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Adverse Drug Reactions of Atypical Antipsychotics: A Review

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Abstract:
Background: Adverse Drug Reactions (ADRs) as responses to drugs that are dangerous, unwanted, and occurring at doses typically used for prophylaxis, diagnosis, or modification of physiological function in humans. ADRs are a very important health problem to pay attention to. Currently, information on ADRs of atypical antipsychotics is lacking. Therefore, this literature study aims to summarize the adverse drug reactions (ADR) that occur due to the use of atypical antipsychotics and to examine their causality, severity, prevention, and predictability.
Methods: The method used in the writing of this article is a literature study using computerized databases such as Science Direct, Pubmed, Semantic Scholar, and Google Scholar. The keywords used were "Adverse drug reactions" OR "ADRs" and "Atypical antipsychotics" OR "Second-generation antipsychotics".
Results: The most common adverse drug reactions are weight gain, constipation, insomnia, dry mouth, tremor, sedation, hypersalivation, somnolence, extrapyramidal signs and symptoms (EPS), and headache. Assessment of causality by using the Naranjo's scale and the WHO assessment scale the results were "probable" followed by "possible" and "certain". Assessment of the severity by using the Hartwig and Siegel scale the results were "mild" followed by "moderate" and "severe". Prevention assessment of ADRs for atypical antipsychotics by using the Modified Schumock and Thornton scale the results were "probably preventable", followed by "not preventable" and "definitely preventable". The majority of ADRs from these atypical antipsychotics are predictable.
Conclusion: The majority of ADRs of these atypical antipsychotics are predictable. However, to ensure patient safety, a large enough prospective study should be considered to clarify this issue.
Key Word: Adverse Drug Reactions, Atypical Antipsychotics, Naranjo's Scale, WHO assessment scale, Hartwig and Siegel scale, Modified Schumock and Thornton scale

I. INTRODUCTION

Adverse drug reactions (ADRs) are important health problems. ADRs cause significant morbidity and mortality over the centuries. ADR is also responsible for about 0.3% to 11% of the incidence of hospitalizations [1]. ADRs are believed to be the fourth to sixth cause of death in hospitalized patients [2]. World Health Organization (WHO) defined Adverse Drug Reactions (ADRs) as responses to drugs that are dangerous, unwanted, and occurring at doses typically used for prophylaxis, diagnosis, or modification of physiological function in humans [3].

Adverse drug reactions (ADRs) are commonly found in a class of drugs that act on the central nervous system. Types of reactions commonly reported are dizziness, drowsiness, headache, hallucinations, neuroleptic malignant syndrome, serotonin syndrome, anxiety, depression, extrapyramidal reactions, ataxia, hyperactivity, insomnia, malaise, pain, vertigo, dystonia, asthenia, and seizures[2]. These adverse drug reactions cannot be avoided, especially with the use of drugs such as antipsychotics [4].

Antipsychotics are a pharmacological mainstay in the treatment of schizophrenia and other symptoms of psychosis [5]. Antipsychotics are divided into two main groups, namely, First-Generation Antipsychotics (FGAs) or better known as typical antipsychotics, and Second-Generation Antipsychotics (SGAs) which are more commonly known as atypical antipsychotics [5,6]. With the discovery of atypical antipsychotics, namely, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, the trend in psychosis treatment began to leave the typical antipsychotic therapy. These atypical antipsychotics are preferred because of the lack of extrapyramidal side effects and tardive dyskinesia and are effective in treating both positive and negative symptoms of schizophrenia and have the potential to improve cognitive function in patients [5]. However, this is still controversial [6]. Although atypical antipsychotics are less likely to produce extrapyramidal side effects, they exhibit a spectrum of side effects of their own [7].

Adverse Drug Reactions (ADRs) of atypical antipsychotics have a negative impact on long-term adherence and in achieving the prescribed treatment outcome [7]. Several adverse drug reactions were identified during the pre-marketing study. Therefore, a pharmacovigilance system for detecting adverse drug reactions is very important [8]. ADR signals can be captured via the spontaneous reporting method in Pharmacovigilance, however the lack of awareness at the health professional and patient level is a drawback of this method [9]. Therefore, this article review is needed to determine and summarize the adverse drug reactions (ADRs) that occur due to the use of atypical antipsychotics and see their causality, severity, prevention, and predictability.

II. METHODS

The method used in the writing of this article is a literature study using computerized databases such as Science Direct, Pubmed, Semantic Scholar, and Google Scholar. A literature search was done by writing keywords in the search column. The keywords used were "Adverse drug reactions" OR "ADRs" combined with the keywords as follows: "Atypical antipsychotics" OR "Second-generation antipsychotics". The literature used as material for scientific data was articles with a publication span of 10 years (2010-2020). Data extraction was carried out in August-October 2020.

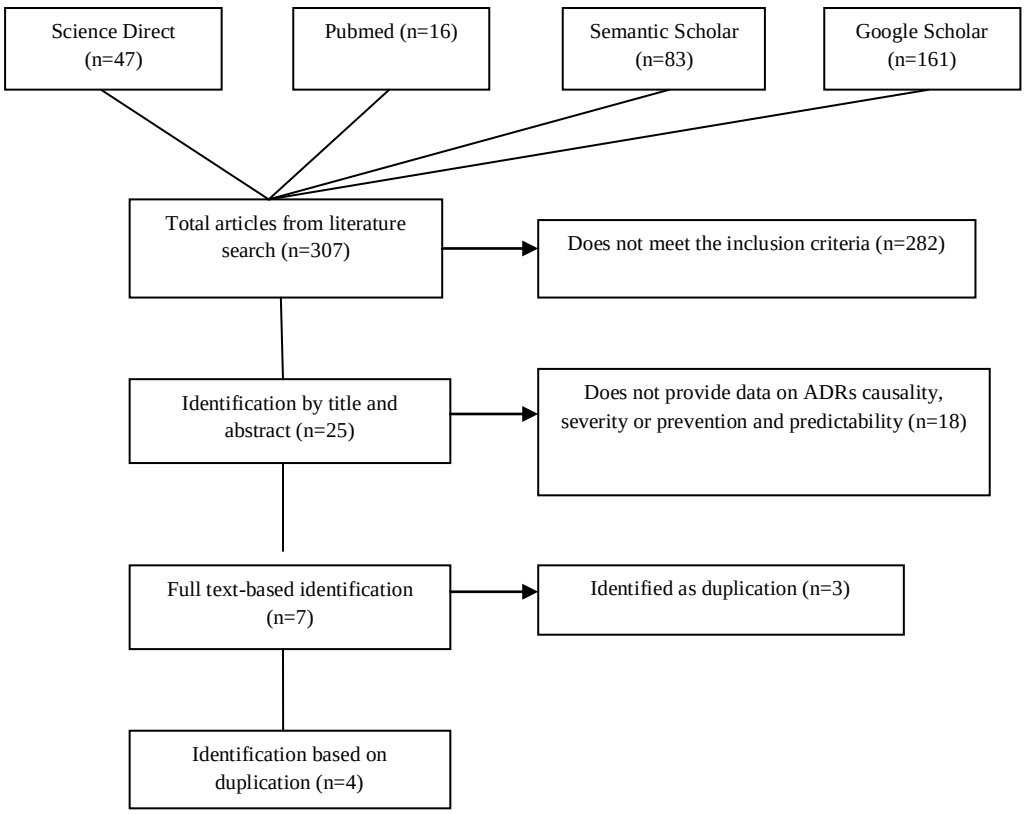
The inclusion criteria for selected articles were research articles containing the search keywords used, articles assessing causality or severity or prevention and predictability of atypical antipsychotics, and articles published in the last ten years. The data collected in this article that discusses Adverse Drug Reactions (ADRs) are in the form of the number of patients, gender, age, the most frequently prescribed drugs, the drugs that most often cause ADRs, and the resulting ADRs

The assessment was carried out on the selected articles. The assessment of causality was done by using the Naranjo's scale or the WHO assessment scale, the assessment of the severity was done by using the Hartwig's Severity Assessment Scale, and the assessment of predictability and prevention was done by using the Modified Schumock and Thornton scale method.

III. RESULT

The initial search resulted in 307 articles (Fig. 1). After identifying the title and abstract, it was found that 282 articles did not meet the intended criteria. The remaining 25 articles were identified by studying the full text and it was found that 18 articles did not meet the required criteria, namely not presenting data on causality, severity or prevention, and predictability of ADRs from atypical antipsychotics. 7 articles met the inclusion criteria, but 3 of them were the same article. Finally, 4 articles were included in the literature study.

Figure 1. Flow chart of the literature search



The four articles analyzed were prospective observational studies. These four articles discuss adverse drug reactions (ADRs) from atypical antipsychotics [4, 7, 9, 10]. Three of these four articles stated that ADRs were more common in males than females [4, 9, 10]. Of the 102 patients who showed symptoms of ADRs, 68 patients (66.6%) were male and 34 patients (33.3%) were female [4]. Of the 74 patients who came with ADRs complaints, 52 patients (70.27%) were male and 22 patients (29.72%) were female [9]. Of the 71 patients who presented with ADRs, 46 patients (64.78%) were male and 25 patients (35.21%) were female [10]. Another article stated that ADRs were more common in women than men. Of the 49 patients who came with ADRs complaints, 25 patients (51%) were female and 24 patients (49%) were male [7] (Table 1). Combined, the total number of patients who came with ADRs was 296 patients, of which 190 patients (64.18%) were male and 106 patients (35.81%) were female. By age group, one article stated that ADRs were common in the 30-40 year age group [7]. Whereas the other three articles did not present data on age groups likely to cause ADR problems [4, 9, 10] (Table 1).

Most frequently prescribed atypical antipsychotic agents

Based on the type of drug most frequently prescribed, olanzapine and risperidone occupied the highest positions [4, 7, 9, 10] (Table 1). Of the 71 prescriptions, 54 prescriptions (76.05%) were olanzapine, followed by 8 (11.26%) prescriptions for risperidone [10]. Of the 84 existing prescriptions, 38 prescriptions (45.24%) were risperidone, followed by 34 prescriptions (40.48%) for olanzapine [9]. A total of 16 prescriptions (27%) were risperidone and olanzapine as well as 16 (27%) [7]. Of all the available prescriptions, olanzapine was the most frequently prescribed drug, followed by risperidone (no%) [4].

Apart from the above olanzapine and risperidone, the next position was followed by amisulpride in 7 prescriptions (9.85%) and quetiapine 2 recipes (2.81%) [10]. Then clozapine as much as 6 recipes (7.14%), quetiapine 5 recipes (5.95%), and aripiprazole 1 recipe (1.19%) [9]. Then there were 14 recipes of quetiapine (23%), 10 recipes of aripiprazole (16.95%), 2 recipes of ziprasidone (3.39%), and 1 recipe of amisulpride (1.69%) [7]. Then followed by Aripiprazole, Amisulpride, Quetiapine, and Clozapine (without%) [4].

Atypical antipsychotic agents with a high risk of causing ADRs

Based on the type of drug that causes ADRs most often, olanzapine and risperidone have the highest positions [4, 7, 9, 10] (Table 1). Of the 143 ADRs found, 61 events (42.6%) were due to olanzapine, and 40 events (27.9%) were due to risperidone [4]. Of the 63 ADRs, 22 events (44.89%) were attributable to olanzapine and 18 events (36.73%) to risperidone [7]. Of the 93 ADRs, 44 events (47.13%) were due to olanzapine and 34 events (36.55%) to risperidone [9]. Of the 166 ADRs, 120 events (72.28%) were due to olanzapine and 28 events (16.86%) to risperidone [10].

Apart from the above olanzapine and risperidone, the next position was followed by amisulpride in 28 events (19.5%), clozapine in 6 events (4.19%), quetiapine in 5 events (3.49%), and aripiprazole in 3 events (2.09%) [4]. Then aripiprazole as many as 14 events (28.57%), quetiapine 8 events (16.32%), and ziprasidone 1 event (2.04%) [7]. Then clozapine in 10 events (10.75%), and quetiapine in 5 events (5.37%) [9]. Then amisulpride in 11 events (6.62%) and quetiapine in 7 events (4.21%) [10].

Table 1. Number of patients, gender, age, and antipsychotic agent atypical that causes ADRs

Reference	Number of patients Male / Female (%)	Age (Years)	Prescribing Number (%) of Antipsychotic Atypical	Atypical Antipsychotic that causes ADRs
[4]	102 68 (66.6%) / 34 (33.3%)	-	Olanzapine Risperidone Aripiprazole Amisulpride Quetiapine Clozapine	Olanzapine (42.6%) Risperidone (27.9%) Amisulpride (19.5%) Clozapine (4.19%) Quetiapine (3.49%) Aripiprazole (2.09%)
[7]	49 25 (51%) / 24 (49%)	30-40	Risperidone (27%) Olanzapine (27%) Quetiapine (23%) Aripiprazole (16.95%) Ziprasidone (3.39%)	Olanzapine (44.89%) Risperidone (36.73%) Aripiprazole (28.57%) Quetiapine (16.32%) Ziprasidone (2.04%)

			Amisulpride (1.69%)	
[9]	74 52 (70.27%) / 22 (29.72%)	-	Risperidone (45.24%) Olanzapine (40.48%) Clozapine (7.14%) Quetiapine (5.95%) Aripiprazole (1.19%)	Olanzapine (47.13%) Risperidone (36.55%) Clozapine (10.75%) Quetiapine (5.37%)
[10]	71 46 (64.78%) / 25 (35.21%)	-	Olanzapine (76.05%) Risperidone (11.26%) Amisulpride (9.85 %) Quetiapine (2.81%)	Olanzapine (72.28%) Risperidone (16.86%) Amisulpride (6.62%) Quetiapine (4.21%)

Adverse drug reactions (ADRs)

Adverse drug reactions from all articles are in the form of weight gain, constipation, and insomnia [4,7,9,10]. Dry mouth, tremor, and sedation [4,7,10]. Hypersalivation [4,9,10]. Somnolence, extrapyramidal signs and symptoms (EPS), and headache [7,9,10]. Tardive dyskinesia and akathisia [4,7]. Edema [4,10]. Anxiety, restlessness, and blurred vision [7,10]. Fatigue, increased appetite, dizziness, and leg muscle cramp [9,10]. Increase in lipids, pin rolling movements, restless leg syndrome, drug-induced parkinsonism, galactorrhea, agranulocytosis, myoclonic jerks, delirium, perioral movements, menstrual disturbances possible, itching, hypertension, bradykinesia, increase in serum prolactin, joint pain, impairment in hearing and blepharospasm [4]. Triglyceride levels, salivary hypersecretion, rash, lethargy, dystonia, ECG deviation, cholesterol levels, nasal congestion, orthostatic hypotension, personality disorder, priapism, and suicidal thoughts [7]. Seizure, decreased appetite, increased frequency of micturition, vomiting, diarrhea, palpitation, and mouth ulcers [9]. Gastrointestinal upset, aggressive behavior, anorexia, concentration difficulty, asthenia, anemia, burning sensation on the palm, abdominal pain, sexual dysfunction, amenorrhea, myalgia, burning sensation on sole, and confusion [10]. (Table 2).

Table 2. Design study, Method of assessment, and ADRs

No	Reference	Study design (number of ADRs)	Method of assessment	ADRs
1	[4]	Prospective observational (143)	● Causality assessment: 55.5% ADRs were certain, 29.6% were probable and 14.8 % were possible (WHO causality assessment). ● Severity assessment: 36% ADRs were categorized as mild, 46% moderate, and 18% ADR were categorized as severe (Modified Hartwig and Siegel scale). ● Preventability assessment: 67.8% ADR's were not preventable, 29.6% ADR's were definitely preventable and 3.70% probably preventable (Modified Schumock and Thornton scale). ● Predictability assessment: 92% were predictable and 7.4% unpredictable (Modified Schumock and Thornton scale).	● Weight Gain ● Tardive Dyskinesia ● Dry Mouth ● Increase in Lipids ● Tremors ● Sedation ● Pin rolling movements ● Restless leg syndrome, ● akathisia ● Constipation ● Drug-induced Parkinsonism ● Galactorrhea ● hypersalivation ● agranulocytosis ● Myoclonic Jerks ● Delirium ● Perioral movements ● Menstrual disturbances

				● Itching ● Hypertension ● Bradykinesia ● Increase in serum prolactin ● Joint pain ● Insomnia ● Impairment in hearing ● Blepharospasm ● Edema
2	[7]	Prospective observational (63)	● Causality assessment: 76% of the ADRs were probable and 14% were possible. The certain was observed in only six ADRs as only a few were challenged (10%) (WHO Probability Assessment Scale). 76% of the reactions were probable, 14% if possible, and 10% of certain (Naranjo's Causality Assessment Scale). ● Severity assessment: 46% of the reactions were categorized as moderate, 30% as mild, and 24% were severe (Hartwig's Severity Assessment Scale). ● Preventability assessment: 67% of the ADRs to be probably preventable, 30% of the ADRs to be definitely preventable and 3% to be not preventable (Modified Schumock and Thornton scale). ● Predictability assessment: 76% were predictable (Modified Schumock and Thornton scale).	● Weight gain ● Sedation ● Constipation ● Tremor ● Dyskinesia ● Triglyceride levels ● Somnolence ● Dry mouth ● Insomnia ● Anxiety ● salivary hypersecretion ● restlessness ● EPS ● Rash ● Akathisia ● lethargy ● Dystonia ● ECG deviation ● Headache cholesterol levels ● Nasal congestion ● Orthostatic hypotension ● Personality disorder ● priapism ● Blurred vision ● Suicidal thoughts
3	[9]	Prospective observational (93)	● Causality assessment: 91.81% of the ADRs were probable, 7.5% was possible and 1.07% was definite (Naranjo's scale).	● Seizure ● Weight gain ● Increased appetite ● Dizziness ● Decreased appetite ● Insomnia ● reaction ● Extrapyramidal Somnolence ● Fatigue ● Increased frequency of micturition ● Vomiting and diarrhea ● Headache ● Hypersalivation ● Seizure

				● Constipation ● Perioral tremor ● Fatigue ● Palpitation ● Constipation ● Headache ● Mouth ulcer ● Leg muscle cramp
4	[10]	Prospective observational (166)	● Causality assessment: 51.20% of events were found to be probable and 48.79% were found to be possible (Naranjo's scale). ● Severity assessment: 65.06% ADRs were assessed as mild and 34.93% ADRs were assessed as moderate (Hartwig's severity assessment scale).	● Weight gain ● Gastrointestinal (GI) upset ● Insomnia ● Sedation ● Aggressive behavior ● Anxiety ● Tremor ● Headache ● Restlessness ● Anorexia ● Fatigue ● Concentration difficulty ● Extrapyramidal signs and symptoms (EPS) ● Asthenia ● Increased appetite ● Anemia ● Somnolence ● Burning sensation on the palm ● Constipation ● Dizziness ● Dry mouth ● Edema ● Abdominal pain ● Sexual dysfunction ● Amenorrhoea ● Myalgia ● Leg muscle cramp ● Burning sensation on sole ● Confusion ● Hypersalivation ● Blurred vision

Causality assessment

Assessment of causality (Table 2) was done by using the Health Organization (WHO) causality assessment scale [4,7,9,10]. From the assessment by using the WHO causality assessment scale, a total of 143 cases 55.5% ADRs were certain, 29.6% were probable and 14.8% were possible [4]. Another study said that out of 63 cases 76% of the ADRs were probable and 14% were possible [7]. The other two studies did not use the WHO causality assessment scale [9,10]. In the assessment using Naranjo's scale, a total of 63 cases, 76% of the reactions were probable, 14% if possible, and 10% of certain [7]. Another study reported that out of 93 cases 91.81% of the ADRs were probable, 7.5% were possible and 1.07% were definite [9]. Subsequent studies said that out of 166 cases 51.20% of the events were found to be probable and 48.79% were found to be possible [10]. One other study did not use Naranjo's scale [4].

Severity assessment

The severity assessment (Table 2) was done by using the Hartwig and Siegel assessment scale [4,7,10]. It is known that 36% of ADRs were categorized as mild, 46% moderate, and 18% ADRs were categorized as severe [4]. Subsequent studies reported 46% of the reactions were categorized as moderate, 30% as mild and 24% were severe [7] and another study reported that 65.06% of ADRs were assessed as mild and 34.93% ADRs were assessed as moderate [10]. One subsequent study did not perform a severity assessment [9].

Preventability assessment

The prevention assessment (Table 2) was done by using the Modified Schumock and Thornton scale [4,7]. It is known that 67.8% of ADR's were not preventable, 29.6% of ADR's were definitely preventable and 3.70% were probably preventable [4] and were significantly different from subsequent studies which reported that 67% of the ADRs were probably preventable, 30% of the ADRs were definitely preventable and 3% were not preventable [7]. The other two studies did not perform a preventive assessment [9,10].

Predictability assessment

The predictability assessment (Table 2) was done by using the Modified Schumock and Thornton scale [4,7]. It was found that 92% of ADRs were predictable and 7.4% unpredictable [4]. Subsequent studies reported that 76% were predictable [7]. The other two studies did not perform predictability assessments [9,10].

IV. DISCUSSION

This literature study aimed to summarize the adverse drug reactions (ADRs) that occur due to the use of atypical antipsychotics and to examine their causality, severity, prevention, and predictability. Because the assessment of ADRs is important for patient safety. The databases used were ScienceDirect, Pubmed, Semantic Scholar, and Google Scholar. We used these databases because they are trusted journal provider sites. Of the 307 total search results, we reviewed 4 literature assessing adverse drug reactions (ADRs) of atypical antipsychotics [4,7,9,10]. The four articles selected were prospective observational studies. One study stated that prospective studies have higher accuracy and efficiency [11].

Of all the articles reviewed, the total number of patients presenting with ADRs was 296 patients, whereas the incidence of ADRs was higher in men (64.18%) than in women (35.81%). This is inversely proportional to research conducted by Hofer-Dueckelmann, Prinz, Beindl et al. which stated that women experience ADRs significantly more frequently than men [12]. This difference may occur because of the vast differences between the number of male patients and female patients who were involved in the study. This increased vulnerability in women is thought to be due to their longer QTc interval compared to men [8]. One study did state that women have a longer QTc interval than men [13]. We found that patients aged 30-40 years were prone to developing ADRs. This is under the study conducted by Aashal Shah et al. which stated that the most common age group to cause ADRs is 31–40 years [14]. This is because at older age there is decreased metabolic ability and drug elimination from the body or they also have multiple comorbidities [8].

Olanzapine and risperidone are the most commonly prescribed atypical antipsychotic drugs. Olanzapine and risperidone are also the main agents for adverse drug reactions (ADRs). This is following a study conducted in 2014 by Lucca et al. where the adverse drug reactions of atypical antipsychotics were analyzed and the results showed that olanzapine and risperidone were involved more frequently in the reported incidence of ADRs and that they were the most frequently used atypical antipsychotic agents [15].

Adverse drug reactions (ADRs) that are often found in the use of atypical antipsychotics are weight gain, constipation, insomnia, dry mouth, tremor, sedation, hypersalivation, somnolence, extrapyramidal signs and symptoms (EPS), and headache. Weight gain is the most commonly observed ADR [4,7,9,10]. A study that linked atypical antipsychotics with weight gain concluded that all atypical antipsychotics cause weight gain, and it is known that risperidone has a more synergistic effect in this regard [16]. Constipation is associated with the use of clozapine and olanzapine; constipation is mediated by anticholinergic activity which impairs normal bowel function [17].

Naranjo's scale and WHO assessment scale was used in the assessment of causality [18,3]. Assessment with the Naranjo's scale can be found in 3 articles [7,9,10]. The mean yield of the 3 articles was 73% probable ADRs. "Probable" means that the reaction has a reasonable temporal relationship with the drug, follows a recognized response to the suspected drug, confirmed by discontinuation but not by drug exposure, and cannot reasonably be explained by the known characteristics of the patient's clinical state [18]. The average yield of possible reactions was 23.43%. "Possible" means that the reaction has a temporal relationship with the drug, possibly following a recognized pattern of the suspected drug, and can be explained by the characteristics of the patient's disease [18]. The average yield for certain reactions was 3.69%. "Certain" means a reaction that has a reasonable temporal relationship with the drug or where the toxic drug level has been established in body fluids or tissues, following an acknowledged response to the suspected drug and confirmed by improvement in drug

withdrawal and reoccurrence on re-exposure [18]. Assessment with WHO assessment scale is available in 2 articles [4,7]. The mean results of the 2 articles were 52.8% probable, 32.75% certain, and 14.4% possible. The assessment of causality using each of these methods showed quite different results, where the assessment using the Naranjo's scale shows that most ADRs are in the probable category, followed by possible and certain. Whereas an assessment using the WHO scale showed that ADRs mostly range in the probable category, followed by certain and possible. If the results of these methods are combined and the average value is drawn, the results show that 62.9% is probable, 18.91% possible, and 18.22% certain.

Hartwig and Siegel's assessment scale was used to assess the severity of ADRs [19]. Assessment of the severity of ADRs is provided in 3 articles [4,7,10]. The mean results of the assessment were 43.68% in the mild category, 42.31% moderate, and 14% severe. Mild categories include fatigue, dry mouth, insomnia, weight gain, and GI disturbances. Moderate categories included tardive dyskinesia, pill-rolling movements, drug-induced parkinsonism, and hypersalivation. Disturbances in lipid profile, delirium, menstrual disturbances, and hypertension are ADRs in the severe category [4].

A modified Schumock and Thornton scale was used to assess the prevention and predictability of ADRs. Assessment of prevention and predictability is provided in 2 articles [4,7]. The mean results of the prevention assessment were 35.35% probable preventable ADRs, 35.4% not preventable, and only 29.8% definitely preventable ADRs. The predictability assessment of these two articles shows that the majority of ADRs are predictable, namely 84%.

V.CONCLUSION

Our literature study of Adverse Drug Reactions (ADRs) on atypical antipsychotic drugs showed that the most common and common ADRs are weight gain, constipation, insomnia, dry mouth, tremor, sedation, hypersalivation, somnolence, extrapyramidal signs and symptoms (EPS), and headache. The causality of atypical antipsychotic ADRs was probable, followed by possible and certain. Atypical antipsychotic ADRs were of mild severity, followed by moderate and severe. The prevention assessment of ADRs for atypical antipsychotics is probable preventable, followed by not preventable, and definitely preventable. The majority of ADRs from these atypical antipsychotics were predictable. ADRs are a very important health problem to pay attention to. Information is currently lacking on antipsychotic ADRs, and to ensure patient safety a large enough prospective study should be considered to clarify this issue.

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