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Systematic Review

Adverse Drug Reaction of Antipsychotic Medications Among Geriatric Patients: A Review

Sholikhah Rosvita Oktasari[1], Zullies Ikawati[1], Bambang Hastha Yoga Legawa Budiman[2]

[1]Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2]Department of Psychiatry, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

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Correspondence Author:
Email: zullies_ikawati@ugm.ac.id

Abstracts

Introduction: Antipsychotics is are the drug of choice in patients with mental disorders, especially schizophrenia. The use of antipsychotics in geriatric patients raises presents a concern, as age can lead to physiological changes that can impact both therapeutic effects and side effects. Problems related to drug therapy, if unaddressed, may results in not resolved, can lead to decreased quality of life, increased health care costs, increased clinical consequences, and even mortality. The aim of this study was to systematically evaluate and assess adverse drug reactions of antipsychotics among geriatric patients. **Methods:** Systematic literature search using Cochrane, ProQuest, Science Direct, Scopus, PubMed, and Google Scholar with a limited to publications time limit from 2013 to 2023. We the review was conducted the review in accordance with PRISMA provisions. We identified a total of 1145 articles and included 7 of them in the review. **Results:** This review presents the incidence of antipsychotic side effects in geriatric patients. The side effects that were observed included low blood pressure, increased blood pressure, somnolence, dizziness, constipation, agitation, weight gain, tremors and extra-pyramidal symptoms, hyperprolactinemia, tachycardia, bradycardia, insomnia, and sedation. Regarding the regimen, four studies reported olanzapine. Two studies reported clozapine and risperidone, and one study reported haloperidol, cariprazine, levomepromazine, and quetiapine. **Conclusion:** Follow-up and long-term studies with larger sample sizes in geriatrics are needed to confirm the side effects of antipsychotics. Knowledge of drug side effects is useful for determining appropriate therapy for geriatric patients with psychiatric disorders.

Keywords: Antipsychotics, Adverse Drug Reaction, Drug Related Problems, Schizophrenia

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INTRODUCTION

Antipsychotics have been widely used as a therapy to treat psychiatric disorders, including schizophrenia. Antipsychotics are effective in treating schizophrenia, but some population groups respond to antipsychotics variously. Antipsychotics are classified into two groups: atypical antipsychotics, or first-generation antipsychotics (FGA), and typical antipsychotics, or second-generation antipsychotics (SGA). The differences between FGAs and SGAs mainly lie in the receptor profile, the incidence of extrapyramidal side effects (SGAs are lower than FGAs), efficacy (especially of clozapine) in groups that do not respond to antipsychotic treatment, and their effect on negative symptoms [1].

Therapy using antipsychotics, especially in schizophrenia patients, is generally chronic. The most common problems related to drug therapy in psychiatric departments are drug-drug interactions and the presence of drug side effects [2]. An adverse drug reaction (ADR) is an unintended and accidental response to a drug, which occurs from the use of a medicinal product at doses normally used in humans for prevention, diagnosis, or therapy of diseases or for modification of physiological functions [3], [4]. Antipsychotic side effect profiles are important in determining treatment options for specific populations. For example, adolescents are more susceptible to the side effects of weight gain and sedation, while geriatrics may be more susceptible to side effects such as orthostatic hypotension, dyskinetic dyskinesia, and anticholinergic effects [5].

Antipsychotic drugs have been used in geriatrics suffering from psychosis or dementia-related behavioral disorders. A meta-analysis showed that geriatrics with psychotic disorders who used antipsychotics had a 1.6 to 1.7-fold increased risk of death. The cause of the increased mortality may be due to sudden cardiac death and cerebrovascular accidents [6].

Treatment of adverse drug reactions in geriatrics needs to be a concern because age can affect physiological changes, such as decreased cardiac output (reduction in hepatic and renal blood flow), possible decrease in liver metabolism, decreased glomerular filtration rate, and changes in body fat composition. These changes can alter the pharmacokinetics of drugs. Changes in fat composition contribute significantly to body mass in the elderly, which can affect changes in the volume of drug distribution. Decreased drug elimination may increase prolonged effects and greater pharmacodynamic sensitivity of both therapeutic response and side effects [1], [7]. This study aims to identify and evaluate adverse drug reactions of antipsychotics that are often used as therapy for mental disorders in geriatric patients so that it is useful to determine the selection of appropriate therapy for geriatric patients.

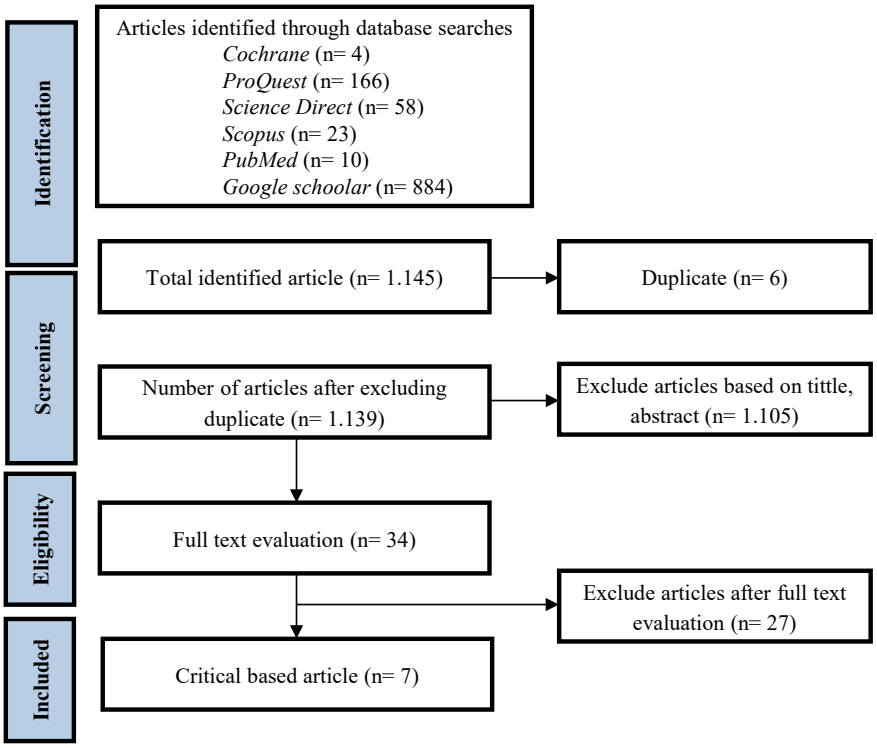
METHODS

This study was a systematic review to collect, assess, and evaluate the side effects of antipsychotics often used in geriatric patients with mental disorders. Searching for articles or literature is carried out using 6 (six) search engines, including Cochrane, ProQuest, Science Direct, Scopus, PubMed, and Google Scholar, with a limited publications time limit with a period of the last 10 years. The a common search strategy used for databases is were searched using Boolean operators. The keywords used are “adverse drug reaction,” “schizophrenia,” and “elderly.”. Articles or literature that have been obtained are then identified and filtered based on predetermined inclusion and exclusion criteria. The inclusion criteria were cohort, case-control, clinical trials, and cross-sectional studies evaluating antipsychotic side effects in elderly patients. Research using Indonesian or English. Exclusion criteria include article reviews, case reports, case studies, and descriptive research.

The systematic review of research follows the provisions of Preferred Reporting Items for Systematic Review (PRISMA). The data

analysis process begins according to the PRISMA method, including the identification, screening, and eligibility of articles to be analyzed. The results will be recorded and presented in table form, accompanied by explanations, discussions, and conclusions.

Figure 1. Flowchart of systematic review research methods using PRISMA



RESULTS

Of the 1.145 articles that were retrieved through visiting search engines, 6 duplicates were identified and removed using Mendeley. A total of 1.139 articles were saved for further screening. Among which, a total of 1,105 records were excluded based on title and abstract. The full texts of the remaining 34 articles were thoroughly assessed for eligibility, and 27 were excluded because they had reported unclear or mixed findings and/or incomplete information. Finally, 7 articles were included in the review.

The limit of the publication year limit for included research ranges from 2013 to 2023. A review of demographic distribution is also included. Four of these studies had employed cohort design [8]–[11], two studies had employed non-randomized, open-labeled, and observational trials [12], [13], and the remaining one study had employed clinical trials [14]. The research sample size ranged from 23 [13] to 61915 [10]. The majority of studies were conducted on geriatric patients older than 60 years with schizoaffective or schizophrenia disorders, while other studies were conducted on bipolar, organic disorder, mood disorder, depression, dementia, and any mental, behavioral, and neurodevelopmental disorder. Two studies were conducted with inpatients [11], [13], whereas five studies were outpatients [8]–[10], [12], [14].

The side effects of antipsychotics found in geriatrics are presented in Table 2. Side effects include low blood pressure [10], [12], [13], increased blood pressure [12]–[14], somnolence [12], [13], dizziness [12], [13], constipation [11], agitation [9], [13], weight gain [9], [14], tremors and extra-pyramidal symptoms [9], [11], [14], hyperprolactinemia [14], tachycardia [9], bradycardia [13], insomnia [14], and sedation [9]. Regarding the regimen, four studies reported olanzapine [8], [10], [12], [13], and one study reported haloperidol [13], cariprazine [14], levomepromazine [12], and quetiapine [10]. Two studies reported clozapine [9], [10] and risperidone [11], [14].

Table 1. Patient criteria

No	Author (year)	Subject (total subject)	Age (n)	Diagnose (n)
1	Suzuki, *et al*. (2013)[13]	23	65.1 ± 7.9 (12) 63.8 ± 1.8 (11)	Schizophrenia
2	Greil *et al*. (2013)[8]	11.446 (39.728)	>60 (11.446)	Addiction (531), Affective disorder (2921), Neuroses/personality disorder (712), Organic disorder (3616), Schizophrenia (3090)
3	Suzuki and Gen (2013)[12]	52	64.2 ± 4.0 (27) 64.5 ± 2.6 (25)	Schizophrenia
4	Iqbal *et al.* (2020)[9]	198 (2835)	61-70 (151) 71-80 (43) >80 (4)	Schizophrenia (2122), Schizoaffective (3660), Bipolar (81), Any mental, behavioral, and neurodevelopmental disorder (60), Any other diagnosis (135)
5	Szatmari *et al.* (2020)[14]	27	65-74 (27)	Schizophrenia
6	Friedrich *et al.* (2020)[10]	61.915 (291.510)	> 65 (61.915)	Organic disorder (36.949), Mood disorder (80.505), Schizophrenia (139.418)
7	Pratheeksha *et al.* (2023)[11]	180	60-69 (114) 70-79 (30) ≥ 80 (5)	Bipolar affective (56), Alcohol dependence syndrome (53), Nicotine dependence syndrome (35), Depression (35), Dementia (19), Schizophrenia (16)

Table 2. Reported side effects among geriatrics patients

No	Drug regimen	Types of research	Reported Side Effects
1	Cariprazine [14]	Clinical Trial	Nasopharyngitis, insomnia, hypertension, weight gain, and glucose increased (11/17)
2	Clozapine [10]	Observational	Hypotension 1 case
3	Clozapine [9]	Cohort	1st month 61-70 year: agitation (38.76%), fatigue (41.09%), feeling sick (10.08%), sedation (41.09%), shaking (4.65%), tachycardia (9.30%), weight gain (6.93%) 71-80 year: agitation (38.46%), fatigue (30.77%), feeling sick (7.69%), sedation (33.33%), shaking (7.69%), tachycardia (2.56%), weight gain (7.69%) 2nd month 61-70 year: agitation (27.13%), fatigue (29.46%), feeling sick (6.98%), sedation (29.46%), tachycardia (6.98%), weight gain (4.65%) 71-80 year: agitation (23.08%), fatigue (20.51%), feeling sick (2.56%), sedation (15.38%), tachycardia (7.69%), weight gain (5.13%) 3rd month 61-70 year: agitation (20.93%), fatigue (27.91%), sedation (19.38%), shaking (6.20%), tachycardia (7.75%), weight gain (3.88%) 71-80 year: agitation (15.38%), fatigue (12.82%), sedation (15.38%), shaking (5.13%), tachycardia (5.13%), weight gain (5.13%)
4	Flupentixol decanoate in combination with Clozapine [10]	Observational	Hypotension 1 cases
5	Haloperidol intramuscular [13]	Non-randomized, open-labeled, not double-blind,	Bradycardia 2 (18.2%), injection site pain 2 (18.2%), blood pressure increased 2 (18.2%), low blood pressure 1 (9.1%), agitation 2 (18.2%)

Table 2. Reported side effects among geriatrics patients

No	Drug regimen	Types of research	Reported Side Effects
		and naturalistic observational trial	
6	Levomepromazine intramuscular [12]	Open-labeled, naturalistic observational trial	Mild pain at the injection site (8.0%), increased blood pressure 1 (4.0%), low blood pressure (systolic < 100 mmHg) 6 (25%), somnolence 3 (12%), and dizziness 3 (12%)
7	Olanzapine [10]	Observational	Hypotension 2 cases
8	Olanzapine intramuscular [13]	Non-randomized, open-labeled, not double-blind, and naturalistic observational trial	Blood pressure increased 3 (25%), somnolence 2 (16.7%), injection site pain 2 (16.7%), suspensibility dizziness 2 (16.7%), thirst 1 (8.3%)
9	Olanzapine intramuscular [12]	Open-labeled, naturalistic observational trial	Mild pain at the injection site (3.7%), increased blood pressure 3(11.1%), somnolence 3 (11.1%), dizziness 2 (7.4%), and thirst 1 (3.7%)
10	Olanzapine [8]	Cohort retrospective	Weight gain 2 (0.17%)
11	Quetiapine [10]	Observational	Hypotension 2 cases
12	Risperidone [14]	Clinical Trial	Hyperprolactinemia, insomnia, and parkinsonism (9/10)
13	Risperidone [11]	Cohort retrospective	Constipation 22 (34.88%) Daytime drowsiness 7 (10.47%) Tremors and extra-pyramidal symptoms 4 (6.98%)

DISCUSSION

Geriatric individuals are more vulnerable to the effects of orthostatic hypotension (resulting in falls) and anticholinergic effects (leading to cognitive impairment). Orthostatic hypotension occurs when the systolic blood pressure decreases ≥ 20 mmHg or ≥ 10 mmHg in diastolic blood pressure when changing from a lying to a standing position [5]. Three articles in a review identified hypotension as a side effect of antipsychotics. Suzuki et al. (2013) observed hypotension with intramuscular haloperidol [13]. Suzuki and Gen (2013) found a decrease in systolic blood pressure to <100 mmHg after intramuscular administration of levomepromazine [12]. Friedrich et al. (2021) reported a 37.6% occurrence of hypotension in 174 cases, with drugs such as quetiapine, olanzapine, and flupentixol decanoate in combination with clozapine and clozapine being implicated [10]. The American Psychiatric Association (APA) practice guidelines support these findings, highlighting clozapine's frequent association with hypotension, occasional occurrences with olanzapine and quetiapine, and rare instances with haloperidol [7]. Antipsychotics' antagonism of α1 receptors is linked to hypotension [15]. It is recommended to use the lowest effective dose, manage dose-related effects and behavioral changes, ensure adequate hydration, or consider substituting other antipsychotics to achieve treatment goals [5].

Dizziness is largely correlated with antagonisms at α1, muscarinic, and serotonin (5-HT2A, 5-HT2C) receptors [15]. Two articles cited the effects of dizziness on geriatrics with a diagnosis of schizophrenia following the intramuscular use of olanzapine [12], [13]. Sedation is a common side effect associated with antipsychotic use. Iqbal et al. (2020) reported sedation in geriatrics in 1-to-3-months after using clozapine [9]. Prathekshaa et al. (2023) found that risperidone is the most common drug causing daytime drowsiness in 10.47% of subjects [11]. Excessive sedation can lead to somnolence, as observed in two studies in geriatrics after intramuscular administration of olanzapine [12], [13]. Sedation is associated with antagonists against histaminergic receptors. The highest receptor blockades for clozapine, chlorpromazine, and zotepine, gradually decreasing from quetiapine, olanzapine, ziprasidone, asenapine, haloperidol, and risperidone [15], [16]. Considerations for managing sedation include reducing the daily dose, for example, at a divided dose changed to a single dose at night or selecting

antipsychotics with minimal side effects to reduce the severity of sedation [7].

Psychomotor agitation associated with psychosis is sometimes difficult to differentiate from akathisia, so psychiatrists will increase the dose of antipsychotics, which causes an increase in the side effects of akathisia [7]. Patients usually appear agitated, unable to sit still and perform repetitive motor movements [17]. Iqbaal et al. (2020) said that agitation occurred after using clozapine in the 1-to-3 month period. This study combines information using ADEPt (Adverse Drug Event Annotation Pipeline) with treatment episodes taken from clinical texts to investigate the relationship between clozapine and adverse drug events. ADEPt is used to detect and validate the presence of medication side effects in mental health clinical records [9]. The general principle of management for treating patients with drug-associated psychiatric side effects like agitation is to identify the causes, review medication history, communicate with the primary treating team, monitor patient status, and educate the caregiver about the side effects. Dose adjustment may be considered to reduce side effects while optimizing treatment [18], [19].

Extrapyramidal symptoms are often referred to as drug-induced movement disorders; the symptoms include akathisia, dystonia, pseudo-parkinsonism, and tardive dyskinesia. The mechanism of extrapyramidal symptoms is excessive inhibition of dopamine receptors in the nigrostriatal pathway [20], [21]. Two studies say that risperidone is a drug that generally causes extrapyramidal side effects in geriatrics [11], [14]. Iqbal et al. (2020) say clozapine can cause shaking after the 1st month and the 3rd month of use [9]. Haloperidol has the highest risk of causing extrapyramidal symptoms, while risperidone, paliperidone, lurasidone, and chlorpromazine are associated with moderate events, and quetiapine, olanzapine, sertindole, and clozapine have milder effects [16]. To manage parkinsonism, such as tremor and rigidity, one approach is to decrease the dose and switch from high-risk to low-risk antipsychotics. Caution is needed when using anticholinergic agents like benztropine, especially in the elderly, although they may be useful for akathisia with concomitant parkinsonism. Amantadine in doses of 100–400 mg per day may be given to elderly patients not suitable for anticholinergics. In cases of acute dystonia, intramuscular anticholinergics (biperiden 5 mg) or antihistamines (diphenhydramine 50 mg) may be administered. Propranolol, a beta-adrenergic inhibitor, is a traditional first-line therapy for akathisia, with moderate efficacy supported by placebo-controlled trials. Valbenazine and deutetrabenazine have been approved by the FDA for treating tardive dyskinesia [5].

Weight gain is generally caused by SGAs and certain FGAs. Clozapine, zotepine, and olanzapine may increase extreme body mass index (BMI) [16]. Two articles found the potential for antipsychotics to induce weight gain. Szatmari et al. (2020) found that 11 patients experienced increased weight gain and glucose levels after using cariprazine [14]. Iqbal et al. (2020) found side effects of weight gain after using clozapine for 3 months [9]. In the elderly population (aged 65-87 years), the duration of clozapine treatment correlated positively with weight changes, predicting a +0.46% weight gain for each month ($P < 0.001$) [22]. Various antagonistic receptor interactions, including 5-HT2c, M3, and H1 receptors, contribute to increased body weight [15]. Antipsychotics bind to histamine receptors, especially H1, which influences weight gain and obesity [23], [24]. Monitoring for metabolic side effects is essential for patients. Lifestyle modification can be carried out if there is an increase in body weight. Consideration switching to a lower-risk antipsychotic is effective for reducing weight and improving metabolic profile [5].

Hyperprolactinemia is an increase in prolactin concentration above normal (15-20 g/L in men and 15-25 g/L in women). The increase in prolactin secretion is generally due

to lack of inhibition of the hypothalamus by prolactin inhibition factor (PIH). Psychotropic drugs that have an antagonistic effect on dopamine can affect the main regulatory mechanism of prolactin but with different levels. This difference is thought to be due to antagonist or partial agonist effects on dopamine-2 receptors [25], [26]. Side effects are generally dose-dependent, although antipsychotics such as risperidone, paliperidone, and amisulpride may exert significant effects on serum prolactin at relatively low doses [26]. Szatmari et al. (2020) say 9 patients experience hyperprolactinemia after taking risperidone [14]. Management of antipsychotic-induced hyperprolactinemia therapy includes discontinuing or reducing the dose, switching to prolactin-sparing drugs (such as aripiprazole, lurasidone, quetiapine, or clozapine), or adding a dopamine agonist. But it should be noted that the addition of dopamine agonists may worsen psychotic symptoms. Recent research has shown that prolactin-sparing drugs such as metformin and raloxifene demonstrate safety and efficacy in lowering prolactin [25], [27].

Antipsychotics can increase sympathetic tone, which has effects on the cardiovascular system such as cardiovascular hypertrophy, arrhythmias, and pathogenesis of essential hypertension by increasing peripheral resistance, cardiac output and heart rate, and renin production [24]. Two articles find that patients had an increase in blood pressure after intramuscular administration of olanzapine [12], [13]. Another article mentioned hypertension side effects occurred in patients taking cariprazine [14]. Hypertensive management can be given beta blockers to cope with increased adrenergic activity. The administration of FGA may be considered as it provides favorable somatic and psychiatric outcomes [24], [28].

Antipsychotics have anticholinergic effects that can cause cardiovascular side effects due to muscarinic type 2 receptor antagonism. This antagonistic effect causes tachycardia and systemic anticholinergic [28]. The most reported antipsychotic-induced tachycardia was the use of clozapine [7], [28]. Iqbal et al. (2020) found patients taking clozapine experienced tachycardia in months 1 to 3 [9]. Management strategies to overcome tachycardia due to antipsychotics are to reduce the dose, stop anticholinergic or stimulant treatment, and use strategies to overcome orthostatic hypotension. Beta blockers have been reported as persistent and significant tachycardia therapy due to clozapine. However, beta blockers should not be given if the heart rate is less than 120 bpm due to insufficient research data and fear of causing other side effects such as orthostatic hypotension [7], [28].

SGAs (such as clozapine, olanzapine, quetiapine, and risperidone) have been reported to lower heart rate. This case generally occurs in geriatric patients [28]. In contrast to the previous study, Suzuki et al. (2013) mentioned 2 patients (18.2%) experienced bradycardia side effects after using intramuscular haloperidol [13]. Antipsychotic-induced bradycardia may occur due to changes in the pharmacokinetics and pharmacodynamics of the drug due to geriatric patients, so the risk of side effects of psychotropic drugs also increases [28].

The limitation of this study is that it only reviews existing research. Research about the side effects of antipsychotics in the geriatric population is still limited. However, differences in age, dosing regimen, pharmacokinetics, and drug pharmacodynamics may significantly influence the occurrence of antipsychotic side effects in geriatrics.

CONCLUSION

Antipsychotic side effects can occur in all patients with psychiatric disorders, including geriatrics. The increased risk of side effects can be influenced by the dosage regimen and changes in physiological conditions in geriatrics. Doctors should be careful when choosing appropriate medications for geriatric patients with mental disorders to maximize the effectiveness of therapy and

minimize the risk of side effects. However, to confirm the side effects of antipsychotics in geriatric patients, further and long-term research with larger sample sizes and cross-ethnicity is needed.

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