., Lyon, R. & Every-Palmer, S. Clozapine in the treatment of refractory schizophrenia: a practical guide for healthcare professionals. *Br Med Bull* (2020).
107. Larsen, J. R. *et al.* Effect of Liraglutide Treatment on Prediabetes and Overweight or Obesity in Clozapine- or Olanzapine-Treated Patients With Schizophrenia Spectrum Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* (2017).
108. Svensson, C. K. *et al.* One-Year Follow-up on Liraglutide Treatment for Prediabetes and Overweight/Obesity in Clozapine- or Olanzapine-Treated Patients. *Acta Psychiatr Scand* (2018).
109. Poyurovsky, M. & Weizman, A. Beneficial Effect of Betahistine, a Structural Analog of Histamine, in Clozapine-Related Sedation. *Clinical Neuropharmacology* **42**, 145 (2019).
110. Joffe, G. *et al.* Orlistat in clozapine- or olanzapine-treated patients with overweight or obesity: a 16-week randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* **69**, 706–711 (2008).
111. Tchoukhine, E. *et al.* Orlistat in clozapine- or olanzapine-treated patients with overweight or obesity: a 16-week open-label extension phase and both phases of a randomized controlled trial. *J Clin Psychiatry* **72**, 326–330 (2011).
112. Li, C.-H., Shi, L., Zhan, G.-L., Rao, S.-Z. & Zhang, H. A twenty-four-week, open-label study on Ziprasidone's efficacy and influence on glucolipid metabolism in patients with schizophrenia and metabolic disorder. *Eur Rev Med Pharmacol Sci* **17**, 2136–2140 (2013).
113. Roy-Desruisseaux, J. & Grignon, S. Protracted, dose-dependent weight loss after addition of ziprasidone to a stable regimen of clozapine. *Hum Psychopharmacol* **25**, 428 (2010).
114. Fleischhacker, W. W. *et al.* Effects of adjunctive treatment with aripiprazole on body weight and clinical efficacy in schizophrenia patients treated with clozapine: a randomized, double-blind, placebo-controlled trial. *Int. J. Neuropsychopharmacol.* **13**, 1115–1125 (2010).
115. Muscatello, M. R. A. *et al.* Effect of aripiprazole augmentation of clozapine in schizophrenia: a double-blind, placebo-controlled study. *Schizophr. Res.* **127**, 93–99 (2011).

116. Chang, J. S. *et al.* Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: an 8-week, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* **69**, 720–731 (2008).
117. Tiihonen, J., Taipale, H., Mehtälä, J., Vattulainen, P., Correll, C. U. & Tanskanen, A. Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia. *JAMA Psychiatry* **76**, 499 (2019).
118. Chang, J. S., Lee, N. Y., Ahn, Y. M. & Kim, Y. S. The sustained effects of aripiprazole-augmented clozapine treatment on the psychotic symptoms and metabolic profiles of patients with refractory schizophrenia. *J Clin Psychopharmacol* **32**, 282–284 (2012).
119. Otsuka Pharmaceuticals (UK) Ltd *Abilify Summary of Product Characteristics* (08-Oct-2021). https://www.medicines.org.uk/emc/product/7969/smpc.
120. Reddymasu, S., Bahta, E., Levine, S., Manas, K. & Slay, L. E. Elevated lipase and diabetic ketoacidosis associated with aripiprazole. *JOP* **7**, 303–305 (2006).
121. Church, C. O., Stevens, D. L. & Fugate, S. E. Diabetic ketoacidosis associated with aripiprazole. *Diabet. Med.* **22**, 1440–1443 (2005).
122. Makhzoumi, Z. H., McLean, L. P., Lee, J. H. & Ibe, A. I. Diabetic ketoacidosis associated with aripiprazole. *Pharmacotherapy* **28**, 1198–1202 (2008).
123. Hahn, M. K., Remington, G., Bois, D. & Cohn, T. Topiramate augmentation in clozapine-treated patients with schizophrenia: clinical and metabolic effects. *J Clin Psychopharmacol* **30**, 706–710 (2010).
124. Afshar, H. *et al.* Topiramate add-on treatment in schizophrenia: a randomised, double-blind, placebo-controlled clinical trial. *J Psychopharmacol* **23**, 157–162 (2009).
125. Liu, Z., Zheng, W., Gao, S., Qin, Z., Li, G. & Ning, Y. Metformin for treatment of clozapine-induced weight gain in adult patients with schizophrenia: a meta-analysis. *Shanghai Arch Psychiatry* **27**, 331–340 (2015).
126. Varma, S., Bishara, D., Besag, F. M. C. & Taylor, D. Clozapine-related EEG changes and seizures: dose and plasma-level relationships. *Ther Adv Psychopharmacol* **1**, 47–66 (2011).
127. Taylor, D., Barnes, T. E. & Young, A. *The Maudsley Prescribing Guidelines in Psychiatry, 13th Edition* (Wiley Blackwell, UK, 2018).
128. Naguy, A., Alamiri, B. & Khraibut, B. Weight Loss During Atomoxetine Add-on to Clozapine-Responsive Schizophrenia. *Am J Ther* **25**, e774-e775 (2018).
129. Dr. Reddy's Laboratories (UK) Ltd *Atomoxetine Summary of Product Characteristics* (04-Jun-2021). https://www.medicines.org.uk/emc/product/12645/smpc.
130. Pfizer Limited *Reboxetine Summary of Product Characteristics* (18-Mar-2022). https://www.medicines.org.uk/emc/product/1578.
131. Koller, E., Schneider, B., Bennett, K. & Dubitsky, G. Clozapine-associated diabetes. *Am J Med* **111**, 716–723 (2001).
132. Yood, M. U. *et al.* The incidence of diabetes in atypical antipsychotic users differs according to agent--results from a multisite epidemiologic study. *Pharmacoepidemiol Drug Saf* **18**, 791–799 (2009).
133. Kessing, L. V., Thomsen, A. F., Mogensen, U. B. & Andersen, P. K. Treatment with antipsychotics and the risk of diabetes in clinical practice. *Br J Psychiatry* **197**, 266–271 (2010).
134. Fernandez-Egea, E., Walker, R., Ziauddeen, H., Cardinal, R. N. & Bullmore, E. T. Birth weight, family history of diabetes and diabetes onset in schizophrenia. *BMJ Open Diabetes Res Care* **8** (2020).
135. Henderson, D. C. *et al.* Elevated hemoglobin A1c as a possible indicator of diabetes mellitus and diabetic ketoacidosis in schizophrenia patients receiving atypical antipsychotics. *J Clin Psychiatry* **68**, 533–541 (2007).

136. Lund, B. C., Perry, P. J., Brooks, J. M. & Arndt, S. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. *Arch Gen Psychiatry* **58**, 1172–1176 (2001).
137. Sernyak, M. J., Leslie, D. L., Alarcon, R. D., Losonczy, M. F. & Rosenheck, R. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* **159**, 561–566 (2002).
138. Gianfrancesco, F. D., Grogg, A. L., Mahmoud, R. A., Wang, R.-h. & Nasrallah, H. A. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. *J Clin Psychiatry* **63**, 920–930 (2002).
139. Guo, J. J. *et al.* Risk of diabetes mellitus associated with atypical antipsychotic use among patients with bipolar disorder: A retrospective, population-based, case-control study. *J Clin Psychiatry* **67**, 1055–1061 (2006).
140. Hirsch, L., Yang, J., Bresee, L., Jette, N., Patten, S. & Pringsheim, T. Second-Generation Antipsychotics and Metabolic Side Effects: A Systematic Review of Population-Based Studies. *Drug Saf* (2017).
141. Lee, H., Song, D.-H., Kwon, J.-W., Han, E., Chang, M.-J. & Kang, H.-Y. Assessing the risk of type 2 diabetes mellitus among children and adolescents with psychiatric disorders treated with atypical antipsychotics: a population-based nested case-control study. *Eur Child Adolesc Psychiatry* **27**, 1321–1334 (2018).
142. Schimmelbusch, W. H., Mueller, P. S. & Sheps, J. The positive correlation between insulin resistance and duration of hospitalization in untreated schizophrenia. *Br J Psychiatry* **118**, 429–436 (1971).
143. Waitzkin, L. A survey for unknown diabetics in a mental hospital. I. Men under age fifty. *Diabetes* **15**, 97–104 (1966).
144. Kasanin, J. The blood sugar curve in mental disease. II. The schizophrenia (dementia praecox) groups. *Arch Neurol Psychiatry*, 414–419 (1926).
145. Braceland, F. J. Delayed action of insulin in schizophrenia. *Am J Psychiatry*, 108–110 (1945).
146. Kohen, D. Diabetes mellitus and schizophrenia: historical perspective. *Br J Psychiatry Suppl* **47**, S64-6 (2004).
147. Tomasik, J. *et al.* Association of Insulin Resistance With Schizophrenia Polygenic Risk Score and Response to Antipsychotic Treatment. *JAMA Psychiatry* **76**, 864 (2019).
148. Hackinger, S. *et al.* Evidence for genetic contribution to the increased risk of type 2 diabetes in schizophrenia. *Transl Psychiatry* **8**, 252 (2018).
149. Nihalani, N. D. *et al.* Diabetic ketoacidosis among patients receiving clozapine: a case series and review of socio-demographic risk factors. *Ann Clin Psychiatry* **19**, 105–112 (2007).
150. Foley, D. L. *et al.* Predictors of type 2 diabetes in a nationally representative sample of adults with psychosis. *World Psychiatry* **13**, 176–183 (2014).
151. Pack, S. Poor physical health and mortality in patients with schizophrenia. *Nurs Stand* **23**, 41–45 (2009).
152. Fountoulakis, K. N. *et al.* Obesity and smoking in patients with schizophrenia and normal controls: a case-control study. *Psychiatry Res* **176**, 13–16 (2010).
153. Ishibashi, M. *et al.* Clinical Factors Associated with New-Onset Glucose Intolerance among Patients with Schizophrenia during Clozapine Treatment: All-Case Surveillance in Japan. *Tohoku J Exp Med* **252**, 177–183 (2020).
154. Bai, Y. M., Lin, C.-C., Chen, J.-Y., Chen, T. T., Su, T.-P. & Chou, P. Association of weight gain and metabolic syndrome in patients taking clozapine: an 8-year cohort study. *J Clin Psychiatry* **72**, 751–756 (2011).
155. Manu, P. *et al.* Insulin secretion in patients receiving clozapine, olanzapine, quetiapine and risperidone. *Schizophrenia Research* **143**, 358–362 (2013).

156. Smith, G. C., Chaussade, C., Vickers, M., Jensen, J. & Shepherd, P. R. Atypical antipsychotic drugs induce derangements in glucose homeostasis by acutely increasing glucagon secretion and hepatic glucose output in the rat. *Diabetologia* **51**, 2309–2317 (2008).
157. Smith, G. C., Vickers, M. H., Cognard, E. & Shepherd, P. R. Clozapine and quetiapine acutely reduce glucagon-like peptide-1 production and increase glucagon release in obese rats: implications for glucose metabolism and food choice behaviour. *Schizophr Res* **115**, 30–40 (2009).
158. Smith, G. *et al.* Clozapine directly increases insulin and glucagon secretion from islets: Implications for impairment of glucose tolerance. *Schizophrenia Research* **157**, 128–133 (2014).
159. El-Seweidy, M. M., Sadik, N. A. H., Malek, M. M. & Amin, R. S. Chronic effects of clozapine administration on insulin resistance in rats: Evidence for adverse metabolic effects. *Pathol Res Pract* **210**, 5–9 (2014).
160. Liu, X., Wu, Z., Lian, J., Hu, C.-H., Huang, X.-F. & Deng, C. Time-dependent changes and potential mechanisms of glucose-lipid metabolic disorders associated with chronic clozapine or olanzapine treatment in rats. *Sci Rep* **7**, 2762 (2017).
161. Chen, V. C.-H., Chen, C.-H., Chiu, Y.-H., Lin, T.-Y., Li, F.-C. & Lu, M.-L. Leptin/Adiponectin ratio as a potential biomarker for metabolic syndrome in patients with schizophrenia. *Psychoneuroendocrinology* **92**, 34–40 (2018).
162. Fang, X. *et al.* Association Between SIRT1, Cytokines, and Metabolic Syndrome in Schizophrenia Patients With Olanzapine or Clozapine Monotherapy. *Front Psychiatry* **11**, 602121 (2020).
163. D'Alessio, D. A., Kahn, S. E., Leusner, C. R. & Ensinck, J. W. Glucagon-like peptide 1 enhances glucose tolerance both by stimulation of insulin release and by increasing insulin-independent glucose disposal. *J Clin Invest* **93**, 2263–2266 (1994).
164. Prigeon, R. L., Quddusi, S., Paty, B. & D'Alessio, D. A. Suppression of glucose production by GLP-1 independent of islet hormones: a novel extrapancreatic effect. *Am J Physiol Endocrinol Metab* **285**, E701-7 (2003).
165. Nagata, M., Kimura, Y., Ishiwata, Y., Takahashi, H. & Yasuhara, M. Clozapine-Induced Acute Hyperglycemia Is Accompanied with Elevated Serum Concentrations of Adrenaline and Glucagon in Rats. *Biol Pharm Bull* **41**, 1286–1290 (2018).
166. Nasrallah, H. A. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. *Mol Psychiatry* **13**, 27–35 (2008).
167. Anini, Y., Hansotia, T. & Brubaker, P. L. Muscarinic receptors control postprandial release of glucagon-like peptide-1: in vivo and in vitro studies in rats. *Endocrinology* **143**, 2420–2426 (2002).
168. Deacon, C. F. What do we know about the secretion and degradation of incretin hormones? *Regul Pept* **128**, 117–124 (2005).
169. Ruiz de Azua, I., Gautam, D., Jain, S., Guettier, J.-M. & Wess, J. Critical metabolic roles of β-cell M3 muscarinic acetylcholine receptors. *Life Sciences* **91**, 986–991 (2012).
170. Weston-Green, K., Huang, X.-F. & Deng, C. Second Generation Antipsychotic-Induced Type 2 Diabetes: A Role for the Muscarinic M3 Receptor. *CNS Drugs* **27**, 1069–1080 (2013).
171. Patel, S. S. & Allin, M. P. G. Physical complications in early clozapine treatment: a case report and implications for safe monitoring. *Therapeutic Advances in Psychopharmacology* **1**, 25–29 (2011).
172. Porras-Segovia, A. *et al.* Rapid-onset clozapine-induced loss of glycaemic control: case report. *BJPsych Open* **3**, 138–140 (2017).
173. Chathoth, V., Ramamurthy, P. & Solomon, S. Clozapine-induced Insulin-resistant Hyperglycemia in a Diabetic Patient. *Indian J Psychol Med* **40**, 375–377 (2018).
174. Brown & Burk UK Ltd *Metformin Summary of Product Characteristics* (12-Apr-2021). https://www.medicines.org.uk/emc/product/10759/smpc.

175. Vuk, A., Baretic, M., Osvatic, M. M., Filipcic, I., Jovanovic, N. & Kuzman, M. R. Treatment of Diabetic Ketoacidosis Associated With Antipsychotic Medication. *Journal of Clinical Psychopharmacology* **37**, 584–589 (2017).
176. Lipscombe, L. L. *et al.* Atypical antipsychotics and hyperglycemic emergencies: Multicentre, retrospective cohort study of administrative data. *Schizophrenia Research* **154**, 54–60 (2014).
177. Alex, S. M., Menon, V. P., B, S., P, U. & Ts, D. Clozapine-induced diabetic ketoacidosis: a case report. *Asian J Pharm Clin Res* **11**, 1 (2018).
178. Polcwiartek, C., Vang, T., Bruhn, C. H., Hashemi, N., Rosenzweig, M. & Nielsen, J. Diabetic ketoacidosis in patients exposed to antipsychotics: a systematic literature review and analysis of Danish adverse drug event reports. *Psychopharmacology* **233**, 3663–3672 (2016).
179. Sadibasic, B., Macic-Dzankovic, A., Sabic, A., Torlak, B., Lastric, G. & Custovic, A. The incidence of dyslipidemia (hypertriglyceridemia and hypercholesterolemia) in patients treated with the new generation of antipsychotic drugs compared to conventional therapy. *Med Glas (Zenica)* **11**, 350–355 (2014).
180. Procyshyn, R. M. *et al.* Changes in serum lipids, independent of weight, are associated with changes in symptoms during long-term clozapine treatment. *J Psychiatry Neurosci* **32**, 331–338 (2007).
181. Hert, M. de, Schreurs, V., Vancampfort, D. & van Winkel, R. Metabolic syndrome in people with schizophrenia: a review. *World Psychiatry* **8**, 15–22 (2009).
182. Meyer, J. M. & Koro, C. E. The effects of antipsychotic therapy on serum lipids: a comprehensive review. *Schizophr. Res.* **70**, 1–17 (2004).
183. Lindenmayer, J.-P. *et al.* Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry* **160**, 290–296 (2003).
184. Canfran-Duque, A. *et al.* Atypical antipsychotics alter cholesterol and fatty acid metabolism in vitro. *J Lipid Res* **54**, 310–324 (2013).
185. Birkenaes, A. B. *et al.* Dyslipidemia independent of body mass in antipsychotic-treated patients under real-life conditions. *J Clin Psychopharmacol* **28**, 132–137 (2008).
186. Kang, S. H. & Lee, J. I. Metabolic disturbances independent of body mass in patients with schizophrenia taking atypical antipsychotics. *Psychiatry Investig* **12**, 242–248 (2015).
187. Larsen, J. R. *et al.* High prevalence of prediabetes and metabolic abnormalities in overweight or obese schizophrenia patients treated with clozapine or olanzapine. *CNS Spectr*, 1–12 (2018).
188. Kim, D. D., Barr, A. M., Fredrikson, D. H., Honer, W. G. & Procyshyn, R. M. Association between serum lipids and antipsychotic response in schizophrenia. *Curr Neuropharmacol* (2019).
189. Cai, H. L. *et al.* A potential mechanism underlying atypical antipsychotics-induced lipid disturbances. *Transl Psychiatry* **5**, e661 (2015).
190. Koskinen, S. *et al.* INSIG2 polymorphism and weight gain, dyslipidemia and serum adiponectin in Finnish patients with schizophrenia treated with clozapine. *Pharmacogenomics* **17**, 1987–1997 (2016).
191. Kang, S. H., Han, H. R., Lee, J.-I., Karmacharya, R., Jeon, H. J. & Roh, S. Effects of LEP, LEPR, ADIPOQ, MC4R and FTO polymorphisms on dyslipidemia in Korean patients with schizophrenia who are taking clozapine. *Psychiatry Research* **228**, 177–178 (2015).
192. Wang, W. *et al.* Clozapine-induced reduction of l-carnitine reabsorption via inhibition/down-regulation of renal carnitine/organic cation transporter 2 contributes to liver lipid metabolic disorder in mice. *Toxicol Appl Pharmacol* **363**, 47–56 (2018).
193. Chukhin, E. *et al.* Is there an interrelationship between the effects of antipsychotics on psychopathology and on metabolism? *Nordic Journal of Psychiatry*, 1–5 (2015).
194. Suraweera, C., Silva, V. de & Hanwella, R. Simvastatin-induced cognitive dysfunction: two case reports. *J Med Case Rep* **10**, 83 (2016).

195. Kritharides, L., Chow, V. & Lambert, T., JR. Cardiovascular disease in patients with schizophrenia. *Med J Aust* **206**, 91–95 (2017).
196. Mucheru, D., Hanlon, M.-C., Campbell, L. E., McEvoy, M. & MacDonald-Wicks, L. Cardiovascular disease lifestyle risk factors in people with psychosis: a cross-sectional study. *BMC Public Health* **18**, 742 (2018).
197. Stolz, P. A. *et al.* Effects of Cigarette Smoking and Clozapine Treatment on 20-Year All-Cause & Cardiovascular Mortality in Schizophrenia. *Psychiatr Q* (2019).
198. Storch Jakobsen, A. *et al.* Associations between clinical and psychosocial factors and metabolic and cardiovascular risk factors in overweight patients with schizophrenia spectrum disorders - Baseline and two-years findings from the CHANGE trial. *Schizophr Res Cogn* **199**, 96–102 (2018).
199. van der Zalm, Y., Termorshuizen, F., Sommer, I. E. & Selten, J.-P. Use of cardiovascular and antidiabetic drugs before and after starting with clozapine versus other antipsychotic drugs: a Dutch database study. *Int Clin Psychopharmacol* **35**, 36–41 (2020).
200. Hayes, R. D. *et al.* The Effect of Clozapine on Premature Mortality: An Assessment of Clinical Monitoring and Other Potential Confounders. *Schizophr Bull* (2014).
201. Olfson, M., Gerhard, T., Huang, C., Crystal, S. & Stroup, T. S. Premature Mortality Among Adults With Schizophrenia in the United States. *JAMA Psychiatry* **72**, 1172 (2015).
202. Vermeulen, J. M. *et al.* Clozapine and Long-Term Mortality Risk in Patients With Schizophrenia: A Systematic Review and Meta-analysis of Studies Lasting 1.1-12.5 Years. *Schizophr Bull* **45**, 315–329 (2019).
203. Yuen, J. W. Y., Kim, D. D., Procyshyn, R. M., White, R. F., Honer, W. G. & Barr, A. M. Clozapine-Induced Cardiovascular Side Effects and Autonomic Dysfunction: A Systematic Review. *Front Neurosci* **12**, 203 (2018).
204. Nair, G. M., Skaria, D. S., James, T. & Kanthlal, S. K. Clozapine Disrupts Endothelial Nitric Oxide Signaling and Antioxidant System for its Cardiovascular Complications. *Drug Res (Stuttg)* (2019).
205. Axelsson, S., Hagg, S., Eriksson, A. C., Lindahl, T. L. & Whiss, P. A. In vitro effects of antipsychotics on human platelet adhesion and aggregation and plasma coagulation. *Clin Exp Pharmacol Physiol* **34**, 775–780 (2007).
206. Shulman, M., Jennifer Njoku, I. & Manu, P. Thrombotic complications of treatment with antipsychotic drugs. *Minerva Med* **104**, 175–184 (2013).
207. Leung, J. Y., Barr, A. M., Procyshyn, R. M., Honer, W. G. & Pang, C. C. Cardiovascular side-effects of antipsychotic drugs: The role of the autonomic nervous system. *Pharmacology & Therapeutics* **135**, 113–122 (2012).
208. Zhang, D., Wang, W. & Li, F. Association between resting heart rate and coronary artery disease, stroke, sudden death and noncardiovascular diseases: a meta-analysis. *CMAJ* **188**, E384 (2016).
209. Modai, I. *et al.* Sudden death in patients receiving clozapine treatment: a preliminary investigation. *J Clin Psychopharmacol* **20**, 325–327 (2000).
210. La Grenade, L., Graham, D. & Trontell, A. Myocarditis and cardiomyopathy associated with clozapine use in the United States. *N. Engl. J. Med.* **345**, 224–225 (2001).
211. Fineschi, V., Neri, M., Riezzo, I. & Turillazzi, E. Sudden cardiac death due to hypersensitivity myocarditis during clozapine treatment. *Int. J. Legal Med.* **118**, 307–309 (2004).
212. Walker, A. M., Lanza, L. L., Arellano, F. & Rothman, K. J. Mortality in current and former users of clozapine. *Epidemiology* **8**, 671–677 (1997).
213. Henderson, D. C. *et al.* Clozapine, Diabetes Mellitus, Hyperlipidemia, and Cardiovascular Risks and Mortality. *J. Clin. Psychiatry* **66**, 1116–1121 (2005).
214. Lappin, J. M. *et al.* Cardio-metabolic risk and its management in a cohort of clozapine-treated outpatients. *Schizophr Res* (2018).

215. Leon, J. de & Diaz, F. J. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia Research* **76**, 135–157 (2005).
216. Wijesundera, H., Hanwella, R. & Silva, V. A. de. Antipsychotic medication and tobacco use among outpatients with schizophrenia: a cross-sectional study. *Ann Gen Psychiatry* **13**, 7 (2014).
217. Kelly, D. L. *et al.* Cardiovascular disease mortality in patients with chronic schizophrenia treated with clozapine: a retrospective cohort study. *J Clin Psychiatry* **71**, 304–311 (2010).
218. Tiihonen, J. *et al.* 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* **374**, 620–627 (2009).
219. Jönsson, A. K., Schill, J., Olsson, H., Spigset, O. & Hagg, S. Venous Thromboembolism During Treatment with Antipsychotics: A Review of Current Evidence. *CNS Drugs* **32**, 47–64 (2018).
220. Sarvaiya, N., Lapitskaya, Y., Dima, L. & Manu, P. Clozapine-Associated Pulmonary Embolism: A High-Mortality, Dose-Independent and Early-Onset Adverse Effect. *Am J Ther* **25**, e434-e438 (2018).
221. Heetla, H., Spoelstra, H. & Knegtering, S. Antipsychotica en metabole disregulatie. *Tijdschr Psychiatr* **62**, 393–394 (2020).
222. Mendelsohn, C. P., Kirby, D. P. & Castle, D. J. Smoking and mental illness. An update for psychiatrists. *Australas Psychiatry* (2014).
223. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* **27**, 596–601 (2004).
224. Citrome, L. & Volavka, J. Consensus development conference on antipsychotic drugs and obesity and diabetes: response to consensus statement. *Diabetes Care* **27**, 2087-8; author reply 2089-90 (2004).
225. Isaac, M. T. & Isaac, M. B. Consensus development conference on antipsychotic drugs and obesity and diabetes: response to consensus statement. *Diabetes Care* **27**, 2088; author reply 2089-90 (2004).
226. Siskind, D. *et al.* Does Switching Antipsychotics Ameliorate Weight Gain in Patients With Severe Mental Illness? A Systematic Review and Meta-analysis. *Schizophrenia bulletin* **47**, 948–958 (2021).
227. Whitney, Z., Procyshyn, R. M., Fredrikson, D. H. & Barr, A. M. Treatment of clozapine-associated weight gain: a systematic review. *Eur J Clin Pharmacol* **71**, 389–401 (2015).
228. Tse, L., Procyshyn, R. M., Fredrikson, D. H., Boyda, H. N., Honer, W. G. & Barr, A. M. Pharmacological treatment of antipsychotic-induced dyslipidemia and hypertension. *Int Clin Psychopharmacol* **29**, 125–137 (2014).
229. Zimbron, J., Khandaker, G. M., Toschi, C., Jones, P. B. & Fernandez-Egea, E. A systematic review and meta-analysis of randomised controlled trials of treatments for clozapine-induced obesity and metabolic syndrome. *European Neuropsychopharmacology* **26**, 1353–1365 (2016).
230. Ellul, P., Delorme, R. & Cortese, S. Metformin for Weight Gain Associated with Second-Generation Antipsychotics in Children and Adolescents: A Systematic Review and Meta-Analysis. *CNS Drugs* (2018).
231. Wadden, T. A. *et al.* Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity. *JAMA* **325**, 1403 (2021).
232. Brown & Burk UK Ltd *Simvastatin Summary of Product Characteristics* (12-Apr-2021). https://www.medicines.org.uk/emc/product/10665/smpc.
233. Ranbaxy (UK) Limited *Fenofibrate Summary of Product Characteristics* (11-May-2018). https://www.medicines.org.uk/emc/product/4436/smpc.
234. Fan, X. *et al.* Metabolic effects of adjunctive aripiprazole in clozapine-treated patients with schizophrenia. *Acta Psychiatr Scand* **127**, 217–226 (2013).

235. Mossaheb, N. Role of aripiprazole in treatment-resistant schizophrenia. *Neuropsychiatric Disease and Treatment* **8**, 235 (2012).
236. Narula, P. K., Rehan, H. S., Unni, K. E. S. & Gupta, N. Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: a double-blind, placebo-controlled trial. *Schizophr. Res.* **118**, 218–223 (2010).
237. Hofer, A., Fleischhacker, W. W. & Hummer, M. Worsening of psychosis after replacement of adjunctive valproate with topiramate in a schizophrenia patient. *J Clin Psychiatry* **64**, 1267–1268 (2003).
238. Millson, R. C., Owen, J. A., Lorberg, G. W. & Tackaberry, L. Topiramate for Refractory Schizophrenia. *AJP* **159**, 675 (2002).
239. Ball, M. P., Warren, K. R., Feldman, S., McMahon, R. P., Kelly, D. L. & Buchanan, R. W. Placebo-controlled trial of atomoxetine for weight reduction in people with schizophrenia treated with clozapine or olanzapine. *Clin Schizophr Relat Psychoses* **5**, 17–25 (2011).