PHARMACEUTICAL JOURNAL OF INDONESIA 2019. 4(2): 35-44

PHARMACEUTICAL JOURNAL OF INDONESIA

Available online at http://.pji.ub.ac.id

Side Effects of Antipsychotics on Schizophrenia Patients : A Literature Review

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ARTICLE HISTORY

Manuscript submission: April 15th 2019

Manuscript acceptance for review: July 2nd 2019

Aprroval for publication: July 24th 2019

Keywords :

Atypical Antipsychotics; Mental Disorder; Schizophrenia; Side Effects; Typical Antipsychotics.

A B S T R A C T

Schizophrenia is a chronic mental disorder that is characterized by distracted mind, behavioral changes, including delusions and hallucinations. The incidence of schizophrenia is 1.25% of the 2.47% of the psychotic disorder population. Pharmacological therapy given to schizophrenia patient is antipsychotic agents that work on the brain neurotransmitters including dopamine, serotonin, and glutamate. Atypical antipsychotic agents are the first-line therapy for schizophrenia, whereas typical antipsychotics are used as the second line when there is no improvement in symptoms. However antipsychotics agents have frequent side effects such as weight gain and extrapyramidal symptoms. Other reported side effects are including increased prolactin level (sexual dysfunction and menstrual irregularity), cardiovascular system disturbance (hypotension and prolonged QT interval), and lipid changes (elevated triglyceride and cholesterol). Consequences of these side effects can lead to poor adherence of patients, disease progressiveness and increase of physical morbidity and mortality. This article uses 42 literatures with literature parameters used over the past ten years. The purpose of this article is to provide a concise review of schizophrenia and discusses the side effects of atypical and typical antipsychotics based on literature reviews.

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1. Introduction

Schizophrenia is one of the most frequent mental health problems to be encountered. According to the study by Chang *et al.* in 2017, the study results showed that lifetime prevalence for schizophrenia is 1.25% of total psychotic disorder population.[1] Schizophrenia disorder is characterized by positive symptoms (for instance, delusion, hallucination, uncontrolled mumbling), negative symptoms (such as withdrawal from social life and decreased life motivation) and cognitive impairments.[2] Additionally, patients are often difficult to differentiate between reality and their thoughts.[3]

EugenBleuler created a term that is called "schizophrenia" in 1991. According to him, annual schizophrenia incidence was 15-20/100.000 with lifetime risk as many as 0.7%, and higher risk was found more in men than in women (1.4:1).[3] Study in the United States with sample based on households showed that prevalence of schizophrenia and other psychotic disorders ranged between 0.25% and 0.64%; while estimated prevalence of schizophrenia on non-institutionalized sample ranged between 0.33% and 0.75%.[4]

Pharmacological therapy that was administered on schizophrenia patients was antipsychotic agents that targeted on the change in neurotransmitter in the brain such as dopamine, serotonin, norepinephrine, and glutamate. Antipsychotic agents that were used as the first line treatment is the atypical group, whereas typical antipsychotic agents were used if there is no improvement in symptoms. The most frequent side effects of antipsychotic agents including increased body weight and extrapyramidal syndrome. Other side effects that had also been reported including increased prolactin level (sexual dysfunction and irregular menstruation), cardiovascular system disturbance (hypotension and prolonged QT interval), and alteration of lipid level (increased triglyceride and cholesterol level). The impact of these side effects could lead to patients' disobedience, the progressiveness of other diseases and increased physical morbidity and mortality.[5]

2. Discussion

Clinical Limitations of Schizophrenia

Schizophrenia is a complex mental disorder that could impact significantly to an individual and their family[2]. It is because schizophrenia is a chronic mental disorder that could lead the patient to have a distracted mind, including delusion and hallucination. Additionally, patients often difficult to differentiate between reality and their minds.[3,6,7]Schizophrenia consists of 5 subtypes as follows:[3]

a. Paranoid schizophrenia, the most common schizophrenia, in which delusion and auditory hallucination are evident.
b. Catatonic schizophrenia, which is less frequent type (about 7% cases). Typical symptoms include psychomotor disorder, catatonic, change of behaviour, echolalia (repetition of speech) and echopraxia (repetition of action).
c. Hebephrenic schizophrenia (unorganized), which is early onset of schizophrenia followed by a bad prognosis. Irresponsivebehaviour and unpredictable; influenced by inappropriate mood, including exaggerated laugh, inappropriate behaviour and joke are symptoms that can reveal. Additionally, this subtype is often accompanied by delusion and hallucination.
d. Residual Schizophrenia (chronic), which is schizophrenia with a history of one of schizophrenia that has been explained above, yet the disorder is currently showing "negative" symptoms and often dominated by cognitive symptoms.
e. Simple schizophrenia, is uncommon schizophrenia; whereas negative symptom without exhibit psychotic trait.

Etiopathophysiology of Schizophrenia

Causes of Schizophrenia are as follows:[3]

a. Genetic

Studies showed that schizophrenia is caused by family inheritance (genetic). Relative risk of schizophrenia inheritance from first line biological family is 10%. If both parents have schizophrenia, then the risk to be schizophrenia on their child will be 40%. Schizophrenia concordance is 10% for dizygotic twins and 40-50% on monozygotic twins.[7]

b.Neurochemical alteration

Some neurotransmitters have been associated with this disorder. Dopamine, serotonin, norepinephrine, GABA, and glutamate are some neurotransmitters that have shown involvement in schizophrenia pathogenesis (Figure 1).[7,8]

Figure 1a explains about glutamatergic, GABAergic, and dopaminergic from cortical area and substantianigra to accumbens nucleus and striatum, and hippocampus. Whereas figure 1b reveals about the effects of NMDA antagonist receptor on this cortex; reduced GABAergic innervations, reduced tonic dopamine and increased of phasic dopamine release in the striatum.

Dopamine role is based on two dopamine hypotheses. First, there is a group of agents that block dopamine function, known as phenothiazine and could reduce psychotic symptoms. Second, amphetamine, which increases dopamine release inducing paranoid psychotic and aggravate schizophrenia, and disulfiram that inhibits hydroxylase of dopamine and exacerbation of schizophrenia.[6,7]

Glutamate role in schizophrenia is majorly based on a hypothesis that glutamate reduces the function of NMDA glutamate receptors involved in schizophrenia pathophysiology. Besides, excessive serotonin could lead to the positive and negative symptoms of schizophrenia.

Norepinephrine as a neurotransmitter could also be included to cause schizophrenia. Selective neural degeneration in norepinephrine reward system explains anhedonia that occurs in schizophrenia patient. Other neurotransmitters that are involved in the occurrence of schizophrenia are G-Aminobutyric Acid (GABA) which has a regulation effect on dopamine activity and the loss of inhibitory GABAergic neurons could lead to the hyperactivity of dopaminergic neurons.[6,7]

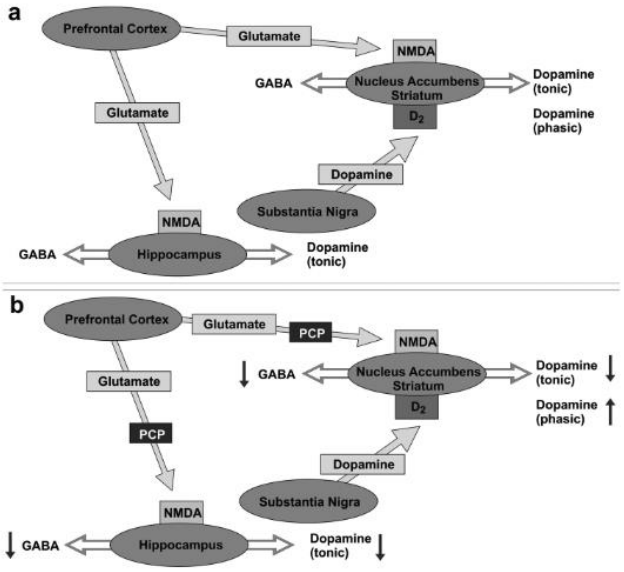

Figure 1. Role of Dopamine, Glutamate, GABA in Schizophrenia Pathogenesis[8]

Disorder in neurotransmission has yielded fundamental of pathophysiology theory of schizophrenia. This theory mainly focused on excessive or deficiency of neurotransmitters in the brain including dopamine, serotonin, norepinephrine, and glutamate. Other theories stated that the pathophysiology of schizophrenia involves aspartate, glycine, and gamma-aminobutyric acid as part of the neurochemical imbalance in schizophrenia.[6]

Abnormal activities on dopamine receptor particularly D_2 dopamine receptor is suspected to be associated in many of schizophrenia symptoms. Four dopaminergic pathways have been implicated (see Figure 2). The first pathway is the nigrostriatal pathway that is originated from substantianigra and ended in the caudate nucleus. Low dopamine level in this pathway is considered affecting the extrapyramidal system that leads to motoric symptoms. The second pathway is the mesolimbic pathway that spread from ventral tegmental area (VTA) to limbic area, also has a role in the positive symptom of schizophrenia to excessive dopamine level. The third pathway is the mesocortical pathway which is spread from the VTA to the cortex. Negative symptoms and cognitive deficits in schizophrenia are suggested to be caused by low mesocortical dopamine level. The fourth pathway is the tuberoinfundibular pathway from the hypothalamus to the pituitary gland, where decreased or blockade on tuberoinfundibular dopamine increases prolactin and as a result, may cause galactorrhea, amenorrhea, and reduced libido.[6,9,10]

Therapeutic Management of Schizophrenia

The therapy used to treat schizophrenia is an antipsychotic agents. Antipsychotic agents are very effective to treat any positive symptoms in acute episodes including hallucination, delusion, and also very useful to prevent relapse. Antipsychotic therapy algorithm for schizophrenia is shown in Figure 3.[10]

Antipsychotic consisted of 2 groups including typical antipsychotic agents (conventional/first generation) and atypical antipsychotic agents (second generation). Antipsychotic grouping is shown in Table 1.[3,7]

Table 1. Atypical and Typical Antipsychotics[3]

Atypical and typical antipsychotics		
Atypical antipsychotics	**Typical antipsychotics**	
Clozapine	Phenothiazines	Chlorpromazine,
Risperidone		Fluphenazine,
Quetiapine		Trifuoperazine
Olanzapine	Butyrophenones	Haloperidol
Aripiprazole	Thioxanthenes	Flupentixol,
Ziprasidone		Zuclopenthixol
Amisulpride	Diphenylbutylpiperidines	Pimozide
Paliperidone	Substituted benzamides	Sulpiride

Side Effects of Antipsychotic & Therapy Management

Atypical group of antipsychotic agents has a lot more metabolic side effects such as increased body weight, cardiac arrhythmia, hyperlipidemia, and diabetes which is caused by insulin resistance; whereas typical group of antipsychotic agents has more significant side effects such as extrapyramidal syndromes (EPS), hyperprolactinemia, and tardive dyskinesia, because of stronger dopaminergic effects of the these agents.[9,3,12,5,10] Table 2 shows a comparation among the side effects of typical and atypical group of antipsychotic agents in causing body weight and extrapyramidal syndromes.Side effect comparison among antipsychotic agents, FGA (first-generation antipsychotics) and SGA (second-generation antipsychotics), is showed on Table 3. Prevalence side effects in the first and second generation of antipsychotic drug that occurred in Indonesia is shown on Table 4.

Side Effects of Antipsychotic Agents on Endocrine System

Hyperprolactinemia has been reported up to 87% patients that were administered with antipsychotic agents including risperidone, haloperidol, and paliperidone.[9,16,6,17]Hyperprolactinemia is clinically defined as plasma prolactin level > 20 ng/ml for male and > 25 ng/ml for female. Hyperprolactinemia could lead to sexual dysfunction,anddecrease libido, cause irregular

menstruation and gynecomastia.[18,19]It is suggested that these side effects are

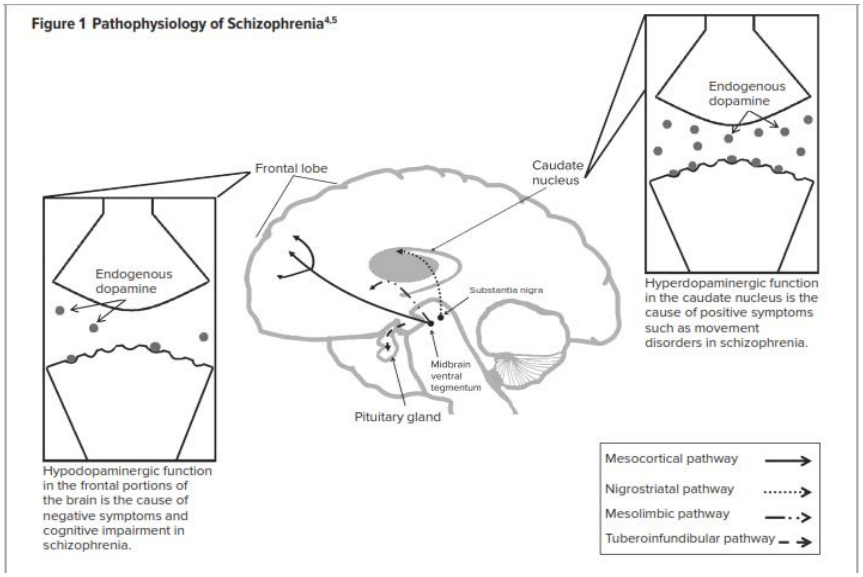

Figure 2. Pathophysiology of Schizophrenia[5]

caused by antipsychotic agents that block D_2 dopamine receptor in tuberoinfundibular thus remove inhibition of prolactin secretion and increase prolactin plasma level. Aripiprazole or ziprasidone is preferred for patients with increased prolactin level because this antipsychotic agent has a relatively low sexual dysfunction compared to some antipsychotic agents including clozapine, olanzapine, risperidone, and other conventional antipsychotic agents.[22,23,17]

Therapeutic management to resolve sexual dysfunction side effects is by using dopamine agonist (e.g.bromocriptine and cabergoline) and by using dopamine release agents such as amantadine, although the usage of the agents needs further study. Additionally, these side effects could also be done by sildenafil therapy. Then, recent study showed that more erection that was enough to penetrate is found more in the sildenafil group than placebo group (p=0.001).[16,24]

According to study by Takachi*et al.* in 2017, a study of 83 women, mean prolactin serum level was higher in patients with irregular menstruation than patients without menstruation disorder (89.3 ± 36.9 vs 42.5 ± 54.5; 95% confidence interval (CI): 46.8 [19.3 – 74.3]).[25]How antipsychotics promote menstruation disorder or stopped menstruation is not fully elucidated.However, dopamine blockade induced hyperprolactinemia is believed to become a major cause. Increased prolactin level promotes hormonal disorder that releases gonadotropin, which in the end causes irregular menstruation and amenorrhea.[26]

Increased body weight is another significant side effect on patients with antipsychotic agents. This side effect remains to happen in the early therapy of schizophrenia patients with antipsychotic agents and could lead to patient disobedience to consume their antipsychotic agents. Then, these antipsychotic agents could promote some side effects that have been related to increased risk of diabetes mellitus and cardiovascular and cerebrovascular mortality.[8,5,27] Clozapine and olanzapine have shown to have the biggest risk of increasing body weight and the highest risk of diabetes mellitus, followed by risperidone and quetiapine. However, risperidone and quetiapine had a minimal risk in increasing body weight.[9,12,28,6,29]

Table 2. Side Effects Comparison Between Typical and Atypical Antipsychotic in Causing Body Weight and Extrapyramidal Syndromes[5]

Drug	Weight Gain	Extrapyramidal Syndromes
Typical Antipsychotics (First-generation Antipsychotics)		
Chlorpromazine (Thorazine)	+ +	+ + +
Fluphenazine (Prolixin)	+	+ + + +
Haoperidol (Haldol)	+	+ + + +
Perphenazine (Trilafon)	+	+ + + +
Thioridazine (Mellaril)	+	+ + +
Thiothixene (Navane)	+	+ + + +
Atypical Antipsychotics (Second-Generation Antipsychotics)		
Aripiprazole (Abilify)	+	+
Anesapine (Saphris)	+	+ +
Clozapine (Clozaril)	+ + + +	+
Iloperidone (Fanapt)	+ +	±
Lurasidone (Latuda)	±	+
Olanzapine (Zyprexa)	+ + + +	+ +
Paliperidone (Invega)	+ +	+ +
Quetiapine (Seroquel)	+ +	+
Risperidone (Risperdal)	+ +	+ +
Ziprasidone (Geodon)	+	+ +

± = negligible risk;
+ = low risk;
+ + = moderate risk;
+ + + = moderately high risk;
+ + + + = high risk

Prevalence of metabolic syndrome in schizophrenia is exceptionally high, supported by a meta-analysis of 77 publications that reported the prevalence was

as high as 32,5% (95% CI = 30,1-35%). Based on Adult Treatment Panel III of the National Cholesterol Education Program Criteria estimated that this worrying proportion as many as 49,4% was obese.[27] This side effect, increased body weight, has been associated with the antipsychotic mechanism of action on 5-HT2A and 5-HT2C serotonin, dopamine D2 and D3, H1 Histamine and M3 muscarinic receptors. Antipsychotic agents also affect neuropeptide that controls appetite and energy metabolism. Other mechanisms that involve in increasing body weight are increased leptin level and reduced adiponectin level that was produced in adipose tissue, and alteration ghrelin level which acts on the arcuate nucleus of the hypothalamus to increase appetite and adipose tissue deposition.[29,27]

Therapeutic management to overcome this increasing body weight as a comorbid of diabetes, can be considered by administering metformin therapy. There is convincing evidence that supported metformin use in antipsychotic side effects management on increasing body weights. Based on two randomized controlled trials

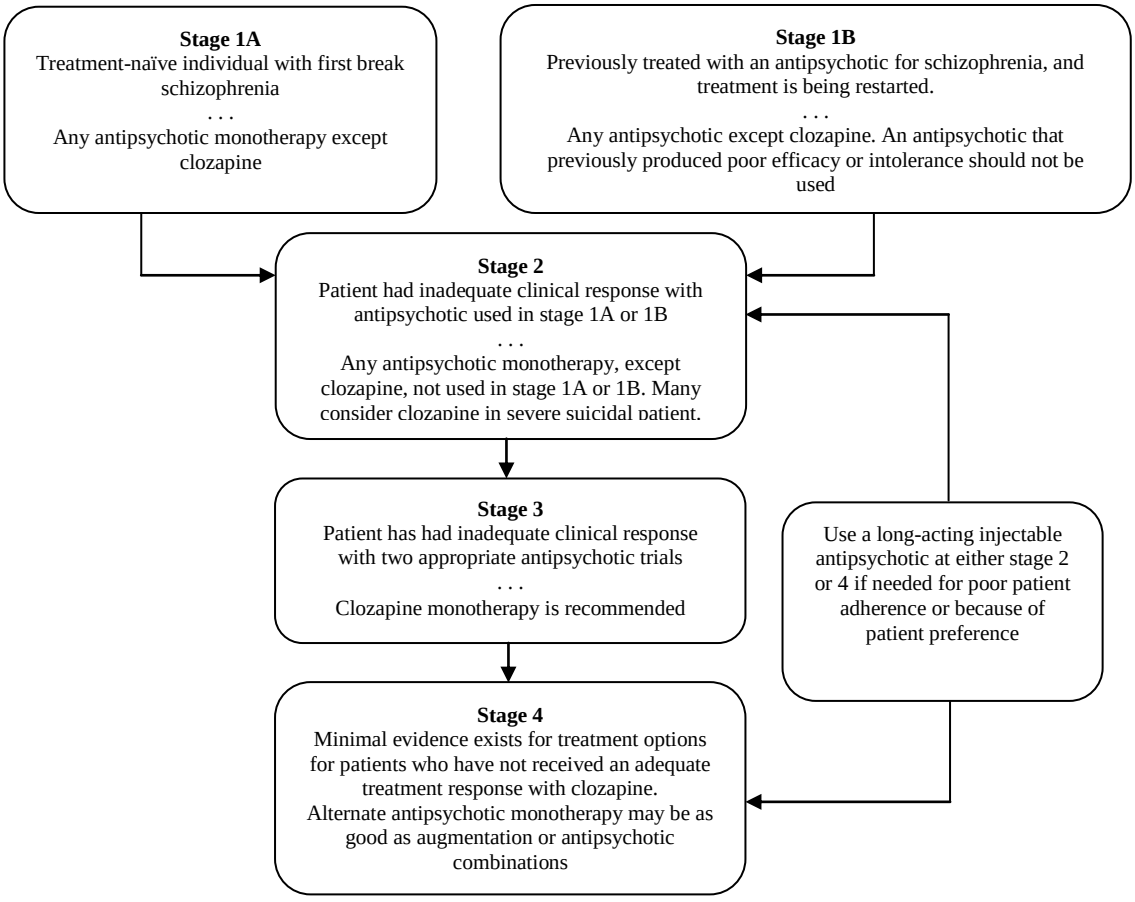

Figure 3. Antipsychotic Therapeutic Algorithm for Schizophrenia[10]

Side Effects of Antipsychotic Agents on Central Nervous System

The main extrapyramidal syndromes that are caused by antipsychotic agents are acute dystonia, akathisia, pseudoparkinsonism, and tardive dyskinesia.[32]These symptoms could lead to inconvenience, social stigma, and disobedience for patients. Dystonia often leads to disobedience and could threat patient's life. A dystonic reaction usually occurred in patients that were treated with FGA (first generation antipsychotics/typical) and often seen in the younger male. Dystonia can be minimalized by using SGA (second generation of antipsychotics/atypical) or by using FGA with lower dose.[9,6]

Akathisiaincludes 50% of extrapyramidal syndrome. Akathisia often concurred with dysphoria, which was seen 20% up to 40% patients that were treated with high potent FGA such as haloperidol and fluphenazine; whereasquetiapine and clozapine are seemed to have the lowest akathisia side effect. Based on a study that was conducted in McGann District Care Teaching Hospital, ShivamoggaInstitue of Medical Science, prevalence of akathisia is 10% to 20% in patients with atypical antipsychotic therapy; whereas patients with typical antipsychotic therapy with akathisia are about 20% to 52% [33%].

Pseudoparkinsonsism is another side effect which is occurred in patients that were treated with antipsychotic therapy FGA mostly seen in women and geriatric patient 15% and 36%, respectively. The mechanism of this antipsychotic side effect on parkinsonism is neurotransmitter imbalance such as hypoactivity of the D2 dopaminergic neuron, GABA, and acetylcholine, and hyperactivity of muscarinic cholinergic neuron M4.[34]

Hypoactivity of dopamine occurs after administration of FGA and SGA therapy. Dopaminergic

neurons on substansianigra activate D1 dan D2 dopaminergic neurons in the caudate nucleus. In the nucleus, D1 dopaminergic neuron weakly activatedynorphin neurons; while D2 dopaminergic neurons activate GABAergic neurons

Table 3. Side Effects of Antipsychotic FGA and SGA[8]

Side Effects	Low-potency FGAs[a]	High-potency FGAs[b]	SGAs					
			Aripiprazole (Ability)	Clozapine (Clozaril)	Olanzapine (Zyprexa)	Quetiapine (Seroquel)	Risperidone (Risperdal)	Ziprasidone (Geodon)
Anticholinergic effects	+ + +	+	0	+ + +	+	+	0	0
Dyslipidemia	+ +	+	0	+ + +	+ + +	+ +	+	0
Extrapyramidal symptoms	+	+ + +	+	0	+	0	+ +	+
Hyperprolactinemia	+ +	+ + +	0	0	+	0	+ + +	+
Neuroleptic malignant syndrome	+	+ +	+	+	+	+	+	+
Postural hypotention	+ + +	+	+	+ + +	+	+ +	+ +	+
Prolonged QT interval	+ + [c]	+	+	+	+	+	+	+ +
Sedation	+ + +	+	+	+ + +	+ +	+ +	+	+
Seizures	+	+	+	+ + +	+	+	+	+
Sexual dysfunction	+ + +	+ +	+	+	+	+	+ +	+
Type 2 Diabetes Mellitus	+	+	+	+ +	+ +	+	+	+
Weight Gain	+ +	+	0	+ + +	+ + +	+ +	+ +	0

Note : 0 = rare; + = lower risk; + + = medium risk; + + + = higher risk.
FGAs = first-generation antipsychotics; SGAs = second-generation antipsychotics.
* --- Effect are approximate, and relative to other antipsychotic medications rather than absolute risk of an adverse effects occuminng.
a --- FGAs with lower potency dopamine D_2 neuroreceptor blockade, including chlorpromazine and thioridazine.
b --- FGAs with higher potency dopamine D_2 neuroreceptor blockade. These include fluphenazine, haloperidol (formely haldol), thiothixene (Navane), and influoperazine. Please note that the FGA perphenazine is considered to have intermediate dopamine D_2 neuroreceptor blockade, with an adverse effect profile between the low and high-potency FGAs.
c --- individually, thioridazine has a higher risk of prolonged QT interval and should be used only when no other appropriate options are available.

Adapted with permission from Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic agents : a critical overview. CMAJ. 2005; 172(13):1703-1711, with additional information from reference 6.

in external globuspallidus. In internal globuspallidus, M4 muscarinic cholinergic neurons which are located in the putamen can increase hyperactivity of acetylcholine. In putamen, there is antagonist interaction between D2 dopaminergic neurons and 5-HT2A serotonin neurons by glutamatergic neurons that inhibit presynaptic NMDA. Thus, SGA with the antagonist effect of 5-HT2A in lower level could promote extrapyramidal syndrome.[34]

Tardive dyskinesia risk ranged between 0.5% and 62%. This side effect occurred in patients that were treated with long-term typical group antipsychotic therapy and the risk continued to increase in older patients. Risk of tardive dyskinesia significantly lower in patients with atypical group antipsychotic therapy and no case to be reported in patients treated with clozapinemonotherapy. This is because antipsychotic agents such as chlorpromazine, thioridazine, mesoridazine, clozapine, olanzapine, and quetiapine have been reported to be the highest sedation potential.[9,6]

Neuroleptic Malignant Syndrome (NMS) is a rare side effect of antipsychotic therapy, but it is a life-threatening condition. This side effect is found about 0.5% to 1.0% in patients that are treated with FGA therapy. Mental side effects such as psychosis and delirium could also be found in patients with FGA therapy with higher dose or patients with combination therapy with anticholinergic.[6]Therapy management to treat extrapyramidal side effects, that are often occurred, is showed on Table 6.

Side Effects of Antipsychotic Agents on Cardiovascular System

Orthostatic hypotension has been occurred up to 75% of patients with antipsychotic therapy.

Tabel 4. Prevalence of Side effects of Antipsychotic Agents in Indonesia[13,14,15]

At Bangli Mental Hospital, Bali Province[13]	At SambangLihum Mental Hospital, South Kalimantan[14]	In the Hospital Inpatient Ward, Grhasia Yogyakarta[15]
Extrapyramidal syndrome (EPS) (33,3%)	Extrapyramidal syndrome (98,3%)	Extrapyramidal syndrome
Tardif dyskenia (42,9%)	Orthostatic hypotension (86,4%)	Hypotension
Insulin resistance and hyperglycemia (19%)	Anticholinergic effect (76,3%)	
Dyslipidemia (4,8%)	Sedation (44,1%)	
	Nausea (27,1%)	
	Insomnia (16,9%)	
	Anorexia (5,1%)	
	Shortness of breath and cough (1,7%)	

Patients with diabetes mellitus, with the previous history of cardiovascular disease, or elder patients had the greatest risk of orthostatic hypotension.[9,6] Orthostatic hypotension is defined as decreased blood pressure (>20/10 mmHg) in 3 minutes on standing position. The antipsychotic agent that frequently causes orthostatic hypotension side effect is aripiprazole. However, some studies implied that orthostatic hypotension was caused by aripiprazole and clozapine. This side effect was mainly because aripiprazole and clozapine were competitive to α1 adrenoreceptor, thus promote a higher risk of orthostatic hypotension. As a 5-HT2A antagonist and 5-HT1A partial agonist, aripiprazole could increase the risk of orthostatic hypotension.[36]

Table 5. Metformin Therapy to Overcome Increasing Body Weight [30,31,29].

Characteristics	Studies			
	Wu et al (2012)		Wang et al (2012)	
Arms	Metformin 1g/day vs placebo		Metformin 1g/day vs placebo	
Trial duration	6 months		12 weeks	
No. of patients (completers/total)	76/84		66/72	
Primary outcome	Restoration of menstruation. Change in weight and BMI.		Change in body weight.	
Result	Metformin	Placebo	Metformin	Placebo
Mean Weight	-2,3 kg	+2,1 kg	-3,3 kg	+2,5 kg
Mean BMI	-0,93 kg/m^2	0,85 kg/m^2	-1,3 kg/m^2	+0,9 kg/m^2

This orthostatic hypotension side effect could be resolved by administrating fludrocortisone or ephedrine therapy if non-pharmacology therapies were failed. However, this administration should be done with caution because of the side effects. If there was still severe and refractory hypotension, it should be considered to cease clozapine therapy by stepping down the dose gradually in 2 weeks to prevent any cholinergic rebound and to switch into other alternative antipsychotics.[37]

Alteration in electrocardiography, particularly prolonged QTc could be found in a few patients with antipsychotic agents such as thioridazine, ziprasidone, risperidone, clozapine, olanzapine, and haloperidol.[38] Widened or prolonged QTc must be monitored during therapy, and antipsychotic agents must be ceased if this interval consistently surpassed 500 msec. Patients with a history of cardiac or cerebrovascular diseases, also patients in diuretic therapy, should take antipsychotic with caution because the risk of prolonged QTc interval.[9,6]

Side Effects of Antipsychotic Agents on Alteration of Lipid Profile

Patients treated with atypical antipsychotic therapy such as phenothiazine tended to show increasing triglyceride and cholesterol level. Atypical antipsychotic agents that showed a low risk of lipid alteration were risperidone, ziprasidone, and aripiprazole.[9,6] Antipsychotic effects on lipid alteration had been associated with increased triglyceride and very low-density lipoprotein release from adiposity. Additionally, antipsychotic could promote expression of sterol regulatory element-binding proteins (SREBP) and very low-density lipoprotein (VLDL) genes.[27]

Sterol regulatory element-binding proteins (SREBPs) were the centres to control allosteric from any lipid biosynthesis pathway. Notably, SREBP-1 was responsible as metabolism controller of triglyceride and fatty acid whereas SREBP-2 was the main controller of cholesterol metabolism.[39,40]

Table 6. Therapy to Treat Extrapyramidal Side Effects[35]

Side effect	Prevention	Treatment
Acute dystonic reactions	* Select antipsychotic with low rate EPS	* Oral or intravenous application of anticholinergic drug, e.g., 2,5-5 mg biperien, if necessary repeat procedure after 30 min, continue with biperiden oral (maximal 12 mg/d).
	* Start with low dose	
	* Increase dose slowly and stepwise	
Parkinsonism	* Select antipsychotic with low risk for parkinsonism	* Dose reduction or discontinuation of antipsychotic medication
	* Increase dose slowly and stepwise	* Switch to SGA
		* Oral application of anticholinergic drug
Akathisia	* Select antipsychotic with low risk for akathisia	* Dose reduction
	* Increase dose slowly and stepwise	* Oral application of beta-receptor blocking agent (e.g., propanolol 30-90 mg/dl)
		* Switch to certain SGAs
		* Oral application of benzodiazepines
		* Trial of an anticholinergic or an antihistaminic agent
		* Application of vitamin B6
		* Application of trazodone
Tardive Dyskinesia	* Select antipsychotic with low risk for tardive dyskinesia	* Switch to cozapine (alternatively to certain other SGAs)
	* Evaluate risk factors for tardive dyskinesia	* Administration of vitamin E
		* (Admnitration of tiapride)
		* ECT (only case reports and case series)
		* Deep brain stimulation (treatment in severe cases)
		* Pallidotomy (last resort treatment in extremely severe cases)
Neuroleptic malignant syndrome (NMS)	* Select antipsychotics with low risk for NMS	* Intensive care management
		* Stop antipsychotic treatment

	* (Application of dantrolene I.V (2,5-10 mg/kg body weight daily)
	* (Application of lorazepam 4-8 mg I.V/d).
	* In single cases ECT

In the liver, excessive SREBP activity could lead to increased circulation of cholesterol, free fatty acid (FFA), and triacylglycerol. Olanzapine, clozapine, and risperidone could promote significant upregulation of SREBP-1 and SREBP-2, and their downstream target genes that directed to increased lipid and cholesterol synthesis. Even single intraperitoneal injection with clozapine and olanzapine could induce increased FFA serum, followed by hepatic lipid accumulation.[40]

Monitoring Side Effects of Antipsychotic Agents

While on therapy with antipsychotic agents, patients must regularly be monitored by recording therapy effectivity, the side effect of agents, adherence, and physical health of the patients. Besides, they also should be monitored periodically for body weight, lipid and glucose profile, and ECG.[3] Guideline to prevent and monitor metabolic alteration side effect on patients with antipsychotic therapy SGA is showed in Table 7.[9,42,35]

Table 7. Monitoring Side Effect of SGA on Metabolic Alteration[9,42,35]

Assessment parameter	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annualy	Every 5 years
Medical and family history, including cardiovascular disease	x					x	
Weight (body mass index)	x	x	x	x	x		
Waist circumference	x					x	
Blood pressure	x			x		x	
Fasting plasma glucose level	x			x		x	
Fasting lipid profile	x			x			x

X = more frequent assessments may be warranted based on clinical status

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3. CONCLUSION

Antipsychotic therapy in schizophrenic patients has side effects such as:

1. Extrapyramidal syndrome. This is caused by imbalance of neurotransmitters such as hypoactivity of the D_2 dopaminergic neuron, GABA, and acetylcholine, and hyperactivity of muscarinic cholinergic neuron M4.
2. Weight gain. This is related to the action of antipsychotics on 5-HT2A and 5-HT2C serotonin, dopamine D_2 and D_3, H_1 Histamine and M_3 muscarinic receptor, increased body weight including increased leptin level, reduced adiponectin level, and alteration in ghrelin level.
3. Sexual dysfunction, decreased libido, irregular menstruation, and gynecomastia due to hyperprolactinemia. This side effects are caused by antipsychotic agents that block D_2 dopamine receptor in tuberoinfundibular thus remove inhibition of prolactin secretion and increase prolactin plasma level.
4. Orthostatic hypotension. This is because antipsychotics were competitive to α1 adrenoreceptor. Antipsychotics that work as 5-HT2A antagonists and 5-HT1A partial agonists can increase the risk of orthostatic hypotension.
5. Increased level of triglyceride and cholesterol. This relates to increasing triglyceride, sterol regulatory element-binding proteins (SREBP) and very low-density lipoprotein (VLDL) genes.

The impact of these side effects could lead to discomfort and patient disobedience, the progressiveness of other diseases and increased physical morbidity and mortality. Therefore, it is very important to monitor side effects in schizophrenia patients treated with antipsychotics.

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