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THE METABOLIC ADVERSE EFFECTS OF WEIGHT GAIN IN THE PHARMACOTHERAPY OF ANTIPSYCHOTICS IN ADULTS AND OPTIONS TO REDUCE THEM

Nathaniel A. Caldwell* and Yuliya Modna

Department of Physiology, Trinity Medical Sciences University, Kingstown, St. Vincent and the Grenadines.

***Corresponding Author: Nathaniel A. Caldwell**
Department of Physiology, Trinity Medical Sciences University, Kingstown, St. Vincent and the Grenadines.

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ABSTRACT

Since their introduction as the novel treatments of psychosis in the mid 20th century, antipsychotics (APs) have played a critical role in the treatment of psychotic disorders and mood disorders for the past 70 years. Presently in the COVID-19 global pandemic, mental health issues have come to the forefront of public health, but with the usage of these drugs comes certain side effects. **Purpose:** to determine the metabolic adverse effects of weight gain in the pharmacotherapy of antipsychotics in adults and options to reduce them. **Research objectives:** To provide summary on the use of antipsychotics, their metabolic side effects, and which, if any, should be used in patient populations to minimize the development of metabolic adverse effect. To find novel adjunct therapies that can be used with antipsychotics to minimize, negate, or reverse associated weight gain and metabolic complications. Results. Clozapine and olanzapine scored high with many "strong associations", while risperidone, paliperidone, and quetiapine had mixed results. Ziprasidone, aripiprazole, cariprazine, and other novel antipsychotics scored many "no associations" between our parameters of weight gain, insulin resistance, etc and the drug's usage. In terms of weight lost or managed, behavioral modification with low-calorie diet, metformin, and switching to a partial agonist antipsychotic showed "mildly strong association" with weight lost or managed. Data from CATIE shows olanzapine being the most effective studied antipsychotic, with clozapine being out of use during Phase 1. Clozapine has well documented efficacy as a second-line agent. All other antipsychotics, including first- generation perphenazine, performed equally effectively in Phase 1, beneath olanzapine. **Conclusion:** From our data, two main subcategories of antipsychotics were determined for clinical use. The first subcategory includes olanzapine and clozapine with excellent effectiveness but with high risk of metabolic side effects (among other side effects). The second subcategory includes most SGAs and novel antipsychotics, such as risperidone, paliperidone, quetiapine, ziprasidone, lurasidone, aripiprazole, brexpiprazole, cariprazine, and lumateperone. These drug's demonstrated effectiveness and more favorable side effect profiles warrants usagein mainstream treatment of psychosis and mood stabilization. We have found that the switching to a partial agonist (novel APs), using metformin, having a low-calorie monitored diet, nutritional education, and supportive care allows patients to minimize and reduce weight gainand metabolic complications

KEYWORDS: "antipsychotic", "weight gain", "side effects", "efficacy", "metabolic", "diabetes type 2", "obesity", "dyslipidemia", and "weight loss".

INTRODUCTION

Since their introduction as the novel treatments of psychosis in the mid 20th century, antipsychotics (APs) have played a critical role in the treatment of psychotic disorders and mood disorders for the past 70 years.[1] Antipsychotics changed the model of how mental illness was treated by physicians, and have become a mainstay of the treatment of psychosis, mood stabilization, and affective disorders.[2]

Metabolic side effects, including weight gain, dyslipidemia, metabolic syndrome, and an increased risk of obesity and type 2 diabetes mellitus happen to be common adverse effects for many antipsychotics.[1] However, for patients who require maintenance therapy for their chronic, often disabling mental health conditions, this weight gain and metabolic dysfunction can become problematic.[1] Often it is not feasible for patients to switch APs because of a side effect profile if the medication is one of their few effective options.

The major issue is that these antipsychotics are long-term treatment for a life-long chronic condition. But what would happen if the thing that was keeping patient

stable, prosperous, and able to work and provide was causing a metabolic dysfunction?

Purpose

This study seeks to determine the metabolic adverse effect of weight gain in the pharmacotherapy of antipsychotics in adults and options how to reduce them.

RESEARCH OBJECTIVES

- To provide summary on the use of antipsychotics, their metabolic side effects, and which,if any, should be used in patient populations to minimize the development of metabolic adverse effect.
- To find novel adjunct therapies that can be used with antipsychotics to minimize, negate, or reverse associated weight gain and metabolic complications.

MATERIALS AND METHODS

Data Sources

Our data is sourced from PUBMED and we utilized the Free Full Text to find our full sources. We used keywords like "antipsychotic", "weight gain", "side effects", "efficacy", "metabolic", "diabetes type 2", "obesity", "dyslipidemia", and "weight loss" with the specifier "adults".

Eligibility Criteria

A PUBMED search was done to accumulate sources about antipsychotics, their effectiveness, their side effect profiles, as well as specific research done into the metabolic complications of each antipsychotic use. These include, and in this study are limited to,

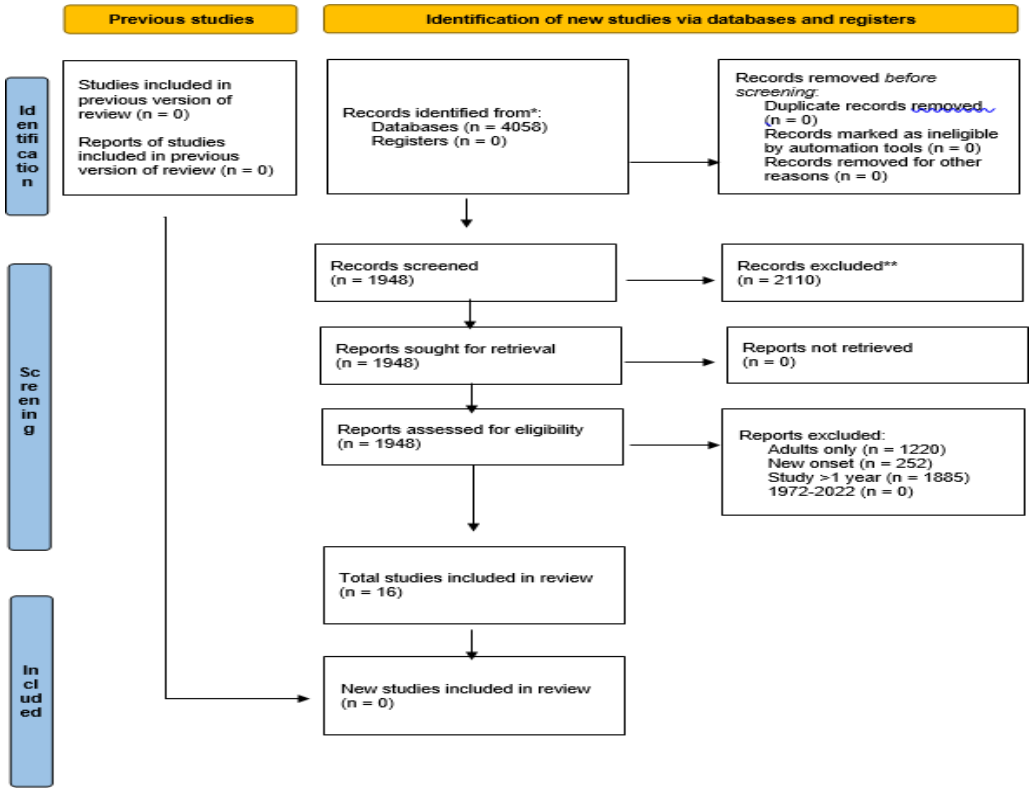
1. weight gain
2. insulin resistance
3. development of type 2 diabetes
4. development of morbid obesity

There are exclusions to our criteria and they are the following

1. We only included studies that are done on adults (18-65)
2. We only included those adults who did not specifically have one of the aforementioned metabolic disorders diagnosed prior to antipsychotic usage.
3. We did not consider it "long-term" weight gain unless it has been studied for a year.
4. We only included articles written in the last 50 years (1972-2022)

Extraction of Sources

Extraction was done by online search filters done on PubMed.gov. The extraction tool, PRISMA, is seen below in Figure 2. This graphical representation of the exclusion criteria needed to extract our sources shows the methods with which we sourced ourtexts.



Statistical Analysis

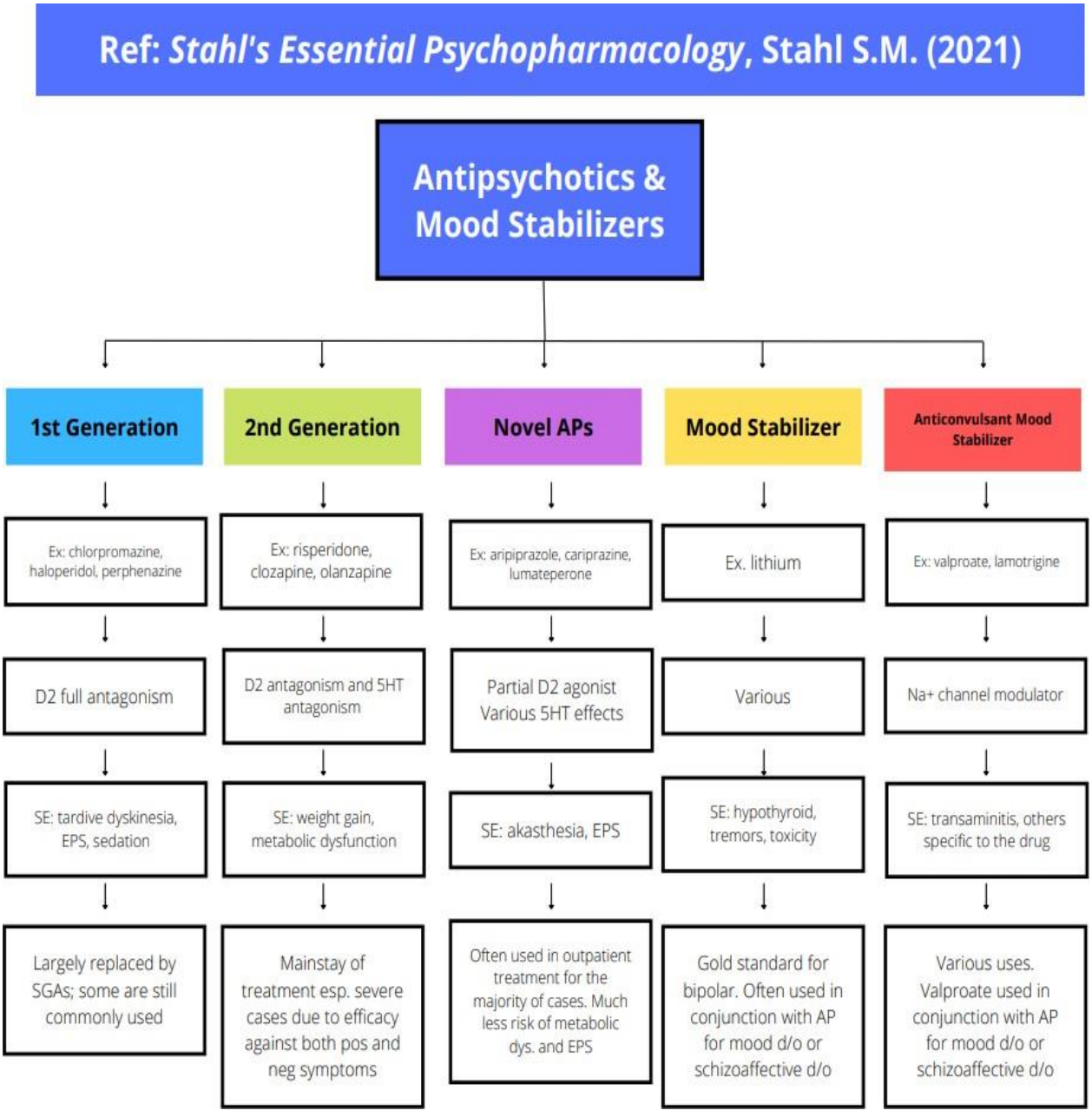
Statistical analysis included correlation between certain antipsychotics and weight gain. We then separated the statistical significance of these studies and qualified each antipsychotic into groups of: strong association, mildly strong association, mildly weak association, weak association, and no association based on keywords in each study. Specifically, "strong association", "weak

association", and "no association" must be accompanied by qualifying words that describe a "…strong predilection to persuade the reader into believing that this association [or lack thereof] is more than statistically significant in either positive or negative correlation." Using each qualifier, we determined the level of strength or absence of an association between the two variables. Finally, in the conclusion we separated the data into a binary of either "strong association" [between agents and metabolic side effects] or "not strong association". This was tailored to provide summary of which antipsychotics clearly demonstrate a strong association dyslipidemia between their usage and metabolic side effects with a low chance for false positives. In this sense, we explained that though there are some antipsychotics who ended up in "not strong association", they are not without risk; the goal of this study was instead to highlight how clearly those who ended up in "strong association" must be taken seriously and with caution in terms of metabolic side effects.

LITERATURE REVIEW & RESULTS

Which antipsychotics cause the most weight gain and metabolic dysfunction?

Figure 1 below explains the differences between the generations of antipsychotics, mood stabilizers such as lithium, and anticonvulsant mood stabilizers – all used in the treatment of severe mood instability accompanied with psychosis.



In 1952, a new medication was synthesized in laboratories in France. Known as Largactil, it had a wide range of pharmacologic activity: gangliolytic, adrenolytic, antipyretic, anti-shock, anticonvulsant,

antiemetic among other attributes.[3] Called chlorpromazine, and later widely marketed as Thorazine in the US, it began the revolution of what we now know as antipsychotic pharmacotherapy. A new wave of opportunity hit the Western world and the invention of these first-generation antipsychotics would revolutionize the treatment of psychosis.

Alongside these promising treatments were their more insidious adverse effects. A new syndrome of neurologic side effects called extrapyramidal symptoms, or EPS, became the norm in many patients. Tremors and motor "shakes" characterized these symptoms.[4] Treatment was to reduce the amount of antipsychotic used or add an anticholinergic agent like trihexyphenidyl or benztropine to reduce the EPS.[2] Sedation was heavy in these first-generation antipsychotics as well, though therapeutically it did not cause one to lose consciousness.[3]

Soon after came the introduction of clozapine, the first second-generation antipsychotic (SGA). With increased serotonin activity, clozapine began to treat positive and negative symptoms of schizophrenia.[2] This was new to the spectrum of the conventional "first- generation" antipsychotics, and so were some of the side effects. Increased histaminergic and antimuscarinic action led to less EPS but more sedation and 5HT action led to polyphagia and increased caloric intake.[2] With the introduction of olanzapine, quetiapine, and risperidone, SGAs saw increased success and usefulness in patients. Caution warnings came to physicians that told them to calculate BMI before and during treatment to mitigate weight gain.[2] Considering the effectiveness of these medications on positive and negative symptoms, and their reduced chance of EPS and tardive dyskinesia, evading side effects seemed unlikely.[2] These medications began being used for mood stabilization in bipolar I and II patients as well, so the patient population that used these medications was growing by a large amount.

As these drugs grew in popularity, so did their use in the general population. Symbyax, a combination drug of olanzapine and fluoxetine, became approved for bipolar depression as well as major depression in 2003.[2]

The novel antipsychotics aripiprazole and brexpiprazole came next. They allowed for a more favorable side effect profile in terms of weight gain, and became more prevalent in the population[2]. They were originally indicated for adjunct treatment for major depression in which one antidepressant was not working to full effect.[2] As these medications became more prevalent in usage in the population, their more favorable side effect profile became a huge player in terms of minimizing weight gain as newer drugs were developed. But the gold standard for many of these treatments remained SGAs and as such, the use of SGAs, and their metabolic side effects, needs to be reassessed in the general patient population.

According to the literature review, weight gain is common in many antipsychotics, but in the cases of clozapine, olanzapine, and other SGAs it can be problematic.[1] At 10 weeks, those on clozapine gained 4.45 kg, olanzapine 4.15 kg, chlorpromazine 2.58 kg, quetiapine 2.18 kg, risperidone 2.10 kg, and ziprasidone 0.04 kg. Statistically significant weight gain occurs in studies at 7%[1] Olanzapine, quetiapine, and risperidone gained 14-27% at 6-8 weeks and as high as 40% by 3.5 years.[1] A landmark study in 1988 showed clozapine superior in efficacy to chlorpromazine in schizophrenic patients resistant to high dosages of haloperidol and to have none of the neurologic side effects of older agents.[1] Though dopamine antagonism has been shown to reduce psychotic side effects, it is not the only mechanism for antipsychotic activity.[1] Mechanisms involved include sedation and inactivity as well as central blockade of H1 and 5HT2C as the increased appetite happens at the 5H2C receptor[1]. Research shows little advantage in measures of efficacy and tolerability in SGAs over conventional agents, and higher doses were poorly tolerated.[1] Efficacy of newer agents is variable due to dropouts and tolerability of these agents. Therefore, we can conclude that side effects of these SGA agents (overall; not separately as agents) are comparable, if not worse, than conventional agents (such as haloperidol or perphenazine) depending, of course, on the needs of each patient.

Figure 2 demonstrates that according to the literature review changes in weight were not found with ziprasidone (SGAs), haloperidol (FGAs), fluphenazine (FGAs), aripiprazole (novel APs), lurasidone (SGAs), cariprazine (novel APs), amisulpride (SGAs), or flupenthixol (FGAs) when compared to placebo.[5] There is evidence of weight gain with brexpiprazole (novel APs), risperidone (SGAs), paliperidone (SGAs), quetiapine (SGAs), iloperidone (SGAs), sertindole (SGAs), olanzapine (SGAs), zotepine (SGAs), and clozapine (SGAs), with haloperidol (FGAs) being the best and clozapine (SGAs) being the worst.[5]

	Weight Gain					
	Strong Association	Mildly Strong	Mildly Weak	Weak Association	No Association	Notes
Gardner 2005	Clozapine, olanzapine	Quetiapine		Aripiprazole, ziprasidone		
Bernardo 2021		Olanzapine vs. lithium, Quetiapine vs. lithium				
Pilinger 2020			brexpiprazole, risperidone paliperidone, quetiapine, iloperidone, sertindole, olanzapine, zotepine, clozapine		Ziprasidone, haloperidol, fluphenazine, aripiprazole, lurasidone, cariprazine, amisulpride, flupenthixol	
Lieberman 2005	olanzapine vs other APs					
Lee 2011		LEPR polymorphisms esp. w/ olanzapine, clozapine				
Edinoff 2020					Lumateperone	Lumateperone showed "statistically significant" improvement vs. maintenance AP
Leucht 2017	Olanzapine, iloperidone, quetiapine	risperidone, paliperidone	brexpiprazole, aripiprazole, haloperidol	lurasidone, ziprasidone		

Figure 2: Association between APs and Weight Gain.

It should be known that these results should be taken in the context of studies that show that patients with schizophrenia who take antipsychotic therapy, especially clozapine, have lower all-cause cardiac mortality rates compared with patients who do not receive antipsychotic treatment.[5] And although symptomatic improvements with these agents leads to metabolic dysfunction, cardiovascular mortality improves with treatments that in turn cause worse metabolic outcomes.[5] This may be due to increased self-care and physical activity which might offset the side effects of the drugs.[5] 74% of patients discontinued the medication before 18 months in the Lieberman trial.[6] The medications were olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone. The times of discontinuation was longer for olanzapine, but the discontinuation because of intolerable side effects was worse for olanzapine, which was associated more with discontinuation for weight gain/metabolic issues.[6]

The use of antipsychotics and lipid metabolism

Figure 3 reflects that in terms of dyslipidemia, clozapine showed an increase in risk; risperidone, olanzapine, quetiapine, and ziprasidone showed mixed results while aripiprazole showed no increased risk.[7] Olanzapine was associated with greater weight gain and an increase in glucose measurement and lipid metabolism.[6] In terms of fasting glucose, in an analysis lasting 6 weeks, clozapine and olanzapine were associated with greater changes in fasting glucose and ziprasidone was associated with the lowest increase.[7] Clozapine, olanzapine and quetiapine were associated with increases in total cholesterol and triglycerides, but risperidone, ziprasidone, and aripiprazole were not associated with these increases.[7] While there are relevant differences between these meds, none of these drugs are fully free of the risk of metabolic disturbances. There was lacking evidence on novel antipsychotics as well as long-acting injectables.[7]

	Dyslipidemia					
	Strong Association	Mildly Strong	Mildly Weak	Weak Association	No Association	Mixed
Bernardo 2021	Clozapine	SGAs overall vs. general population but not vs. FGAs			Aripiprazole	Risperidone, olanzapine, quetiapine, ziprasidone
Piliinger 2020		Quetiapine, olanzapine, clozapine (total cholesterol)			sertindole, ziprasidone, lurasidone, brexpiprazole, aripiprazole, risperidone, paliperidone, haloperidol, amisulpride (total cholesterol)	
Lieberman 2005		olanzapine vs other APs				

Figure 3: Association between APs and Dyslipidemia.

The use of antipsychotics and development of type 2 diabetes mellitus

Type 2 diabetes can be described as hyperglycemia, insulin resistance, impairment in insulin secretion and possible long term complications among many other pathophysiological determinants of disease.[8] While the pathogenesis is not well understood, genetics, obesity, and increased age play a key role.[8] In the last 25 years, obesity has doubled in the USA and increased 3 to 5 times in Asian countries.[8] A direct relationship between BMI and diabetes has been confirmed.[8] An increase of insulin resistance (IR) actually has a toxic effect on islet cells and impair the function of the insulin receptor, creating down regulation.[8] IR also causes an increase in free fatty acids which causes more IR on hepatic, muscular, and adipose tissue and contribute to a chronic inflammatory status.[8]

The pathogenesis of diabetes and obesity are similar, and share pathways of oxidative stress, pro-thrombotic and pro-inflammatory patterns.[9] Fat begins to accumulate in organs that are not specialized in lipid storage, like the endothelium, the liver, and skeletal muscle inducing cardiovascular diseases, cerebrovascular diseases.[9] Studiesshow that in obesity, adipose tissue gives off high levels of circulating non-esterified fatty acids, hormones, and pro-inflammatory cytokines.[9] Through many different pathways, this leads to a reduction in insulin receptor signaling and glucose transport.[9] It can also lead to dysregulation of the circadian clock, disrupting feeding, promoting inactivity, enhancing hyperphagia, hyperlipidemia, hyperglycemia, and hypoinsulinemia.[9] Some of the antipsychotics we reviewed disrupt eating and enhance hyperphagia so this is of utmost importance.[2]

Most studies came to the conclusion that clozapine and olanzapine were associated with an increased likelihood of developing diabetes (Figure 5).[7] Olanzapine runs a 3.4x risk of hyperlipidemia and 4.2 risk of diabetes relative to conventional antipsychotics.[1] The risks were similar with clozapine, and clozapine and olanzapine seem to be the worst culprits.[1] Lowest risk comes with aripiprazole (novel Aps), risperidone (SGAs), and ziprasidone (SGAs) as well as haloperidol (FGAs) (high potency APs).[1] The results for risperidone and quetiapine were mixed, and the results for ziprasidone and aripiprazole showed to not be associated with the occurrence of diabetes.[7]

	Development of type 2 diabetes mellitus					
	Strong Association	Mildly Strong	Mildly Weak	Weak Association	No Association	Notes
Gardner 2005		Clozapine, olanzapine	Aripiprazole, quetiapine risperidone, ziprasidone			
Bernardo 2021		Olanzapine, SGAs as a whole			Risperidone, Quetiapine, ziprasidone	
Edinoff 2020		Olanzapine				Lumateperone showed "statistically significant" improvement vs. maintenance AP

Figure 5: Association between APs and Development of type 2 diabetes mellitus.

Patients with schizophrenia are at a 3-fold higher risk of obesity and 2-to-4-fold higher risk of type 2 diabetes mellitus.[10] This may be due to the fact that SGAs impair the secretion of insulin and glucagon in the pancreas[10]. Olanzapine, clozapine, and chlorpromazine (FGAs) can impair insulin signaling in liver and skeletal muscle, as well as interfere with glucose transport, glycogen synthesis, gluconeogenesis, and insulin resistance.[10] Differences in polymorphisms in the population explain different adverse effects in patients with schizophrenia especially with metabolic side effects of SGAs.[10]

For changes in fasting glucose, there was no strong evidence (Figure 5) for a change with amisulpride (SGAs), asenapine (SGAs), sertindole (SGAs), ziprasidone (SGAs), brexpiprazole (novel APs), quetiapine (SGAs), risperidone (SGAs), paliperidone (SGAs), aripiprazole (novel APs), haloperidol (FGAs), cariprazine (novel APs), and iloperidone (SGAs).[5] Fasting glucose actually reduced with lurasidone (SGAs)[5]. It increased with olanzapine (SGAs), zotepine (SGAs), and clozapine (SGAs)[5]. Ranking the 16 antipsychotics, lurasidone (SGAs) is the best and clozapine (SGAs) as the worst.[5] Olanzapine (SGAs) and clozapine (SGAs) exhibited the worst profiles and aripiprazole (novel APs), brexpiprazole (novel APs), cariprazine (novel APs), lurasidone (SGAs), and ziprasidone (SGAs) showed the most benign profiles.[5]

	Insulin Resistance					
	Strong Association	Mildly Strong	Mildly Weak	Weak Association	No Association	Notes
					amisulpride, asenapine, sertindole, ziprasidone, brexpiprazole, quetiapine, risperidone, paliperidone, aripiprazole, haloperidol, cariprazine, iloperidone	
Pilinger 2020		olanzapine, zotepine, clozapine (fasting glucose)			(fasting glucose)	Glusoce concentrations reduced with lurasidone
Grajales 2019		Haloperidol, sulpride, olanzapine, clozapine				
Maayan 2010						Metformin and rosaglitazone "showed significant" benefit for blood glucose/insulin levels
Wei 2020		APs in general, sulpride prolong hyperinsulinemia which desensitizes tissues and contributes to insulin resistance				

***Figure 5*: Association between APs and Insulin Resistance.**

Management of antipsychotic-induced weight gain and options on how to reduce theside effects

Metformin is a medication that enhances the action of insulin in the liver, decreasing the rate of hepatic glucose production.[11] It increases peripheral utilization of glucose and suppresses appetite.[11] Treatment with metformin had a significant weight loss (-3.27 kg) compared to placebo, approximately 5% of body weight.[11] Metformin also resulted in significantly more reduction in BMI than placebo in patients treated with antipsychotics (-1.13 kg/m^2).[11] However, metformin did not result in a significant reduction in fasting blood sugar compared to placebo.[11]

Excessive body weight gain is reported in about 50% of patients treated with a variety of antipsychotics.[12] Empagliflozin, trade name Jardiance, is similar to metformin but with less gastrointestinal side effects, so it could be a possible replacement for metformin in the treatment of excessive body weight gain.[12] Empaglaflozin is an antidiabetic medication used to improve glucose control, and female rats showed body weight gain compared to control, but males did not.[12] In the female rats, empagliflozin showed reduced body weight gain compared to control + olanzapine.[12]

Genetic variations associated with satiety are recognized as contributors to antipsychotic-induced weight gain.[13] Polymorphisms in the leptin gene are potential mechanisms for this weight gain and future pharmacologic intervention.[13] Antipsychotic associated weight gain is believed to stop after the first year of treatment.[13] 5H2C, H1, and D2 are partially responsible for the weight gain.[13]

BGP-15 was able to counteract insulin resistance and weight gain caused byantipsychotic agents in rats when rosiglitazone and metformin were not effective in their specified doses.[14]

Switching antipsychotics may sometimes help. Lumateperone is a partial agonist at the presynaptic receptor and an antagonist at the postsynaptic receptor.[15] There is reduced weight gain, hyperglycemia, and dyslipidemia compared to other antipsychotics.[15] Adequate diet and exercise can control the weight gain in patient receiving atypical antipsychotics. Efficacy of the antipsychotics against negative symptoms improves motivation and could be a causation for a want to lose weight. After patients realized the positive effects of their diet on blood pressure, blood sugar levels, and body weight, they were more likely to make an effort to change their daily habits.[16] Interventions include using diets that do not increase appetite despite calorie restriction, countering thirst as an anticholinergic side effect, discouraging cannabis use and adding metformin as a behavioral intervention.[17] Evidence for the efficacy of these strategies remains limited.[17]

DISCUSSION

On the parameters of weight gain, insulin resistance, development of type 2 diabetes, development of morbid obesity, and dyslipidemia, the worst offenders were clozapine andolanzapine (Figure 6).

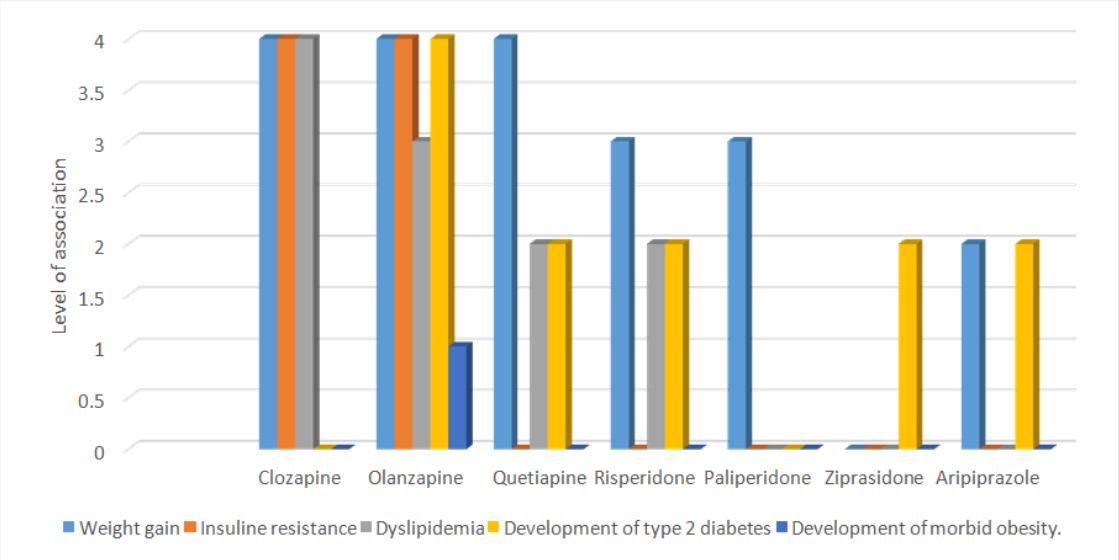


Figure 6: Level of association between the use of antipsychotic drugs and their metabolic side effects.

(0- no association, 1- weak association, 2- mildly weak association, 3-mildly strong association, 4-strong association) Note: Novel antipsychotics (lumateperone, brexpiprazole, cariprazine, etc) that did not score are not included on this graph

Clozapine had a "strong association" with three parameters: weight gain, insulin resistance, and dyslipidemia, while having mixed results with a fourth parameter: development of type 2 diabetes. Olanzapine had a strong association with four parameters: weight gain, insulin resistance, development of type 2 diabetes, and dyslipidemia, with a notable, but weak association in a fifth parameter: development of morbid obesity. The mixed-result antipsychotics, which are the ones that scored on at least one parameter as strongly associated with a disorder, are quetiapine, risperidone, and paliperidone (Figure 6). Quetiapine had a strong association between its use, weight gain, and dyslipidemia. Risperidone and paliperidone had a mixed/mildly strong association between each of them and weight gain. By binarily creating outcomes (strong association vs. not strong association) we are able to discern that these three antipsychotics have more than just a statistically significant increase in weight gain (and dyslipidemia for quetiapine). These strong associations prove that there is significant data to show that weight gain and dyslipidemia are problematic for these medications (quetiapine,risperidone, and paliperidone vs. quetiapine). Among the antipsychotics that did not show a strong association between weight gain, insulin resistance, development of type 2 diabetes, development of morbid obesity, and dyslipidemia are aripiprazole, ziprasidone, amisulpride, asenapine, sertindole, brexpiprazole, haloperidol, cariprazine, lurasidone, and iloperidone (Figure 6). It is important to note that in our binary of outcomes, these medications did not show a strong association, but that does not mean that they are free of side effects in these specified parameters. It is also important to note that genetic and diet factors play large roles in weight gain and subsequently development of metabolic disorders. While these medications do not have a strong association, it is always important for providers to obtain a full medical history of these metabolic disorders before attempting to prescribe any antipsychotics, and to understand the clinical data that is more specific to each of these medications than this analysis alone.

In terms of weight lost while on antipsychotics, we have four strong associations: switching to a partial agonist, using metformin, having a low-calorie monitored diet, and nutritional education with supportive care. For aripiprazole, brexpiprazole, cariprazine, and lumateperone, which are already partial agonists, this first point is moot. However, this may show that using a partial agonist first before a SGA/FGA may reduce the weight that is gained. Metformin has been shown to cause statistically significant weight loss – around 3 kg (Maayan 2010). This is important as is, and should be studied in the long term (approximately over one year) as well as the risk of developing insulin resistance and type 2 diabetes in patients who take it proactively for weight loss, weight minimization, and as treatment for prediabetes or type 2 diabetes. The data on the long term loss is not known. However, it is clear from this study that the weight lost is still a percentage of the weight gained in total; therefore, it is more useful to prevent the weight gain than try to lose it after the fact.

Another interesting finding was that diet change, specifically a low-calorie monitored diet with nutritional education and supportive care, vastly minimized weight gain over a 12- and 18-month period[16]. This is also extremely important in terms of minimizing the weight that is gained while on the antipsychotic. Reducing the weight before it is gained will lower the chance of developing metabolic disorders due to obesity. While genetics still have a play in developing these metabolic disorders, this method of weight minimization lowers the

risk by lowering the weight gained.

CONCLUSION

In conclusion, there seem to be two separated subcategories of these antipsychotics: those whose excellent effectiveness warrants usage regardless of metabolic side effects, and those whose demonstrated effectiveness and more favorable side effect profiles warrants usage in mainstream treatment of psychosis and mood stabilization. The former includes olanzapine and clozapine, both of which carry high risk of metabolic side effects (among other side effects), and the latter includes most SGAs and novel antipsychotics, such as risperidone, paliperidone, quetiapine, ziprasidone, lurasidone, aripiprazole, brexpiprazole, cariprazine, and lumateperone.

Following our research objectives, using the methods of switching to a partial agonist (novel APs), using metformin, having a low-calorie monitored diet, nutritional education, and supportive care allows patients to minimize and reduce weight gain and metabolic complications.Keeping in mind the metabolic side effects of antipsychotics, we can give our patients the best quality of life possible in both reduction of symptoms and minimization of future disease states such as type 2 diabetes, obesity, and cardiometabolic dysfunction. With the advent of the class of novel antipsychotics, which are often partial agonists or combination dopamine-serotonin modulators, we hope to find methods to treat psychosis and mood instability with minimal metabolic effects in the future. Until then, the SGAs and novel antipsychotics in this study remain the gold standard for the treatment of psychosis and mood instability.

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BIBLIOGRAPHY

1. Gardner, D. M., Baldessarini, R. J., & Waraich, P. Modern antipsychotic drugs: a critical overview. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne*, 2005; *172*(13): 1703–1711. https://doi.org/10.1503/cmaj.1041064.
2. Stahl S. M. Grady M. M. & Muntner N. Stahl's essential psychopharmacology: prescriber's guide (Seventh). Cambridge University Press. Retrieved August 29 2022 from https://doi.org/10.1017/9781108921275, 2021.
3. Mendelson W.B. The curious history of medicines in psychiatry. Pythagoras Press, 2020.
4. Ward KM, Citrome L. Antipsychotic-Related Movement Disorders: Drug-Induced Parkinsonism vs. Tardive Dyskinesia-Key Differences in Pathophysiology and Clinical Management. Neurol Ther, 2018 Dec; 7(2): 233-248.
5. Pillinger, T., McCutcheon, R. A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., Beck, K., Natesan, S., Efthimiou, O., Cipriani, A., & Howes, O. D. 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. *The lancet. Psychiatry*, 2020; *7*(1): 64–77. https://doi.org/10.1016/S2215-0366(19)30416-X.
6. Lieberman, J. A., Stroup, T. S., McEvoy, J. P., Swartz, M. S., Rosenheck, R. A., Perkins, D. O., Keefe, R. S., Davis, S. M., Davis, C. E., Lebowitz, B. D., Severe, J., Hsiao, J. K., & Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *The New England journal of medicine*, 2005; *353*(12): 1209–1223. https://doi.org/10.1056/NEJMoa051688.
7. Bernardo M, Rico-Villademoros F, García-Rizo C, Rojo R, Gómez-Huelgas R. Real- World Data on the Adverse Metabolic Effects of Second-Generation Antipsychotics and Their Potential Determinants in Adult Patients: A Systematic Review of Population-Based Studies. Adv Ther, 2021 May; 38(5): 2491-2512. doi: 10.1007/s12325-021-01689-8. Epub 2021 Apr 7. PMID: 33826090; PMCID: PMC8107077.
8. Riobó Serván P. Obesity and diabetes. *Nutricion hospitalaria*, 2013; *28(5):* 138–143. https://doi.org/10.3305/nh.2013.28.sup5.6929.
9. La Sala, L., & Pontiroli, A. E. Prevention of Diabetes and Cardiovascular Disease in Obesity. *International journal of molecular sciences*, 2020; *21*(21): 8178. https://doi.org/10.3390/ijms21218178.
10. Grajales, D., Ferreira, V., & Valverde, Á. M. Second-Generation Antipsychotics and Dysregulation of Glucose Metabolism: Beyond Weight Gain. *Cells*, 2019; *8*(11): 1336. https://doi.org/10.3390/cells8111336.
11. De Silva, V. A., 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*, 2016; *16*(1): 341. https://doi.org/10.1186/s12888-016-1049-5
12. Ashraf, G. M., Alghamdi, B. S., Alshehri, F. S., Alam, M. Z., Tayeb, H. O., & Tarazi, F. I. Empagliflozin Effectively Attenuates Olanzapine-Induced Body Weight Gain in Female Wistar Rats. *Frontiers in pharmacology*, 2021; *12*: 578716. https://doi.org/10.3389/fphar.2021.578716
13. Lee, A. K., & Bishop, J. R. Pharmacogenetics of leptin in antipsychotic-associated weight gain and obesity-related complications. *Pharmacogenomics*,

2011; *12*(7): 999–1016. https://doi.org/10.2217 /pgs.11.45.

14. Literati-Nagy, Z., Tory, K., Literáti-Nagy, B., Kolonics, A., Vígh, L., Jr, Vígh, L., Mandl, J., & Szilvássy, Z. A novel insulin sensitizer drug candidate-BGP-15-can prevent metabolic side effects of atypical antipsychotics. *Pathology oncology research: POR*, 2012; *18*(4): 1071–1076. https://doi.org/10.1007/s12253-012-9546-4.
15. Edinoff, A., Wu, N., deBoisblanc, C., Feltner, C. O., Norder, M., Tzoneva, V., Kaye, A. M., Cornett, E. M., Kaye, A. D., Viswanath, O., & Urits, I. Lumateperone for the Treatment of Schizophrenia. *Psychopharmacology bulletin*, 2020; *50*(4): 32–59.
16. Aquila, R., & Emanuel, M. Interventions for Weight Gain in Adults Treated With Novel Antipsychotics. *Primary care companion to the Journal of clinical psychiatry*, 2000; *2*(1): 20– 23. https://doi.org/10.4088 /pcc.v02n0106.
17. Werneke, U., Taylor, D., & Sanders, T. A. Behavioral interventions for antipsychotic induced appetite changes. *Current psychiatry reports*, 2013; *15*(3): 347. https://doi.org/10.1007/s11920-012-0347-y.