REVIEW ARTICLE

Efficacy and Safety of Second-generation Antipsychotics in Schizophrenia Pharmacotherapy: A Comparative Narrative Review

Mohamed Hassan Elnaem

School of Pharmaceutical Sciences, Universiti Sains Malaysia, George Town 11800, Penang, Malaysia.

ABSTRACT

Antipsychotic medications are essential in schizophrenia pharmacotherapy, with notable differences in efficacy and safety. This review aims to discuss and compare the differences in efficacy and safety among various second-generation antipsychotic drugs (SGAs). A narrative review was conducted involving the English-based published literature in three scientific databases between 2000 and January 2021: Google Scholar, Scopus, and PubMed. Clozapine is widely considered an effective therapy option in cases of resistance. Maintenance of schizophrenia treatment with paliperidone palmitate was effective and resulted in a longer duration between relapses. The risk of weight gain and diabetes mellitus was increased significantly with clozapine and olanzapine. Risperidone caused neuroleptic malignant syndrome (NMS) and significantly elevated prolactin levels. The extent of safety concerns reported varied by study design. While there were minor differences in the dose-dependent role of SGAs in acute episode treatment, there were significant differences in the type and intensity of side effects, and hence adherence determinants.
Malaysian Journal of Medicine and Health Sciences (2022) 18(19) 183-190. doi:10.47836/mjmhs.18.s19.28

Keywords: Schizophrenia, antipsychotics, safety, efficacy, adherence

Corresponding Author:
Mohamed Hassan Elnaem PharmD, PhD
Email: drmelnaem@usm.my
Tel:+60193944726

INTRODUCTION

Schizophrenia is a psychiatric condition that affects nearly 1% of the population (1). The clinical manifestations of this condition are classified as positive and negative symptoms, and cognitive impairment (2). The positive symptoms include delusion, speech disturbance, hallucination, behaviour disturbance, and illusions. Meanwhile, the negative symptoms involve alogia, anhedonia, and social isolation. This cognitive impairment manifests itself through deficits in attention, executive function, and working memory. In addition, individuals with schizophrenia also exhibit social cognition impairment, such as difficulties in identifying emotions, creating emotional connections, understanding people's thinking, and reacting emotionally to others (3).

Antipsychotics are used to treat schizophrenia and can be categorised into first-generation (FGAs) and second-generation antipsychotics (SGAs) (4). The general mechanism of action of antipsychotics includes blocking dopamine receptors and serotonin receptors in the brain. All FGAs and most of the SGAs have dopamine blockade activity. The clinical efficacy of antipsychotics is closely correlated with the drugs' ability to bind to the D2 receptors in the brain's mesolimbic system. However, most SGAs function by blocking serotonin (5-HT) receptors, specifically 5-HT2A receptors. In addition, numerous agents block adrenergic, histaminergic, and cholinergic receptors, resulting in undesirable side effects (5). Therefore, FGAs are mostly referred to as typical antipsychotics, while SGAs are mostly considered atypical antipsychotics (5). Extrapyramidal side effects, effectiveness in resistant patients, and effectiveness against negative symptoms all play a role in making this distinction.

During schizophrenia treatment, attempts to maximise pharmacotherapy effectiveness and assure safety are associated with a better prognosis. However, due

to the continuous emergence of second-generation antipsychotics, it is essential to compare atypical agents in terms of efficacy and safety. While there have been several studies that compared two or three agents in terms of certain parameters or side effects, there has been a relative lack of work that provides an overall review of the differences across a wide range of SGAs. Therefore, a comparative review was undertaken to discuss and compare the differences between different SGAs regarding their efficacy and safety. A total of twelve agents were covered, in this review.

METHODOLOGY

A review of the published literature was conducted from 2000 to January 2021. The search was conducted using predetermined search phrases in three scientific databases: Google Scholar, ScienceDirect, and PubMed. The search phrases used were "second-generation antipsychotics" OR "atypical antipsychotics" OR "schizophrenia pharmacotherapy" OR the individual names of the SGAs AND "efficacy" AND "safety" OR "side effects". In addition, a review of all English-language studies that compared the efficacy and/or safety of different SGAs was performed. Finally, we organised the information into themes by reviewing the main objectives of the comparison across the eligible studies. Then, we conducted a narrative synthesis of the findings. The identified main themes are depicted in figure 1.

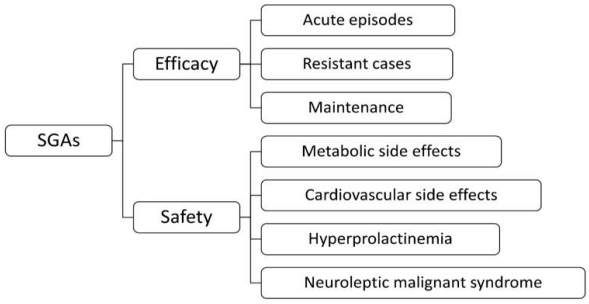

Figure 1. Main identified themes in the comparative review of SGA efficacy and safety.

RESULTS & DISCUSSIONS

This review involved 20 original articles that reported efficacy and safety comparisons of different SGAs. Other types of publications, such as systematic reviews and meta-analyses, were involved to strengthen the discussion of the comparative points. The agents included in this review were olanzapine, clozapine, risperidone, paliperidone, quetiapine, aripiprazole, asenapine, amilsulpride, cariprazine, brexpiprazole, lurasidone, and lumateperone.

Comparative Review of SGAs Efficacy.

Acute schizophrenia

Overall, time to clinical response did not differ significantly across several SGAs, thus opening the role of clinical judgement and balancing benefits and risks in individual cases (6). Dose-dependent antipsychotic effectiveness has been observed in schizophrenia during the acute phase of the illness, where every antipsychotic has its own unique dose-response curve (7).

The efficacy of antipsychotic medications in treating schizophrenia can be assessed by using symptom rating scales. The most common symptom rating scales used by the researchers to observe the efficacy and measure the treatment outcome are the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression (CGI), and the Brief Psychiatric Scale (BPS) (8). However, most of the findings illustrated in this paper used PANSS and CGI scales to assess the efficacy of the antipsychotics. As an example of SGAs, lurasidone showed efficacy in treating schizophrenia acute exacerbations through its positive impact on improving PANSS and CGI-severity of illness (CGI-S) scores (9,10). Furthermore, while the efficacy of lurasidone was comparable to that of olanzapine in a 6-week randomised controlled study, both medicines indicated significant improvement in PANSS and CGI-S total scores compared to placebo (11). Additionally, in a 6-month extended open-label trial comparing lurasidone and olanzapine, the observed significant improvement in PANSS and CGI-S total scores was consistent for both agents; however, the metabolic side effects and unwanted weight-related effects were significantly less prevalent in lurasidone patients (12). Compared to quetiapine-XR in a 12-month randomised controlled trial, lurasidone showed the efficacy of relapse prevention and lower relapse rate (23.7% vs 33.6%), and lower risk of hospitalisation (9.8% vs 23.1%) (13). Although lurasidone improved the PANSS total and positive subscale scores more than quetiapine, both medications similarly improved the PANSS negative subscale scores. To summarise, lurasidone is equally effective as olanzapine in treating acute schizophrenia and has a better safety profile. Additionally, compared to quetiapine, lurasidone had a lower relapse rate and improved PANSS positive subscale scores.

Furthermore, in a study conducted among Asian patients, asenapine was more effective than a placebo in treating acute exacerbations of schizophrenia (14). In a Chinese study evaluating the efficacy measures of amisulpride and olanzapine, there were no statistically significant differences in terms of the PANSS and CGI-S total scores between the two treatments (15). Recent research suggests that cariprazine is more

effective than risperidone in treating patients with acute exacerbations and primarily negative symptoms (16). While relatively new antipsychotics such as lurasidone, cariprazine, and brexipiprazole had similar efficacy to quetiapine, aripiprazole, and ziprasidone, these newer agents demonstrated additional promising impacts on cognitive, negative, and depressive symptoms (17).

Treatment-resistant schizophrenia (TRS)

In order to be labelled as having treatment-resistant schizophrenia (TRS), a patient must have been unable to respond to at least two antipsychotics at the recommended dosage, duration, and adherence measures (18,19). Clozapine has been shown to improve symptoms over a year in patients who had an unsatisfactory response to at least two antipsychotic drugs (20) In addition, clozapine was more effective than quetiapine for TRS management, but it was associated with a significantly higher incidence of side effects (21).

An earlier meta-analysis examined TRS effectiveness among SGAs; olanzapine was more effective than aripiprazole, quetiapine, and risperidone. However, clozapine in higher doses was superior to risperidone (22). In another meta-analysis comparing clozapine with olanzapine in TRS patients, clozapine improved more positive and negative symptoms than olanzapine (23). Another systematic review and meta-analysis have also supported the superiority of clozapine compared to other FGAs and SGAs in improving positive symptoms in patients with TRS, in both the short and long term (24). Furthermore, clozapine was associated with a lower risk of hospitalisation compared to quetiapine and aripiprazole, as well as a lower risk of all-cause cessation compared to other SGAs, according to a recent meta-analysis (25). Several randomised trials have demonstrated that clozapine is superior to other SGAs and is considered the gold standard in treating TRS (4).

On the other hand, an 18-week randomised, double-blind, parallel research comparing the efficacy and safety of olanzapine and clozapine in treatment-resistant and treatment-intolerant patients found that olanzapine is equally effective as clozapine as an option in treating TRS (26). Additionally, a network meta-analysis of antipsychotics' purported efficacy for TRS found no evidence to support clozapine's higher efficacy over other SGAs, especially in blinded RCTs (27).

Maintenance treatment and adherence to antipsychotics

The simplification of medication regimens positively impacts adherence and clinical outcomes among patients with chronic conditions (28). Therefore, it is essential to note that long-acting injectables (LAIs) have comparable safety and tolerability to their oral counterparts, and SGA LAIs have comparable efficacy to FGA-like preparations. As a result, more scrutiny and education of patients on the differences between the safety profiles of different LAIs and their administration schedules is still required to ensure that it aids in improving adherence (29).

The long-term effectiveness of antipsychotic medications is highly associated with medication adherence, which could prevent symptom relapse, whereas a short-term period of partial adherence will increase relapse rates (30). Patients with schizophrenia who take long-acting injectable (LAI) antipsychotics such as paliperidone palmitate are more likely to adhere to their treatment regimens (31). In addition, paliperidone palmitate is more effective at preventing relapse in newly diagnosed patients than other antipsychotics (32).

Patients taking oral risperidone were converted to paliperidone palmitate in two case studies, and their adherence and clinical course improved. This suggests that paliperidone palmitate can help prevent relapses, reduce psychotic symptoms, and improve cognitive performance (31). Concerning the long-term performance of oral SGAs over three years, a study comparing aripiprazole, quetiapine, and ziprasidone found that aripiprazole had higher efficacy and lower discontinuation rates (33). The finding confirmed that the overall safety profile, not only the efficacy, plays a role in reshaping medication adherence over the long term. Table I summarises the main findings of SGAs' efficacy and safety.

Table I: Summary of the main findings of SGAs' efficacy and safety.

Number	Main findings of the efficacy and safety of the SGAs'
1	Clozapine is considered the gold standard for TRS treatment, but more studies should be conducted since the evidence from blinded RCT is still not conclusive.
2	Paliperidone palmitate LAIs showed comparable efficacy and longer relapse time than other SGAs as maintenance treatment.
3	Compared to quetiapine, lurasidone showed more significant improvement in PANSS total and positive subscale and lower relapse rate.
4	Lurasidone and olanzapine showed comparable effectiveness for treating acute schizophrenia.
5	Clozapine and olanzapine have a higher likelihood of causing weight gain and diabetes mellitus than other SGAs.
6	Risperidone had the highest number of cases than other SGAs for SGAs-induced NMS.
7	Risperidone was associated with a significant increase in prolactin level.
8	Ziprasidone showed the highest tendency to cause QT prolongation, while olanzapine was the less likely drug to cause this effect.

Comparative Review of SGAs Safety.

Safety of the indicated therapeutic interventions is affected by several factors such as the patients' demographics or the intervention type (34). Determinants for antipsychotic safety can be linked in many cases to the prescribed dose

and antipsychotic dose dependence varies significantly across adverse effect types. Parkinsonism, weight gain, hyperprolactinemia, and cognition impairment have been documented as dose-related side effects. Akathisia, myocardial infarction, diabetes mellitus, QT prolongation, neuroleptic malignant syndrome, tardive dyskinesia, sexual dysfunction, somnolence, pneumonia, and osteoporosis were less likely to be dose-dependent side effects (7) . A summary of the important considerations for comparing SGAs' efficacy and safety is provided in Table II.

Table II: The important considerations for comparing SGAs' efficacy and safety

No	Important considerations regarding the comparison between SGAs' efficacy and safety
1	No significant differences in the time to clinical response between several SGAs opening the role of clinical judgement and balancing benefits and risks across individual cases.
2	In the acute phase, the effectiveness tended to be dose-dependent, with each antipsychotic having its own dose-response curve
3	The degree of the dose dependence of antipsychotic adverse effects varies significantly across adverse effect types.
4	Dose-related adverse effects were reported for parkinsonism, hyperprolactinemia, weight gain, and neurocognitive impairment.
5	Less evidence of dose-dependent adverse effects was reported for akathisia, tardive dyskinesia, osteoporosis, sexual dysfunction, diabetes mellitus, QT prolongation, and neuroleptic malignant syndrome
6	Metabolic side effects depend on the prescribed antipsychotic, the number (monotherapy, 2 or 3), and the cumulative dose received by patients in the long term.

SGAs induced metabolic syndrome

Metabolic abnormalities manifested as obesity, diabetes, weight changes, or atherogenic dyslipidemia are some of the perplexing issues associated with the use of SGAs (42). The increased risk of metabolic syndrome and weight gain is related to the affinity for blocking serotonin, dopamine, histamine, and muscarinic receptors (35). Compared to several SGAs, clozapine is linked to an increased risk of weight gain and type 2 diabetes mellitus (25). A 12-month clinical trial compared the weight gain induced by olanzapine, risperidone, and aripiprazole; risperidone caused the most significant weight gain, while aripiprazole caused the least (36). This study highlighted that the weight changes occurred primarily in the first 6-month of the treatment, followed by weight stabilisation.

Diabetes risk was also affected by the number of antipsychotic medications a patient was prescribed, with those taking three antipsychotics more likely to develop type 2 diabetes than those taking only two (37). A matched cohort study comparing those receiving antipsychotics to those receiving placebo reported a threefold increase in diabetes risk that increased with cumulative dose increment and remained at increased risk one year after treatment discontinuation (38). Clozapine and olanzapine have the highest risk of developing metabolic syndrome, including high blood sugar, abnormal lipid levels, and weight gain; quetiapine and risperidone have a moderate risk; and aripiprazole, ziprasidone, asenapine, and lurasidone have a low risk (39). Amisulpride showed a lower incidence of weight gain and lower fasting glycaemic levels when compared to olanzapine, as well as a decreased risk of somnolence and constipation (15). In order to prevent diabetes and weight gain, SGAs had to be administered in conjunction with antidiabetic medications such as metformin and a healthy lifestyle (40). Overall, it can be deduced that metabolic side effects largely depend on the prescribed antipsychotic, the number (three or two or monotherapy), and the cumulative dose received by patients over the long term.

SGAs induced cardiovascular events

SGAs are also commonly associated with cardiovascular events. The cardiovascular events are partially dose-dependent (41). There is no conclusive evidence regarding the exact mechanism of action that causes the two most common cardiovascular events: ECG abnormalities and sudden death (42). However, it is believed that the ECG abnormalities, specifically QT prolongation, are caused by the inhibition of the delayed rectifier potassium channels that allow sustained potassium efflux (42).

Moreover, in a review of the reports of FDA Adverse Event Reporting Systems from 1997 to 2011, the QT prolongation was primarily caused by olanzapine, quetiapine, aripiprazole, risperidone, and ziprasidone (43). Ziprasidone was linked to the highest risk of QT prolongation; meanwhile, the lowest risk was reported with olanzapine (43). Given the potential for death from cardiovascular events, patients at high risk of having a prolonged QT interval must not receive antipsychotics that cause QT prolongation. Before initiating an antipsychotic regimen, the patient should undergo electrocardiography (ECG). Thus, the patient can be prescribed the most appropriate regimen that is both efficacious and safe.

SGAs induced hyperprolactinemia

SGAs can disrupt prolactin levels in the blood due to the inhibition of dopamine receptors in the anterior pituitary gland (44). Dopamine acts as an inhibitor of prolactin release in the anterior pituitary gland; thus, dopamine inhibition results in sustained prolactin release. This will increase the prolactin level and cause hyperprolactinemia that is increased directly with the dose increments of several SGAs, including risperidone, olanzapine, and ziprasidone (45). Specifically, risperidone was found to raise prolactin levels significantly (46). Compared to amisulpride, olanzapine was found to have a lower risk of insomnia, amenorrhea, and lactation (15).

Aripiprazole, on the other hand, may lower prolactin

levels because it can act as both an antagonist and an agonist to dopamine 2 receptors (47). Thus, aripiprazole may act as an adjunctive treatment to the antipsychotic regimen since randomised, double-blind trials have shown that it may reduce the prolactin level in patients taking risperidone (48). In addition, the symptoms of hyperprolactinemia are constantly being overlooked since they may be regarded as psychiatric symptoms. On top of that, hyperprolactinemia may also cause serious complications like breast cancer, pituitary tumours, and sexual dysfunction (49). Thus, prolactin levels should be monitored regularly in patients taking antipsychotic medications, as the symptoms may be asymptomatic or overlap with the primary psychiatric symptoms (47).

SGAs induced neuroleptic malignant syndrome (NMS)

One of the most severe and uncommon adverse reactions (ADRs) associated with antipsychotic treatment is the neuroleptic malignant syndrome (NMS), which can cause muscle rigidity, autonomic dysfunction, and hyperthermia, as well as changes in the patient's mental status (44). The incidence and severity of NMS are lower in the treatment with SGAs when compared with FGAs. However, more rare fatal outcomes were reported. Risperidone was associated with the highest number of cases of SGA-induced NMS (50). The patient may experience severe NMS symptoms characterised by rigidity, extrapyramidal symptoms, fever, and highly elevated CPK levels. Tachycardia and autonomic dysregulation happened more frequently compared to diaphoresis (51). Clozapine, amisulpride, and aripiprazole were frequently reported to have less typical NMS presentations, such as high fever and extrapyramidal symptoms (51).

Besides, studies reported that clozapine-induced NMS occurred because of rapid dose increases, usually less severe than other SGAs and commonly presented with tachycardia, tachypnoea, diaphoresis, and autonomic lability, probably due to its binding to adrenergic and muscarinic receptors (52). Finally, ziprasidone-induced NMS is common and exhibits typical symptoms. However, no fatalities were reported, and the patient may recover in 10 days (53).

CONCLUSION

In terms of efficacy, lurasidone and olanzapine were comparably effective in treating acute schizophrenia. Lurasidone demonstrated a greater degree of improvement in the PANSS total and positive subscale scores and a lower relapse rate when compared to quetiapine. Meanwhile, clozapine is considered the gold standard for TRS treatment, but additional studies should be conducted due to the lack of conclusive evidence from blinded RCTs. Paliperidone palmitate is one of the LAIs that has been shown to be effective in both acute and chronic schizophrenia treatment. It demonstrated more remarkable improvement in the PANSS total score, quality of life, and time to relapse. In terms of safety, clozapine and olanzapine were associated with a greater likelihood of weight gain and diabetes mellitus than other SGAs. Additionally, ziprasidone has the most remarkable proclivity for QT prolongation in SGAs, whereas olanzapine has the least proclivity for this effect. Additionally, risperidone has been shown to significantly increase prolactin levels, suggesting that aripiprazole may be used as adjunctive treatment for risperidone-induced hyperprolactinemia.

ACKNOWLEDGEMENT

Part of this work was presented in abstract form at the 4th 2021 World Congress of Integration and Islamisation organised by International Islamic University Malaysia.

REFERENCES

1. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. The Lancet. 2013 Nov 9;382(9904):1575–86. https://doi.org/10.1016/S0140-6736(13)61611-6
2. Howes OD, Murray RM. Schizophrenia: An integrated sociodevelopmental-cognitive model. Vol. 383, The Lancet. Elsevier B.V.; 2014. p. 1677–87. https://doi.org/10.1016/S0140-6736(13)62036-X
3. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. Nat Rev Neurosci. 2015 Oct;16(10):620-31. doi: 10.1038/nrn4005.
4. Bruijnzeel D, Suryadevara U, Tandon R. Antipsychotic treatment of schizophrenia: An update. Asian J Psychiatr . 2014 Oct;11:3-7. doi: 10.1016/j.ajp.2014.08.002.
5. Conley RR, Kelly DL. Clinical pharmacology and medication-associated side effects: A review of second-generation antipsychotics for schizophrenia [Internet]. Clinical Schizophrenia and Related Psychoses. 2007 [cited 2021 May 12]. Vol. 1, 135-146. Available from: www.clinicalschizophrenia.net/articles/clinical-pharmacology-and-medicationassociated-side-effects-a-review-of-secondgeneration-antipsychotics-for-schizophreni.pdf
6. Taylor JH, Appel S, Eli M, Alexander-Bloch A, Maayan L, Gur RE, et al. Time to Clinical Response in the Treatment of Early Onset Schizophrenia Spectrum Disorders Study. J Child Adolesc Psychopharmacol. 2021 Feb;31(1):46-52. doi: 10.1089/cap.2020.0030.
7. Yoshida K, Takeuchi H. Dose-dependent effects of antipsychotics on efficacy and adverse effects in schizophrenia. Behav Brain Res. 2021 Mar 26;402:113098. doi: 10.1016/j.bbr.2020.113098.
8. Mortimer AM. Symptom rating scales and outcome

in schizophrenia. Br J Psychiatry Suppl. 2007 Aug;50:s7-14. doi: 10.1192/bjp.191.50.s7.
9. Nasrallah HA, Silva R, Phillips D, Cucchiaro J, Hsu J, Xu J, et al. Lurasidone for the treatment of acutely psychotic patients with schizophrenia: A 6-week, randomized, placebo-controlled study. J Psychiatr Res. 2013 May;47(5):670-7. doi: 10.1016/j.jpsychires.2013.01.020.
10. Higuchi T, Ishigooka J, Iyo M, Yeh C Bin, Ebenezer EG, Liang KY, et al. Lurasidone in the treatment of schizophrenia: Results of a double-blind, placebo-controlled trial in Asian patients. Asia-Pacific Psychiatry. 2019 Jun 1;11(2). https://doi.org/10.1111/appy.12352
11. Meltzer HY, Cucchiaro J, Silva R, Ogasa M, Phillips D, Xu J, et al. Lurasidone in the treatment of schizophrenia: A randomized, double-blind, placebo- and olanzapine-controlled study. Am J Psychiatry. 2011 Sep;168(9):957-67. doi: 10.1176/appi.ajp.2011.10060907.
12. Stahl SM, Cucchiaro J, Simonelli D, Hsu J, Pikalov A, Loebel A. Effectiveness of lurasidone for patients with schizophrenia following 6 weeks of acute treatment with lurasidone, olanzapine, or placebo: A 6-month, open-label, extension study. J Clin Psychiatry. 2013 May;74(5):507-15. doi: 10.4088/JCP.12m08084.
13. Loebel A, Cucchiaro J, Xu J, Sarma K, Pikalov A, Kane JM. Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: A 12-month, double-blind, noninferiority study. Schizophr Res. 2013 Jun;147(1):95-102. doi: 10.1016/j.schres.2013.03.013.
14. Kinoshita T, Bai YM, Kim JH, Miyake M, Oshima N. Efficacy and safety of asenapine in Asian patients with an acute exacerbation of schizophrenia: a multicentre, randomized, double-blind, 6-week, placebo-controlled study. Psychopharmacology (Berl). 2016 Jul;233(14):2663-74. doi: 10.1007/s00213-016-4295-9.
15. Men P, Yi Z, Li C, Qu S, Xiong T, Yu X, et al. Comparative efficacy and safety between amisulpride and olanzapine in schizophrenia treatment and a cost analysis in China: A systematic review, meta-analysis, and cost-minimization analysis. BMC Psychiatry. 2018 Sep 5;18(1):286. doi: 10.1186/s12888-018-1867-8.
16. Misiak B, Bieńkowski P, Samochowiec J. Cariprazine - A novel antipsychotic drug and its place in the treatment of schizophrenia. Psychiatr Pol. 2018 Dec 29;52(6):971-981. doi: 10.12740/PP/OnlineFirst/80710.
17. Corponi F, Fabbri C, Bitter I, Montgomery S, Vieta E, Kasper S, et al. Novel antipsychotics specificity profile: A clinically oriented review of lurasidone, brexpiprazole, cariprazine and lumateperone. Eur Neuropsychopharmacol. 2019 Sep;29(9):971-985. doi: 10.1016/j.euroneuro.2019.06.008.
18. Lally J, Gaughran F, Timms P, Curran SR. Treatment-resistant schizophrenia: Current insights on the pharmacogenomics of antipsychotics. Pharmgenomics Pers Med. 2016 Nov 7;9:117-129. doi: 10.2147/PGPM.S115741.
19. Potkin SG, Kane JM, Correll CU, Lindenmayer JP, Agid O, Marder SR, et al. The neurobiology of treatment-resistant schizophrenia: paths to antipsychotic resistance and a roadmap for future research. NPJ Schizophr. 2020 Jan 7;6(1):1. doi: 10.1038/s41537-019-0090-z.
20. Lewis SW, Barnes TRE, Davies L, Murray RM, Dunn G, Hayhurst KP, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull. 2006 Oct;32(4):715-23. doi: 10.1093/schbul/sbj067.
21. Kumar M, Chavan B, Sidana A, Das S. Efficacy and tolerability of clozapine versus quetiapine in treatment-resistant schizophrenia. Indian J Psychol Med. 2017 Nov-Dec; 39(6): 770–776. doi: 10.4103/IJPSYM.IJPSYM_111_17
22. Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: A review and meta-analysis of randomized trials. Am J Psychiatry. 2001 Apr;158(4):518-26. doi: 10.1176/appi.ajp.158.4.518.
23. Souza JS, Kayo M, Tassell I, Martins CB, Elkis H. Efficacy of olanzapine in comparison with clozapine for treatment-resistant schizophrenia: evidence from a systematic review and meta-analyses. CNS Spectr. 2013 Apr;18(2):82-9. doi: 10.1017/S1092852912000806.
24. Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine v . first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry. 2016 Nov;209(5):385-392. doi: 10.1192/bjp.bp.115.177261.
25. Masuda T, Misawa F, Takase M, Kane JM, Correll CU. Association with Hospitalization and All-Cause Discontinuation among Patients with Schizophrenia on Clozapine vs Other Oral Second-Generation Antipsychotics: A Systematic Review and Meta-analysis of Cohort Studies. JAMA Psychiatry. 2019 Oct 1;76(10):1052-1062. doi: 10.1001/jamapsychiatry.2019.1702.
26. Bitter I, Dossenbach MRK, Brook S, Feldman PD, Metcalfe S, Gagiano CA, et al. Olanzapine versus clozapine in treatment-resistant or treatment-intolerant schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2004 Jan;28(1):173-80. doi: 10.1016/j.pnpbp.2003.09.033.
27. Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, et al. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: A network meta-analysis.

JAMA Psychiatry. 2016 Mar;73(3):199-210. doi: 10.1001/jamapsychiatry.2015.2955.
28. Elnaem MH, Irwan NA, Abubakar U, Sulaiman SAS, Elrggal ME, Cheema E. Impact of medication regimen simplification on medication adherence and clinical outcomes in patients with long-term medical conditions. Patient Prefer Adherence. 2020 Nov 2;14:2135-2145. doi: 10.2147/PPA.S268499.
29. Jann MW, Penzak SR. Long-Acting Injectable Second-Generation Antipsychotics: An Update and Comparison Between Agents. CNS Drugs. 2018 Mar;32(3):241-257. doi: 10.1007/s40263-018-0508-6.
30. Subotnik KL, Nuechterlein KH, Ventura J, Gitlin MJ, Stephen M, Mintz J, et al. Risperidone nonadherence and return of positive symptoms in the early course of schizophrenia. Am J Psychiatry. 2011 Mar;168(3):286-92. doi: 10.1176/appi.ajp.2010.09010087.
31. Johnson S, Remtulla R, Poolay RC, Arshed S. Efficacy of paliperidone palmitate in the treatment of schizophrenia and its effect on psychosocial and occupational functioning in patients: 2 Case studies. GSTF Journal of Advances in Medical Research (JAMR). 2016, Vol.1 No.4, doi: 10.5176/2345-7201_1.4.362018
32. Schreiner A, Aadamsoo K, Altamura AC, Franco M, Gorwood P, Neznanov NG, et al. Paliperidone palmitate versus oral antipsychotics in recently diagnosed schizophrenia. Schizophr Res. 2015 Dec;169(1-3):393-399. doi: 10.1016/j.schres.2015.08.015.
33. Gymez-Revuelta M, Pelayo-Terбn JM, Juncal-Ruiz M, Ortiz-Garcнa de la Foz V, Vбzquez-Bourgon J, Gonzбlez-Pinto A, et al. Long-term antipsychotic effectiveness in first episode of psychosis: A 3-year follow-up randomized clinical trial comparing aripiprazole, quetiapine, and ziprasidone. Int J Neuropsychopharmacol. 2018 Dec; 21(12): 1090–1101. doi: 10.1093/ijnp/pyy082
34. Elnaem MH, Mohd Taufek NH, Ab Rahman NS, Mohd Nazar NI, Zin CS, Nuffer W, et al. Covid-19 vaccination attitudes, perceptions, and side effect experiences in malaysia: Do age, gender, and vaccine type matter? Vaccines (Basel). 2021 Oct 9;9(10):1156. doi: 10.3390/vaccines9101156.
35. Dayabandara M, Hanwella R, Ratnatunga S, Seneviratne S, Suraweera C, de Silva VA. Antipsychotic-associated weight gain: Management strategies and impact on treatment adherence. Neuropsychiatric Disease and Treatment. Neuropsychiatr Dis Treat. 2017 Aug 22;13:2231-2241. doi: 10.2147/NDT.S113099.
36. Mustafa S, Joober R, Iyer S, Shah J, Lepage M, Malla A. Early stabilization of weight changes following treatment with olanzapine, risperidone, and aripiprazole: A 12-month naturalistic study of first episode psychosis. J Clin Psychiatry. 2019 Aug 27;80(5):18m12717. doi: 10.4088/JCP.18m12717.
37. Mamakou V, Hackinger S, Zengini E, Tsompanaki E, Marouli E, Serafetinidis I, et al. Combination therapy as a potential risk factor for the development of type 2 diabetes in patients with schizophrenia: The GOMAP study. BMC Psychiatry. 2018; 18: 249. doi: 10.1186/s12888-018-1826-4
38. Bobo W v., Cooper WO, Stein CM, Olfson M, Graham D, Daugherty J, et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. JAMA Psychiatry. 2013 Oct;70(10):1067-75. doi: 10.1001/jamapsychiatry.2013.2053.
39. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA. 2009 Oct 28;302(16):1765-73. doi: 10.1001/jama.2009.1549.
40. Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. Am J Psychiatry. 2006 Dec;163(12):2072-9. doi: 10.1176/ajp.2006.163.12.2072.
41. Polcwiartek C, Kragholm K, Schjerning O, Graff C, Nielsen J. Cardiovascular safety of antipsychotics: A clinical overview. Expert Opin Drug Saf . 2016 May;15(5):679-88. doi: 10.1517/14740338.2016.1161021.
42. De Hert M, Detraux J, Van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2011 Oct 18;8(2):114-26. doi: 10.1038/nrendo.2011.156.
43. Kimura G, Kadoyama K, Brown JB, Nakamura T, Miki I, Nisiguchi K, et al. Antipsychotics-associated serious adverse events in children: An analysis of the faers database. Int J Med Sci. 2015 Jan 5;12(2):135-40. doi: 10.7150/ijms.10453.
44. Pisano S, Catone G, Veltri S, Lanzara V, Pozzi M, Clementi E, et al. Update on the safety of second generation antipsychotics in youths: A call for collaboration among paediatricians and child psychiatrists. Ital J Pediatr. 2016; 42: 51. doi: 10.1186/s13052-016-0259-2
45. Masi G, Milone A, Veltri S, Iuliano R, Pfanner C, Pisano S. Use of Quetiapine in Children and Adolescents. Paediatr Drugs. 2015 Apr;17(2):125-40. doi: 10.1007/s40272-015-0119-3.
46. dos Santos Jьnior A, Henriques TB, de Mello MP, Neto APF, Paes LA, Torre OH della, et al. Hyperprolactinemia in Children and Adolescents with Use of Risperidone: Clinical and Molecular Genetics Aspects. J Child Adolesc Psychopharmacol. 2015 Dec;25(10):738-48. doi: 10.1089/cap.2015.0094.
47. de Bartolomeis A, Tomasetti C, Iasevoli F. Update on the Mechanism of Action of Aripiprazole:

Translational Insights into Antipsychotic Strategies beyond Dopamine Receptor Antagonism. CNS Drugs. 2015 Sep;29(9):773-99. doi: 10.1007/s40263-015-0278-3

48. Chen JX, Su YA, Bian QT, Wei LH, Zhang RZ, Liu YH, et al. Adjunctive aripiprazole in the treatment of risperidone-induced hyperprolactinemia: A randomized, double-blind, placebo-controlled, dose-response study. Psychoneuroendocrinology. 2015 Aug;58:130-40. doi: 10.1016/j.psyneuen.2015.04.011.
49. Miyamoto BE, Galecki M, Francois D. Guidelines for antipsychotic-induced hyperprolactinemia. Psychiatric Annals. 2015 May 1;45(5):266–72. https://doi.org/10.3928/00485713-20150501-09
50. Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T. Neuroleptic malignant syndrome and atypical antipsychotic drugs. J Clin Psychiatry. 2004 Apr;65(4):464-70. doi: 10.4088/jcp.v65n0403
51. Belvederi Murri M, Guaglianone A, Bugliani M, Calcagno P, Respino M, Serafini G, et al. Second-Generation Antipsychotics and Neuroleptic Malignant Syndrome: Systematic Review and Case Report Analysis. Drugs R D. 2015 Mar;15(1):45-62. doi: 10.1007/s40268-014-0078-0
52. Sarkar S, Gupta N. Drug information update. Atypical antipsychotics and neuroleptic malignant syndrome: Nuances and pragmatics of the association. BJPsych Bull. 2017 Aug;41(4):211-216. doi: 10.1192/pb.bp.116.053736