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Review Article

Metabolic, neurological and endocrine safety profiles of atypical antipsychotics: focus on quetiapine, olanzapine and risperidone: an updated review

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ABSTRACT

The atypical antipsychotics (second-generation antipsychotics, SGAs) are commonly used in the treatment of schizophrenia, bipolar disorder and other mental illnesses because they have fewer extrapyramidal side effects than first-generation agents. Nonetheless, their growing utilization has brought to light serious safety issues, especially in metabolic, neurological and endocrine spheres. This review aims at comparing three widely used SGAs, which are Quetiapine, Olanzapine, and Risperidone, with comparison in their pharmacological and safety profiles. Olanzapine presents the greatest metabolic risk often leading to weight gain, dyslipidaemia and insulin resistance. Quetiapine exhibits less sensitive metabolic responses accompanied by reduced pyramidal and prolactin increase rates at low off-label doses but is risky. Risperidone is an effective treatment of psychotic and bipolar disorders, but it is closely linked to hyperprolactinemia and dose-related extrapyramidal symptoms. The review also points out that there is now emerging evidence on changes in gut microbiota and changes in pharmacogenetic variations that affect individual response to drug and drug adverse effects. In general, the results highlight the importance of identifying unique antipsychotic treatment, regular checks of metabolic, endocrine indicators to ensure optimal safety and treatment. It is recommendable that future studies concentrate on genetic predictors, new formulations (e.g. olanzapine-samidorphan), and microbiome-targeted interventions as a way of reducing adverse effects.

Keywords: Endocrine effects, Metabolic syndrome, Microbiota, Neurological safety, Olanzapine, Quetiapine, Risperidone

INTRODUCTION

Atypical (second-generation) antipsychotics (SGAs) are the diverse group of drugs that block the dopamine and the serotonin receptors. They were developed to be more effective for treating the psychotic symptoms while lowering the chances of the severe movement side effects linked to the first-generation medications. SGAs block the dopamine D2 receptors (or partially activate them) and also have broader effects on serotonin receptors, especially 5-HT2A. This combination helps improve negative symptoms and cognitive outcomes in some patients, resulting in a different set of side effects compared to older antipsychotics.[1] Beyond schizophrenia, atypical antipsychotics are now used clinically to treat bipolar disorder, depression, behavioral disorders, and off-label conditions like anxiety and insomnia. This has increased exposure in a variety of populations and raised drug- and population-specific safety concerns.[2] The three main areas of safety concern for SGAs are endocrine, neurological (movement and sedation), and metabolic. Clinically significant weight gain, dyslipidemia, insulin resistance,

and new-onset diabetes mellitus are examples of metabolic side effects that differ significantly between medications (olanzapine and clozapine pose the highest risk, while quetiapine and risperidone pose intermediate risk). Olanzapine has been repeatedly found to be one of the medications with the highest risk of weight gain and metabolic syndrome in extensive meta-analyses and comparative reviews.[1] Extrapyramidal symptoms (parkinsonism, akathisia, dystonia) and sedation are examples of neurological side effects; although the risk is typically lower than with first-generation antipsychotics, it is still clinically significant, especially when dose is increased or in susceptible populations. Sedation and movement disorders are common in umbrella reviews of the negative effects of antipsychotics.[3] Risperidone has been shown to have effects on prolactin, insulin, and leptin particularly in children and adolescents. Endocrine effects are dominated by hyperprolactinemia, particularly with risperidone and paliperidone, which can result in amenorrhea, galactorrhea, sexual dysfunction, and long-term bone health issues.[4] The mechanisms underlying metabolic harms are complex and include mitochondrial/energy-metabolism pathways, effects on appetite/energy balance, direct peripheral effects on insulin sensitivity, and receptor profiles (H1, 5-HT2C, M3 antagonism). These processes aid in the explanation of why various substances have varying metabolic liabilities and why even small dosages or off-label use such as quetiapine for insomnia, may not be metabolically neutral.[5] Thus the present review was designed to check the metabolic, neurological and endocrine safety of atypical antipsychotics, risperidone, olanzapine and quetiapine.

RATIONALE FOR FOCUSING ON QUETIAPINE, OLANZAPINE, AND RISPERIDONE

In recent years, these drugs have become the drugs of choice for acute psychoses, management of schizophrenia, bipolar disorder, and related psychiatric conditions. They are becoming the treatment of choice for patients during their first psychotic break and are indicated throughout their lifetime.[6,7] Despite belonging to the same therapeutic class, these agents exhibit distinct pharmacological profiles, particularly in terms of receptor-binding affinity, which translates into different safety and tolerability patterns. Olanzapine is highly effective but strongly associated with metabolic disturbances, including significant weight gain, dyslipidemia, and insulin resistance.[7] Quetiapine has comparatively lower risk of extrapyramidal symptoms (EPS) and prolactin elevation, but still carries moderate metabolic risks.[8] Risperidone, also linked to hyperprolactinemia and higher rates of EPS, especially at higher doses.[9] Now from the reported safety concerns a questions arises are these drugs safer to take or not. Given these contrasting safety concerns, a focused evaluation of their metabolic, neurological, and endocrine profiles is clinically relevant. Such an analysis helps clinicians to define treatment to individual patient needs, and mitigate long-term complications that often affect adherence and overall quality of life. Thus, the present review was carried out to with the following objectives.

The objectives of this study are to investigate and elucidate the mechanism of action of atypical antipsychotic agents. It aims to compare the metabolic, neurological, and endocrine safety profiles of three specific atypical antipsychotics, as well as to assess their impact on gut microbiota. Additionally, the study seeks to identify the adverse events and overall drug profiles associated with these agents. Finally, it includes a review of pharmacogenetic testing relevant to the use of antipsychotic medications, providing insights into personalized treatment strategies.

Quetiapine

Quetiapine is the second generation (atypical) antipsychotic, with lower affinity to dopamine D2 receptors and increased activity at adrenergic, histamine (H1), and serotonin (5-HT2A) receptors. It exists in immediate and extended-release oral preparations and these properties, which produce antipsychotic, mood-stabilizing, and sedative effects, warrant its approved uses in schizophrenia, as a treatment of bipolar disorder (mania and bipolar depression), and as an adjuvant therapy in major depressive disorder. Due to its sedative properties and seemingly reduced short-term risk of hyperprolactinemia, a quetiapine is often applied in clinical practice. It is however not metabolically neutral; many reviews and meta-analyses are showing dose related weight gain and adverse effects on lipids and glycaemia, especially when used off-label in low doses as a sedative or tranquilizer. Routine monitoring of metabolism is therefore recommended.[10]

Olanzapine

Olanzapine is an atypical antipsychotic, yet its high affinity rates to several receptors (D2, 5-HT2A/2C, H1 and muscarinic M3 among others) is what makes it a strong antipsychotic agent with strong sedative and appetite-stimulating activity. It is acceptable in schizophrenia and bipolar I disorder (mania/mixed episodes) and it is also used together with fluoxetine in bipolar depression and treatment-resistant depression in certain jurisdictions. Olanzapine has always been rated as one of the most weight-gaining antipsychotics, dyslipidemia and insulin resistance -inducing drugs - its impact is so significant that some guideline groups have recommended a contraindication against first-episode psychosis. Recent compound formulations and combination therapies (e.g. olanzapine + samidorphan) have been designed to help prevent weight gain, although metabolic risk is the greatest clinical issue with olanzapine.[1] Olanzapine is always treated with serious metabolic side effects like weight gain, dyslipidemia, and poor tolerance to glucose. It has been noted to be among the antipsychotics with the highest metabolic risk in comparative meta-analyses and guidelines, resulting in the recommendation of a specific

caution of patient selection and close cardiometabolic parameter observation during treatment.[11]

Risperidone

Risperidone is an atypical antipsychotic, whose D2 and 5-HT2A antagonism is relatively higher than some other SGAs; it is used to treat schizophrenia, bipolar I disorder (acute mania), and to treat irritability in autism, and comes in both oral and long-acting injectable dosage forms. Risperidone has strong antipsychotic performance, but has a well-documented risk of hyperprolactinaemia (better than quetiapine and most SGAs), which may lead to amenorrhea, galactorrhea and sexual dysfunction; risperidone has moderate metabolic adverse effects, and also results in extrapyramidal symptoms at higher doses, which are moderate in severity. The recent depot formulations and long-acting injectables are expected to increase the compliance and stabilize plasma exposure using both endocrine (prolactin) and metabolic control is essential.[12]

APPROVAL AND INDICATIONS FOR THE USE OF QUETIAPINE, OLANZAPINE, AND RISPERIDONE

Risperidone was the first of three atypical antipsychotics to receive U.S.FDA approval in 1993, followed by olanzapine in 1996, and quetiapine in 1997.[13,14]

Indications for the use of risperidone

This was the first-line antipsychotic, given nearly every patient having psychotic illness. The drug is approved for schizophrenia treatment in adolescents as well as for autistic spectrum disorders (ASD) in children by FDA. Indications for use are as follows.[15]

Atypical antipsychotic agents are indicated for both the acute and maintenance treatment of schizophrenia and psychosis. They are also used in managing schizophrenia and psychotic symptoms in adolescents. In addition, these agents are effective in the treatment of bipolar mania in adults, as well as in children and adolescents. Furthermore, they are employed in addressing irritability associated with autism in paediatric and adolescent populations.

Indications for the use of olanzapine

This medication has approved by FDA for schizophrenia if the patient >13years of age (not approved for age <13years) and in combination with fluoxetine over the age of 10 years (combination is not approved for age <10 years) and bipolar disorder, including mixed or manic episodes.[16,17] Indications for use are as follows: Atypical antipsychotic agents are indicated for the treatment of schizophrenia in patients over 13 years of age. They are also used for managing acute manic or mixed episodes of bipolar disorder. Additionally, certain drugs are approved for use in combination with fluoxetine for patients experiencing depressive episodes associated with bipolar disorder type 1 and for treatment-resistant depression. The FDA has also approved the combination of these agents with samidorphan to mitigate olanzapine-induced weight gain in patients with schizophrenia and bipolar I disorder.

Indications for the use of quetiapine,

This drug is FDA-approved for the treatment of schizophrenia, acute manic episodes associated with bipolar disorder, and as an adjunctive therapy for major depressive disorder. It is also used off-label for several non-FDA-approved indications, including generalized anxiety disorder.[15-18] The indications are as follows; Atypical antipsychotic agents are indicated for the maintenance treatment of mania and for the management of schizophrenia in adults. They are also used to treat acute manic or mixed episodes of bipolar disorder, either alone or in combination with lithium or valproate. These agents can manage acute agitation associated with bipolar disorder or schizophrenia and are indicated for depressive episodes associated with bipolar disease. Additionally, they are employed in the treatment of refractory depression.

FORMULATIONS AND ROUTE OF ADMINISTRATION OF ANTIPSYCHOTICS

The atypical antipsychotics come in oral tablet form, orally disintegrated tablet form, oral solution, short-acting intramuscular (IM) injection and long-acting injectable (depot) formulations. Usually, atypical antipsychotics are not used intravenously (IV) in normal clinical practice.[6]

Oral tablets: This is the most common form given orally. Immediate release (IR) and extended-release (ER) /sustained release forms are available. The disintegrating tablets come in the form of oral form, which dissolves on the tongue enabling patients with low swallowing ability to take in the tablet easily.

Oral solution/liquid formulations: Some agents (such as risperidone) are available as oral solution/liquid formulation to make administration easier in children, in elderly or in patients who cannot swallow tablets.

IM injections: They have short durations are applied in emergency situations where immediate effect is required like in cases of agitation or psychotic outbursts and the patient is unable to ingest oral drugs. Such medications as olanzapine and ziprasidone have IM preparations in such situations.

Long-acting injectables (depot formulations): They are administered intramuscularly (occasionally, subcutaneously, based on the formulation) with intervals of 2-4 weeks or more. They are employed as maintenance therapy, to increase compliance or where there are oral dosing issues on a daily basis. They are risperidone microspheres, paliperidone palmitate, olanzapine pamoate, etc.

Table 1: Comparative pharmacology chart.[2,4,7-21]

Feature	Quetiapine	Olanzapine	Risperidone
Class / generation	2nd generation Atypical antipsychotic.	2nd generation Atypical antipsychotic.	2nd generation Atypical antipsychotic.
Main receptor actions (MOA)	5-HT2A AND D2 antagonist; also blocks H1 and α1 (sedation, hypotension).	5-HT2A and D2 antagonist; also, strong H1, α1 and muscarinic blockade.	Potent 5-HT2A and D2 antagonist; α1,α2, H1 effects.
Pharmacokinetics	Oral absorption; IR: Tmax ~1-2h, XR ~6h; moderate protein binding.	Oral absorption; Tmax within few Bioavailability adequate.	Oral absorption; Tmax 1-2h; active metabolite(9-OH) prolonged exposure.
Metabolism	CYP3A4 metabolism.	CYP1A2 metabolism (also UGT); smoking ↓ levels.	CYP2D6 metabolism to 9 hydroxyrisperidone.
Half-life	~6-7h.	21-54h (variable by sex, age, smoking).	Parent: 3-20h (CYP2D6 status); active metabolite longer.
Typical adult dose range	150-800mg/day	5-20 mg/day.	1-6 mg/day
Noble safety / Clinical notes	Sedation, hypotension, metabolic risks (weight gain, dyslipidemia).	High risk of gaining weight, dyslipidemia, insulin resistance, smoking changes PK.	Dose-dependents, prolactin increase, moderate gain in weight.

FORMULATIONS AND ROUTE OF ADMINISTRATION OF QUETIAPINE, OLANZAPINE, AND RISPERIDONE.

Quetiapine

Quetiapine comes in quetiapine extended-release (ER; taken once a day) form or quetiapine immediate release (IR; taken twice to three times a day) tablets. The pharmacokinetics of the IR preparations are normally administered in divided doses (twice or thrice a day) because of its pharmacokinetic characteristics. XR (extended-release / ER) formulation is manufactured to be administered once a day to enhance the convenience and the adherence. The tablets are available in strength of 25 mg, 50mg, 100mg, 200mg, 300mg, and 400mg, with the ER formulation available in 50mg, 150mg, 200mg, 300 mg, and 400 mg tablet strength.[18-22] Formulation, dosage, Starting Dose and titration had been summarized in table 2.

Olanzapine

Oral tablet: Olanzapine comes in forms of oral film-coated tablet in various doses (2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20 mg). These are tablets that are taken orally, and are the most widespread method of maintenance therapy.[16]

Orally disintegrating: There is also a disintegrating (orodispersible) tablet preparation of olanzapine that is water-free and dissolves on the tongue. This is beneficial in patients who have a problem with swallowing or in acute/agitated conditions.[16]

Intramuscular (IM) injection short-acting: Olanzapine is provided as a short-acting IM injection in case of agitation or in acute psychosis in a situation where patients cannot swallow medication.

Long-acting injectable (depot) formulation olanzapine pamoate

Long-acting (depot) intramuscular olanzapine as pamoate salt has also been worked out as a maintenance therapy with dosage intervals of every 2-4 weeks. Due to low solubility of olanzapine pamoate, it is slowly released (flip-flop kinetics) and thus maintains drug levels in weeks. Nevertheless, one adverse event that is scarcely common yet has a high level of severity postinjection.[16-25]

Combination oral formulation (olanzapine + samidorphan)

The fixed-dose oral combination therapy of olanzapine and samidorphan (OLZ/SAM) under LYBALVI was developed as a mitigation measure to the weight gain of olanzapine, without any impairment of the antipsychotic effect of olanzapine. The OLZ/SAM therapy (olanzapine + samidorphan) showed a much lower rate of weight gain over 24 weeks than olanzapine itself, regardless of patient subgroup.[26]

Risperidone

Risperidone also comes in various oral doses such as: regular tablets, orally disintegrating/dispersible tablets and liquid/oral solution so that it is flexible enough to be used by patients who have issues with swallowing or require an increase or decrease in dose.[27] Besides oral preparations, there exists a long-acting injectable (LAI / depot) version risperidone microspheres (brand Risperdal Consta) that is sent intramuscularly after every two weeks to help maintain compliance in patients who may have trouble taking their medications orally every day.[28] In 2016 pharmacokinetic research indicates that the orally disintegrating tablets and oral solution are bioequivalent to regular tablet with important parameters such as C n o o

and AUC, i.e. give similar exposure, thus one can switch between the two types of preparations without significant concerns about differences in dose.[27] Risperidone is a second generation (atypical) antipsychotic that comes in different formulations and routes in order to maximize clinical use and patient compliance. The most widespread route is the oral mode, and the formulations are standard film-coated tablets, orally disintegrating tablets (ODT), and oral solution (1mg/mL). These forms offer flexibility of dosing and are bioequivalent, meaning they may interchange without loss of activity within formulation or alterations in plasma concentration.[12] Along with oral preparations, long-acting injectable (LAI) preparations of risperidone, such as Risperdal Consta ®, provide sustained plasma concentrations of risperidone of up to two weeks after intramuscular (IM) administration. This depot preparation is particularly useful with patients with low oral adherence to drugs, or in chronic schizophrenics who are on maintenance therapy.[15] New developments have brought about long-release subcutaneous preparations like Perseris and RBP-7000, which should be given on a monthly basis. They are depots with stable plasma concentrations, better adherence in patients and require no oral supplementation during commencing. [21]

Table 2: Quetiapine dosage summary.[18,22,23,24]

Indication	Formulation	Dose range (mg/day)	Starting dose	Titration
Schizophrenia	IR	150-750 mg (2-3 divided doses)	25 mg twice daily	Increase by 50-150mg/day; Elderly: +25-50
	ER	400-800 (evening)	300 mg once daily	Increase up to 300 mg/day; do not crush or chew
Bipolar I disorder (manic)	IR	200-400 twice daily (max 800)	50 mg twice daily	Increase 100-200mg/day
	ER	400-800 (evening)	300 mg once daily	Increase 200mg /day as needed
Acute depressive bipolar disorder	IR	300(max 600) at bedtime	50 mg at bedtime	Increase 50 -100mg/day; elderly: +25-50 mg/day
	ER	300 at bedtime	50 mg at evening	Increase 50-100mg/day; do not crush/chew
Major depressive disorder (adjunct)	IR	50-300 mg/day	50 mg/day	Increase gradually to max 300 mg/day
	ER	150-300 mg/day	150 mg/day	Similar titration; do not chew/crush
For optimal efficacy, a daily dose ranging from 300mg to 800mg is generally recommended. In certain patients, clinicians may consider using higher, non-FDA-approved doses of 1200mg to 1600mg per day, provided that QT interval monitoring is conducted.				

MECHANISM AND CLINICAL IMPLICATIONS OF DRUG INTERACTIONS OF ANTIPSYCHOTICS

Antipsychotics also have interactions with other drugs primarily by (1) cytochrome P450 (CYP)-mediated pharmacokinetic (e.g. inhibitors increase and inducers decrease antipsychotic plasma levels), (2) additive (e.g. sedation, orthostatic hypotension, QT prolongation, anticholinergic effect) and (3) clinically significant (e.g. smoking, genetic CYP polymorphisms) patient factors.

Clinicians are encouraged to check concomitant drugs and always evaluate therapeutic drug monitoring where possible, as well as check on toxicity and defeat of efficacy.[29]

Quetiapine: main interactions and management

Mechanism/key points: Quetiapine is mainly metabolized by CYP3A4 (to a small degree CYP2D6); thus, CYP3A4 inhibitors significantly up regulate quetiapine levels, whereas CYP3A4 inducers down regulate them.[30]

Important interacting drugs (examples and effects)

CYP3A4 inhibitor: This increase Quetiapine levels/ risk of sedation, hypotension, QT prolongation e.g. Ketoconazole, itraconazole, clarithromycin, ritonavir, strong macrolides. Avoid co-administration or reduce quetiapine dose and monitor.[31]

CYP3A4 inducers: This decrease Quetiapine level/ possible loss of efficacy e.g., Carbamazepine, rifampin, phenytoin, phenobarbital, strong herbal inducers (St John's wort) inducers can substantially lower quetiapine exposure; dose increase may be needed but use caution and monitor clinical response.[32] Notably, co-administration with the multiple UGT-inhibitor valproic acid results in a 77% increase in quetiapine concentrations.

Grapefruit juice: In the gastrointestinal tract, grapefruit juice inactivates CYP3A4 which causes the levels of

quetiapine to increase, and increases the probability of side effects. Grapefruit products are recommended to be avoided in the course of quetiapine.[33]

The clinical implication is that patients taking quetiapine should be advised not to take grapefruit juice and other citrus fruits that contain furanocoumarins (seville oranges or pomelos), which have a similar inhibitory effect on the activity of CYP3A4.

A single glass of grapefruit juice daily could change the stable quetiapine levels in several days, and this is likely to cause too much sedation or even cardiovascular effects.[34]

Pharmacodynamics interactions

Additive CNS depression with the benzodiazepines, opioids, sedating antihistamines; additive orthostatic hypotension with antihypertensive. Monitor for over sedation and falls.[35]

Practical management

Review other drugs with high CYP3A4 modulators, and avoid initiating quetiapine in the presence of an inhibitor; watch out on reemergence of symptoms and may have to change quetiapine dose or may switch antipsychotic. Therapeutic drug monitoring should be considered in case it is available.[36]

Olanzapine its main interactions and management

Mechanism / key points: Mainly by CYP1A2 (a little bit by UGT pathways) Olanzapine is metabolized. CYP1A2 is induced by smoking (polycyclic aromatic hydrocarbins) and tends to reduce the levels of olanzapine, occasionally reducing its efficacy; on the other hand, CYP1A2 inhibitors (e.g., fluvoxamine) raise the levels of Olanzapine.[36]

Important interacting drugs (examples and effects)

Smoking: It decreases Olanzapine concentration / possible treatment failure. Smoking cessation often needs a reduction in dose of olanzapine; however, in heavy smokers, the opposite effect can happen and lead to toxicity unless the dose is lowered. Follow-up changes in smoking status closely.[37]

CYP1A2 inhibitor: It increase the Olanzapine levels / increase adverse effects e.g., Fluvoxamine markedly increases olanzapine concentrations and may require dose reduction.[36]

Drugs that prolonged QT / CNS depressants: Additive effects possible –use caution with concomitant QT-prolonging agent or sedatives.[35]

Pharmacodynamic issues

The anticholinergic and sedative properties of olanzapine can be enhanced by other anticholinergics or CNS sedatives; metabolic interactions (e.g., with drugs that increase glucose/lipids) can help increase cardiometabolic risk.[38]

Practical management

Inquire about smoking and observe response to the clinical treatment; change dose in case of smoking initiation/cessation in patients. Not to be used with the strong CYP1A2 inhibitors or decrease dose of olanzapine and watch out of sedation/metabolic. Use other agents when there is a need to use major interacting drugs.[39]

Risperidone: main interactions and management

CYP2D6 is the primary metabolite of risperidone to 9-hydroxyrisperidone (paliperidone). Genetic polymorphism (poor vs ultrarapid metabolizer) and CYP2D6 inhibitors have an impact on pharmacokinetics and side-effect hazard (e.g., EPS, hyperprolactinemia) in risperidone (parent) and the CYP2D6 concentrations of its metabolite (risperidone).[40] Important interacting drugs (examples and effects) are as follows;

CYP2D6 inhibitors: It Increase Risperidone levels / increase side effects e.g., Fluoxetine, paroxetine, bupropion, quinidine. In case of co-prescription, reduce the dose and watch out on extrapyramidal symptoms and sedation.[41] Risperidone is also moderately susceptible to CYP3A4 inhibitors/inducers (due to the presence of several pathways), whereas the primary metabolism pathway is CYP2D. Strong modulators should be used carefully.[42]

Pharmacodynamics interactions

Additive QT-prolongation risk in combination with other QT-prolonging drugs, additive EPS risk in the combination with other dopamine antagonists, additive sedation in combination with the CNS depressants. Monitor accordingly.[35]

Poor metabolizers of CYP2D6 (genetics)

Parent drugs accumulate in poor metabolizers; and dose modification or alternative drug must be considered in patients known to be poor metabolizers. Actionable recommendations are offered based on clinical pharmacogenetic guidelines (*e.g.,* DPWG).[43]

Practical management

Check CYP2D6 inhibitors comorbidities and contraindications before risperidone; look at EPS and hyperprolactinemia, consider pharmacogenetic testing in case of strange response or in severe side effects. In the case of long-acting formulations, beware of interaction characteristics between oral and transitions to LAIs.[40]

SAFETY CONCERNS OF ATYPICAL ANTI-PSYCHOTICS

Even though the second-generation antipsychotics (SGAs) were invented to add to the only extrapyramidal side effects of the first-generation antipsychotics, they also do not exclude the possibility of the adverse effect. As their use grows to other conditions besides schizophrenia, such as bipolar disease, depression, and even off-label, the issue of safety has become clinically significant. The key three areas of concern are metabolic, neurological and endocrine complications, which may affect adherence and quality of life during long-term treatment.[1-5]

Metabolic safety concerns

One of the most severe shortcomings of SGAs is metabolic disturbances. They are clinically significant weight gain, dyslipidemia, insulin resistance, and the development of diabetes mellitus.

Consistent results of large network meta-analyses and reviews indicate that olanzapine (and clozapine) is associated with the greatest metabolic risk, with quetiapine and risperidone having intermediate risk levels (nonetheless, clinically relevant).[1]

Mechanism (how these drugs cause metabolic harm) Receptor –driven appetite/sedation effects

Strong H1 and 5-HT2C antagonism (which is strong with olanzapine) enhanced the hunger and sedation leading to greater caloric intake and decreased activity and thus weight gain.[44]

Direct peripheral effects on glucose/insulin: There are SGAs that change the insulin signaling and adipocyte activity to encourage insulin resistance not depending on the weight gain (animals and humans' evidence).[45]

Inflammatory and mitochondrial effect: The chronic treatment of olanzapine was associated with amplified pro-inflammatory cytokines and mitochondrial/energy-metabolism modifications which lead to dysmetabolism.[45]

Pharmacokinetics and off-label low dose use: Even those doses that are considered low (e.g. quetiapine to induce insomnia) are not metabolically neutral means there are dose-dependent effects.[46]

Drug-specific metabolic liability. Quetiapine-intermediate risk

There are weight gain and changes in lipids/glucose, which are usually less than those of olanzapine; severe hyperglycemia in case reports. Even in low doses (use as a sleeping aid/anxiety) there is risk of off-label use.[47]
Olanzipine-higest metabolic liability: This leads Serious weight gain, massive triglyceride, LDL and fasting glucose increases; considerable insulin resistance and increased susceptibility to metabolic syndrome and new-onset diabetes.[44]

Magnitude: Several of the studies/meta-analyses indicate that olanzapine is one of the most effective drugs in increasing percent weight and causing harmful changes on lipid/glucose levels within a few weeks/months of treatment.[1]

Mitigation/note: Olanzapine + samidorphan combination formulation minimizes, but does not prevent, olanzapine-related weight gain per RCT/meta-analyses and FDA labelling - still needs metabolic monitoring.[48]

Risperidone –intermediate risk; metabolic + endocrine overlap

This leads moderate weight gain and lipid/glucose changes in many patients; plus, endocrine effect (hyperprolactinemia) that complicates risk in youth. Some studies suggest risperidone also increases metabolic syndrome risk compared with lower-risk agents.[49]

Clinical consequences matters but why?

Short-term clinical consequences: Rapid weight gain, hypertriglyceridemia, impaired fasting glucose - may manifest in 6-12 weeks.[44]

Long term clinical consequences: Raised type 2 diabetes, cardiovascular disease, cut back on life expectancy when unhandled (psychiatric patients already have a higher baseline of cardiometabolic risk). These outcomes are clearly associated with particular SGAs as demonstrated in large meta-analyses.[1]

EFFECT OF ANTIPSYCHOTICS (AP) (QUETIAPINE, OLANZAPINE, AND RISPERIDONE) ON GUT MICROBIOTA

Bacteria and other microbes i.e. microbiota residing within our gut have a crucial role in affecting human metabolism, weight, inflammatory state, and in our overall health.[1]

Within the last decade the use of atypical antipsychotic drugs has increased especially in pediatric population. The effects of these drugs on the gut microbiome are specifically of interest because both these factors are known to affect metabolism and weight gain.[51] These drugs the microbiome of gut is highly, when taken orally. APs also have antibiotic-like properties and are lethal against some bacteria thus change the relative ratios of the various phyla.

The solubilizing agents, lubricants, and vehicles by which drugs are bound into tablets can also affect gut bacteria in a variety way.[52] In a study done by Li et al, 2020 (24-week follow-up) showed that risperidone treatment was associated with change in the gut microbiota, several taxa

changed in abundance. Notably, *Bacteroidetes*, *Proteobacteria*, *Christensenellaceae*, and *Enterobacteriaceae* were among those taxa whose changes correlated with metabolic changes.[53]

Table 3: Pharmacogenetics of quetiapine, olanzapine, and risperidone.[41,43,60,63-67]

Drug	Enzyme (metabolism)	Gene (chromosome)	Genetic variants	Effect on drug
Quetiapine	CYP3A4 (major)	CYP3A4 (7Q22.1)	CYP3A422– reduced enzyme activity variant	Slower metabolism leading to higher plasma levels, causing sedation, dizziness, and other side effects
	CYP2D6 (minor)	CYP2D6 (22Q13.2)	Variants *3,*4,*5-no enzyme activity, resulting in a poor metabolizer status; variant *1XN– multiple gene copies, resulting in an ultrarapid metabolizer status	Poor metabolizers have increased exposure and more side effects; ultrarapid metabolizers have reduced drug levels and poor efficacy
	P-glycoprotein transporter	ABCB1 (7Q21.12)	Variants C3435T and G2677T/A – reduce or alter transporter function	Alters blood–brain barrier penetration, leading to variable central nervous system efficacy
Olanzapine	CYP1A2 (major)	CYP1A2 (15Q24.1)	Variant one F- increased enzyme inducibility leading to overactivity; variant one C- reduced enzyme activity	One F carriers, especially smokers, have faster metabolism and reduced drug levels; one C carriers have slower metabolism with higher drug levels, sedation, and metabolic side effects
	UGT1A4	UGT1A4 (2Q37)	Variants *2,*3– reduced glucuronidation capacity	Slower clearance resulting in higher olanzapine plasma levels
	CYP2D6 (minor)	CYP2D6 (22Q13.2)	Same as above: poor metabolizer variants (*3,*4, *5) and ultrarapid metabolizer variant (gene copy increase)	Minor effect on olanzapine clearance
Risperidone	CYP2D6 (major)	CYP2D6 (22Q13.2)	Variants *3,*4,*5 – no enzyme activity (poor metabolizer); variant ten – reduced activity (intermediate metabolizer); variant one gene copy increase – multiple gene copies (ultrarapid metabolizer)	Poor metabolizers: higher risperidone levels, increased risk of extrapyramidal symptoms and sedation. Ultrarapid metabolizers: reduced drug levels, poor therapeutic efficacy
	CYP3A4 (minor)	CYP3A4 (7Q22.1)	CYP3A4 twenty-two – reduced enzyme activity	Slower clearance, leading to higher plasma levels

A pilot longitudinal study (2022) in pediatric inpatients treated with atypical antipsychotics found that baseline microbiome composition (higher *Parabacteroides* and *Eubacterium hallii* group) predicted risk of weight gain. After 3 months of AP treatment, increases in *Romboutsia* and *Klebsiella* were observed among those gaining weight.[54]A 2023/2024 systematic review concluded that most studies (risperidone, quetiapine, olanzapine) reported changes in gut microbiome associated with antipsychotic use, and associations between bacterial abundance and metabolic parameters. However, studies included were heterogeneous (different durations, doses, species, human vs animals.[5] Another recent meta-analysis of schizophrenia gut microbiota found that antipsychotic treatment is associated with altered alpha and beta diversity (i.e. overall reductions in some diversity metrics, changes in species composition), and specific genera such *as Lactobacillus, Roseburia*, and *Dialister* differ between treated and untreated.[56] A study on bipolar depression patients treated with quetiapine monotherapy: after 4 weeks, some changes were seen in gut microbiota, e.g., *Bifidobacteria, Enterobacteriaceae* and the Bifidobacteria/Enterobacter ratio increased. These changes correlated with symptom improvement.[57] Recent evidence from both animal and human studies indicates that antipsychotics exert significant effects on the gut microbiota, often leading to reduced diversity and shifts in the Firmicutes/Bacteroidetes balance that are closely linked with weight gain, insulin resistance, and other metabolic disturbances. Baseline microbiota profiles may predict the extent of metabolic side effects, highlighting the potential for microbiome-targeted interventions such as probiotics, dietary modification, or microbial modulation to mitigate antipsychotic-induced metabolic burden. However, there is a need for more large-scale, controlled clinical trials for better understanding, clarify drug-specific effects, and translate these findings into practical therapeutic strategies.

PHARMACOGENETICS AND PHARMACO-GENOMICS (PGX)

Pharmacogenetics and Pharmacogenetics are related fields that use genetic information to understand and predict drug response. Pharmacogenetics refers to how single genes affect individual variability in drug response (*e.g.,* variation in a single CYP enzyme gene altering drug metabolism). Pharmacogenomics expands this to study the simultaneous impact of many genetic variants across the genome on drug response and safety. In simple pharmacogenetics is "the study of genetic causes of individual variations in drug response," while pharmacogenomics focuses on genome-wide/multigenic influences.[58-60]

Finding the possible correlations in between variations in gene and clinical effects of the new-generation antipsychotics is important in framework of personalized medicine because antipsychotic treatments show substantial inter-individual variability in efficacy and adverse effects (sedation, extrapyramidal symptoms, metabolic syndrome), many antipsychotics have narrow therapeutic windows or dose-dependent toxicities; small changes in exposure can change can induce good or bad effects Thus it is expected that PGx data will be useful for increasing the treatment efficacy, tolerability, therapeutic adherence, functional recovery, and quality of life in patients with severe psychiatric disorders.[60]

As for as antipsychotic drugs are concerned their pharmacokinetics is influenced by genetic factors beam a single nucleotide polymorphism (SNPs) in pharmacokinetic and pharmacodynamic genes are associated with response and adverse events. Thus, knowing the genotype of cytochrome P 450 isoenzymes (CYP450) can be beneficial for detecting non-responsivity or toxicity. Various single nucleotide polymorphisms (SNPs) in the genes CYP1A2, CYP2D6, and 3A4/5 are being reported in literature to influence the pharmacokinetics of atypical antipsychotics. Various t factors (beside CYP 450 system) that could modulate the responsivity to administered drugs are the transport systems, such as P-glycoprotein (P-GP) or multidrug resistance protein 1 (MDR1), breast cancer resistance protein (BCRP), etc., which are active efflux transporters in the blood-brain-barrier.[60-62]

DISCUSSION

Atypical antipsychotics like quetiapine, olanzapine, and risperidone have good therapeutic effect but differ in terms of safety profile. According to comparative pharmacology, the range of adverse effects is largely dependent on the selectivity of receptor-binding and the pharmacokinetic characteristics. The most potent antagonist of histamine (H 1), muscarinic (M3), and serotonin (5-HT2C) receptors, olanzapine has the highest metabolic burden, and it presents itself in the form of weight gain, insulin resistance, and dyslipidemia.[1-11]

Quetiapine has moderate metabolic risk (although not associated with a high risk of extrapyramidal symptoms or prolactin increase), however, when used off-label and at low doses, there is moderate metabolic risk.[2-10] Risperidone is still effective in treating psychosis and bipolar disorder yet has the highest prevalence of hyperprolactinemia and dose-related extrapyramidal side effects.[4-9] In these agents, patient detail factors in the form of age, sex, smoking and comorbid metabolic disease can play a major role in determining efficacy and tolerability. Thus, rational choice of drugs and continuous monitoring of metabolism and endocrine systems are critical in order to maximize the long-term outcomes.

CONCLUSION

The second-generation antipsychotics, which include olanzapine, quetiapine, and risperidone, continue to be used as a primary treatment of schizophrenia and bipolar disorder. Their various receptor profiles, however, result in different safety burdens with olanzapine having the highest metabolic risk, risperidone having the greatest endocrine effects, and quetiapine having moderate but combined metabolic and sedative effects. Clinicians ought to use personalized, evidence-based choice with periodic observation of the weight, glucose, lipids, and prolactin levels. Pharmacogenomic predictors of adverse effects and designing new types of formulations or mixture therapies, including olanzapine-samidorphan, to reduce metabolic toxicity without affecting therapeutic efficacy, future research should focus on improving safety profiles and developing personalized treatment strategies.

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