

REVIEW

Antipsychotic Polypharmacy Among Patients With Schizophrenia in Africa: A Systematic Review and Meta-Analysis

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Abstract

Objectives: In Africa, antipsychotic polypharmacy (APP) is increasing due to a high antipsychotic dose prescribing, repeated psychiatric hospitalization, uncontrolled psychotic symptoms, and greater side effect burden. Therefore, the aim of this review and meta-analysis is to assess the prevalence and correlates of APP among patients with schizophrenia in Africa.

Methods: A systematic search was performed from August 1 to 31, 2020, on PubMed, MEDLINE, Google Scholar, and Science Direct databases to select articles based on the inclusion criteria. Meta-Analysis of Observational studies in Epidemiology guidelines were employed. Cross-sectional observational studies that reported APP and/or its correlates in schizophrenia patients in English language published in peer-reviewed journals without time limits were included in the review. The quality of included articles was assessed using Newcastle-Ottawa quality assessment tool. Prevalence and correlates of APP were the outcome measures of this review and meta-analysis. Open Meta Analyst and RevMan version 5.3 software were used for meta-analysis. A random effect model was used to synthesize data based on the heterogeneity test.

Results: Six studies that involved 2154 schizophrenia patients met the inclusion criteria in this review and meta-analysis. The quality of included studies ranges from 6.5 to 10 based on the Newcastle-Ottawa quality assessment tool. The pooled prevalence of APP among patients with schizophrenia was 40.6% with 95% confidence interval: 27.6% to 53.7%. Depot first-generation antipsychotics and oral first-generation antipsychotics were the most commonly prescribed APP combinations. Socio-demographic, clinical, and antipsychotic treatment characteristics were significantly associated with APP. There was a wide variation in the correlates of APP assessed by studies and the way that association/correlations was determined and reported.

Conclusions: APP is common and highly prevalent. Advanced age, male gender, longer duration of schizophrenia, hospital admission, and longer antipsychotic treatment were correlates of APP in Africa.

Keywords: Africa, antipsychotic polypharmacy, antipsychotic prescribing, correlates of antipsychotic polypharmacy, prevalence

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Introduction

Antipsychotics are medications primarily prescribed for the treatment of schizophrenia and other psychotic disorders such as schizoaffective, delusion, and bipolar affective disorders. They are classified as first-generation (typical or conventional) and second-generation (atypical) antipsychotics (Jhon and James, 2015).

In countries where antipsychotic treatment guidelines are found, antipsychotics are ideally recommended as a monotherapy (Gaebel et al., 2011). However, antipsychotic polypharmacy (APP) prescriptions that contain 2 or more antipsychotics are common in the world and occur when a combination of antipsychotics are prescribed to control uncontrolled positive and negative psychotic symptoms that are not controlled by a single antipsychotic agent. They have also happened in schizophrenia patients when they were used to improve the unsatisfactory outcome and poor prognosis of schizophrenia. But this APP has been associated with increased antipsychotic doses, adverse effects, treatment cost, hospitalization and length of hospital stay, and mortality rate compared with antipsychotic monotherapy (Bingefors et al., 2003; Centorrino et al., 2004; Joukamaa et al., 2006; Gilmer et al., 2007; Rupnow et al., 2007; Hung and Cheung, 2008; Jerrell and McIntyre, 2008).

Due to this, identifying the antipsychotics, which reduce the psychotic symptoms and produce adverse effects, is difficult when more than 1 antipsychotic is prescribed concurrently. So to reduce this impact, APP is recommended only as a last resort after having exhausted monotherapy alternatives or for treating resistant illness after multiple trials of antipsychotics (Kreyenbuhl et al., 2007; Esock et al., 2011; Sagud et al., 2013).

There are different factors or correlates of APP. Antipsychotic treatment resistance, arrested medication switching, attempt to avoid high-dose monotherapy, insomnia, and use of antipsychotics for acute exacerbation of psychosis were factored for the occurrence of high rate of APP (Langan and Shajahan, 2010).

The global prevalence of APP was 19.6%. The prevalence of APP was higher in Asia (32%) and Europe (23%) than Oceania (16.4%) and North America (16%) (Gallego et al., 2012). A study done in 6 Asian countries and territories (China, Hong Kong, Japan, Korea, Singapore, and Taiwan) showed that the prevalence of APP was 45.7 % (Sim et al., 2004).

Some studies in different countries of Africa showed that APP was high (Igbinomwanhia et al., 2017), but there is no review that showed the prevalence and correlates of APP among schizophrenia patients in the African region. Therefore, this study aims to review, quantitatively estimate, and identify the prevalence and correlates of APP among schizophrenia patients in Africa.

Methods

Study Protocol and Registration

This systematic review and meta-analysis were performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology guidelines (Stroup et al., 2000).

The protocol is registered on PROSPERO and openly available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020202112

Eligibility Criteria

Inclusion Criteria

- ✓ Cross-sectional observational studies were included
- ✓ Studies reporting APP in English language on schizophrenia patients

- ✓ All schizophrenia patients at any age who had taken antipsychotics
- ✓ Studies were published in a peer review journal at any time
- ✓ Studies reporting the prevalence and/or correlates of APP in Africa

Exclusion Criteria

- ✓ Experimental studies were excluded
- ✓ Studies reporting APP for mental illness in general

Information Sources and Search Strategy

An electronic data search was performed from August 1 to 31, 2020, in PubMed, MEDLINE, Google Scholar, and Science Direct using Google Chrome and Mozilla Firefox. Literature searches were limited to APP in schizophrenia patients published at any time in English language. The main key words employed to search in this review were “prevalence,” “correlates,” “antipsychotics,” “combination of antipsychotics,” “polypharmacy,” and “schizophrenia,” “Africa.” A MeSH term search was performed on PubMed. Boolean operators such as AND and OR were used to combine key search words. The reference lists of retrieved articles were screened manually. Then, the available articles from the databases were downloaded and/or contacted with authors to get the full articles. The references of included articles were searched to get additional relevant articles. All published articles were searched by W.A., G.A., and T.B.

Data Extraction

Articles retrieved from the literature search were screened independently by W.A., G.A., and T.B. based on the title and abstract. Then the investigators (W.A., G.A., and T.B.) independently extracted important data from the included articles using standard data abstraction forms. The data extracted from included articles contain study characteristics (country, study year, study design, and sample size), and findings (prevalence and correlates of APP). The discrepancies between the investigators were resolved through discussion.

Quality Assessment

The quality of selected original studies was assessed by using a quality assessment tool. To assess the quality of each original study, the Newcastle-Ottawa quality assessment scale adapted for cross-sectional studies was used (Well et al., 2013). This assessment scale was used to assess the internal and external validity, risk of bias, and methodological quality of each included original studies. The quality assessment tool has 3 sections. The first section focused on the methodological quality of each original study such as objectives, sample size, and sampling technique. This section graded on the bases of 5 stars. The second section of the tool considers the comparability of studies and graded out of 2 stars. The third section of the tool considers the outcome measures and data analysis and graded out of 3 stars. Studies with ≥ 5 scores were included in the review and meta-analysis.

Two authors (W.A. and G.A.) made the quality appraisal of articles. They critiqued each of the included articles individually by using the Newcastle-Ottawa quality assessment scale adapted for cross-sectional studies. Then the authors compared the scores given for each study. If the scores given by the authors differed, it was discussed and resolved through consensus.

Outcomes Measurements

Prevalence and correlates of APP were the 2 outcomes of this review and meta-analysis.

Data Processing and Statistical Analysis

All necessary data from each study were extracted by using Microsoft Excel version 13 spreadsheet form. Then the extracted data were entered to RevMan version 5.3 statistical package software. The pooled estimate of the outcome measure and subgroup analysis was done by RevMan and Open Meta Analyst software. DerSimonian and Laird's random effect model was used to calculate the pooled effect size at 95% confidence level (DerSimonian and Laird, 1986). Forest plots were generated to display the pooled estimates with confidence interval.

Assessment of Heterogeneity

Heterogeneity among studies was assessed using Cochran's Q-statistics and I^2 test (Higgins and Thompson, 2002). Heterogeneity among included studies was quantified by I^2 statistics and its confidence interval. Based on the result of the statistical test, an I^2 statistics value <25% was considered as low heterogeneity, from 50% to 75% was considered as medium, and >75% was considered high (Higgins et al., 2003).

The heterogeneity of included studies was dealt with by conducting a subgroup analysis or meta regression or by choosing a random effect model (Higgins and Thompson, 2002; Higgins and Green, 2011).

Subgroup analysis was performed based on year of publication and study setting. Meta regression was performed based on

sample size, year of publication, study quality score, and study setting.

The presence of potential publication bias and small study size effects were evaluated by using a visual inspection of the funnel plot (Egger et al., 1997).

Sensitivity analysis was done to examine influential studies and change in the degree of heterogeneity and to verify the robustness of the study conclusion (Duval and Tweedie, 2000). To analyze the correlates of APP, the reported odds ratio by 95% confidence interval and P value were used.

Results

Search Results and Study Characteristics of the Included Studies

A total of 606 articles fulfilled the initial search criteria. Five cross-sectional studies and 1 retrospective cross-sectional study were then identified as eligible for inclusion in the review and meta-analysis (Figure 1).

A total of 6 articles was included in this review and meta-analysis. From a total 2154 schizophrenic patients, which are reported in this review and meta-analysis, 797 patients had taken APP combinations.

From 6 articles included, 5 studies were cross-sectional studies and 1 study was a retrospective cross-sectional study. In terms of geographical area, 1 was from Egypt, 1 was from Ethiopia, 2 were from Nigeria, and 2 were from South Africa. All included articles had an outcome measures, that is, prevalence of APP. Five articles showed the risk factors or correlates of APP, whereas the 1 remaining article did not mention the correlates of APP. All of the included studies were published from 2008 to

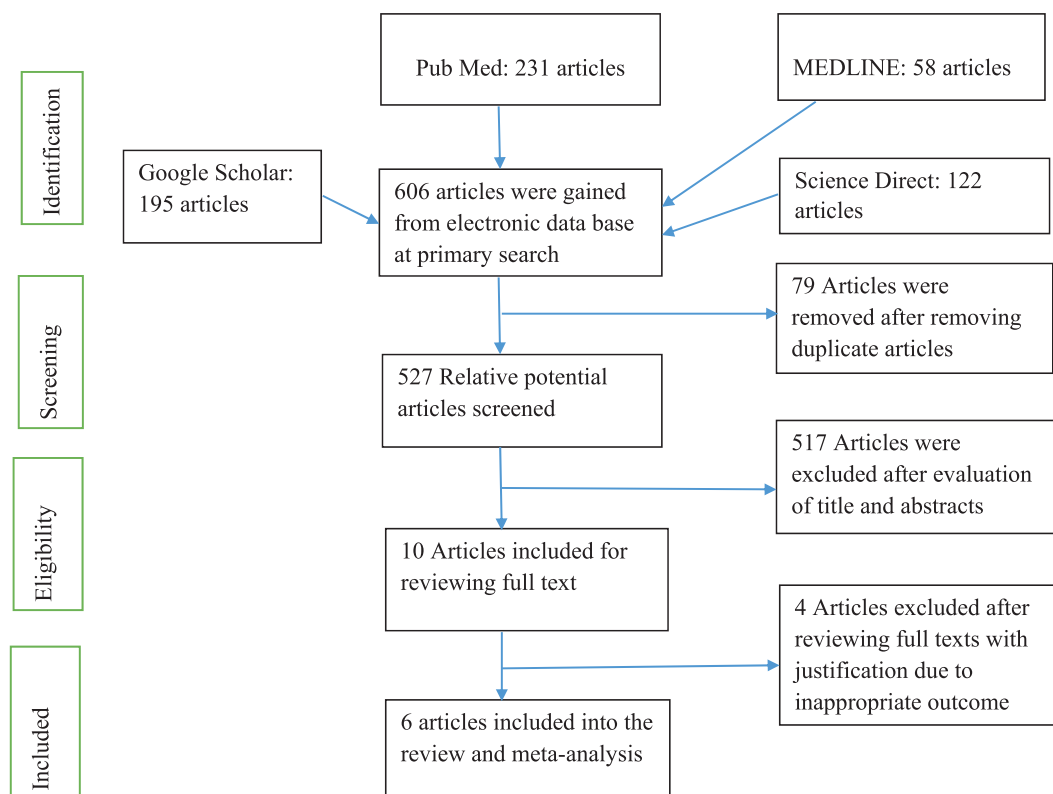


Figure 1. Meta-Analysis of Observational Studies in Epidemiology flow chart showing the screening process.

Table 1. Characteristics of included studies

S.No.	Country	Author and publication year	Study design	Target population	Study setting	Sample size	Patients with APP	Event rate	Prevalence %
1	Egypt	Amr et al., 2012	CS	Schizophrenia	Inpatient	85	32	0.376	37.6
2	Ethiopia	Siranesh et al., 2016	CS	Schizophrenic patients	Outpatient	412	116	0.282	28.2
3	Nigeria	Olotu et al., 2017	CS	Schizophrenic patients	Outpatient	250	176	0.704	70.4
4	Nigeria	Anozie, et al., 2020	CS	Schizophrenia patients	Outpatient	320	163	0.509	50.9
5	South Africa	Armstrong and Temmingh, 2017	CS	Schizophrenia patients	Discharge inpatient psychiatric unit	577	164	0.284	28.4
6	South Africa	Koen, 2008	Retrospective CS	Schizophrenia or schizoaffective disorder	Outpatient	510	146	0.286	28.6

CS, cross-sectional study.

Table 2. Quality assessment of each studies included in the review and meta-analysis based on the Newcastle-Ottawa assessment scale adapted for cross-sectional studies

Study	Methodological quality (5 points)			Comparability of studies (2 points)		Outcome measures and analysis (3 points)		Total quality score (10 points)
	Methodological quality (5 points)	Comparability of studies (2 points)	Outcome measures and analysis (3 points)	Outcome measures and analysis (3 points)	Total quality score (10 points)			
Amr et al., 2012	3	2	1.5	6.5				
Siranesh et al., 2016	5	2	1.5	8.5				
Olotu et al., 2017	5	2	3	10				
Anozie, et al., 2020	4	2	1.5	7.5				
Armstrong and Temmingh, 2017	4	2	2.25	8.25				
Koen, 2008	5	1	1.5	7.5				

2020. The adjusted sample size ranged from 85 to 577. Pediatric, adult, and geriatric schizophrenic patients were included in this review and meta-analysis (Table 1).

Quality Assessment and Score of Included Studies

The quality score of 6 studies assessed ranges from 6.5 to 10 based on the Newcastle-Ottawa assessment scale. The scoring is shown in Table 2.

Outcome Measures

The pooled prevalence of APP among patients with schizophrenia in Africa was 40.6 % (confidence interval between 27.6% and 53.7%). The pooled prevalence of APP had a significant heterogeneity ($I^2=97.65$; $P<.001$) (Figure 2).

Correlates of APP

There was a wide variation in the correlates of APP assessed by studies and the way that associations/correlations was

determined and reported. Generally, socio-demographic characteristics, clinical characteristics, and antipsychotic treatment were significantly associated with APP. Five studies showed the correlates of APP. The details of individual studies that reported correlates of APP are shown in Table 3.

Pattern of Antipsychotic Prescribing and Polypharmacy

In this review and meta-analysis, studies reported that schizophrenia patients had taken monotherapy and/or a combination of antipsychotics.

Five studies reported the commonly prescribed antipsychotics. From the 5 studies, Depot first-generation antipsychotics (FGAs) and oral FGAs were the most commonly prescribed APP combinations, followed by depot FGAs, oral FGAs, and a combination of oral FGAs. A study in Ethiopia showed a combination of FGAs were the most commonly prescribed antipsychotics followed by FGAs with second-generation antipsychotics (SGAs) (Table 4).

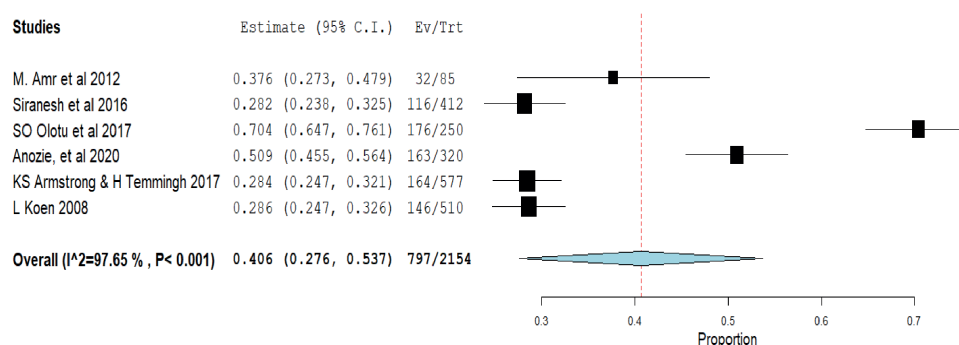


Figure 2. The pooled prevalence of antipsychotic polypharmacy (APP) among patients with schizophrenia in Africa.

Table 3. The correlates of APP among patients with schizophrenia in Africa

Author and year	Correlates of APP
Amir et al., 2012	Increased number of relapse and hospitalization
Siranesh et al., 2016	Patients on antipsychotic treatment for >10 y (AOR=2.24; 95% CI=1.29–3.89) Patients who had 2 or more previous hospital admissions (AOR=3.16; 95% CI=1.68–5.94) Patients using psychoactive substance after initiating psychotic treatment (AOR=1.69; 95% CI=1.06–2.71) Patients with extrapyramidal side effects (AOR=2.76; 95% CI=1.38–5.53) Patients non-adherent to their treatment (AOR=1.96; 95% CI=1.22–3.15)
Olotu et al., 2017	Higher prescribing daily dose of antipsychotic in chlorpromazine equivalent ($P<.001$), increased frequency of dosing ($P<.001$), reduced functioning ($P=.04$), higher side effect burden ($P=.04$)
Anozie, et al., 2020	Male gender (OR=1.75; 95% CI=1.12–2.72; $P=.01$) Patients unmarried (OR=1.80; 95% CI=1.00–3.27; $P=.04$) Patients with longer duration of illness ($t=2.3$, $P=.04$) Patients with concurrent anticholinergic use (OR=40.24; 95% CI=20.66–78.36; $P=.001$) Patients with alcohol use (OR=3.31; 95% CI=1.21–2.72; $P=9.05$) Patients with antidepressant use (OR=4.02; 95% CI=1.10–14.69; $P=.02$) Twice-daily dose interval of antipsychotics (OR=3.90; 95% CI=1.92–7.91; $P=.001$) Current episode of schizophrenia (OR=3.86; 95% CI=2.43–6.1; $P=.001$)
Armstrong and Temmingh, 2017	Age ranges from 30–60 y (AOR=2.81; 95% CI=1.61–4.89; $P<.001$), male gender (AOR=1.86; 95% CI=1.07–3.23; $P=.027$), diagnosis of schizophrenia (AOR=2.79; 95% CI=1.39–5.57; $P=.004$), comorbid intellectual disability (AOR=3.52; 95% CI=1.27–9.73; $P=.015$), comorbid substance use (AOR=1.8; 95% CI=1.03–3.14; $P=.039$), >6 hospital admissions (AOR=2.64; 95% CI=1.07–6.51; $P=.04$), high dose prescribing (AOR=8.99; 95% CI=4.97–16.29; $P<.001$), combined anticholinergic prescription ($\chi^2=16.30$, $P<.001$), and sodium valproate use ($\chi^2=8.18$, $P=.004$)

Table 4. The prescribing pattern of antipsychotics among patients with schizophrenia in Africa

Author and year	Antipsychotic therapy class		Oral FGA mono	Oral SGA monotherapy	IM FGA monotherapy	IM SGA mono-therapy	Comb PO FGAs	PO FGAs +PO SGAs	IM FGAs +PO FGAs	IM FGAs + PO SGAs
	Monotherapy	Polypharmacy								
Amr et al., 2012	32 (37.6%)	53 (62.4%)	45 (52.9%)	20 (23.5%)	20 (23.5%)	32 (0.71%)	4 (4.7%)	12 (14.1%)	11 (12.9%)	0%
Olotu et al., 2017	74 (29.6%)	176 (70.4%)	37 (15.2%)	34 (13.6%)	3 (1.2%)	0%	30 (12.0%)	1 (0.4%)	111 (44.0%)	34 (14.0%)
Anozie, et al., 2020	157 (49.06%)	163 (50.94%)	218 (68.2%)	110 (34.4%)	168 (52.5%)	0%	2 (1.2%)	1 (0.6%)	72 (44.3%)	75 (46.0%)
Armstrong and Temmingh, 2017	413 (71.57%)	164 (28.43%)	189 (46.0%)	196 (47.0%)	25 (5.93%)	3 (0.7%)	0%	1 (0.6%)	74 (4.9%)	68 (41.0%)
Koen, 2008	364 (71.37%)	146 (28.63%)	298 (58.5%)	40 (78.4%)	252 (49.4%)	0%	65 (45.77%)	0%	77 (54.2%)	11 (22.0%)

FGA, first generation antipsychotic; IM, intra muscular ; SGA, second generation antipsychotic; PO, oral.

A study done in South Africa showed that mood stabilizers and anticholinergics were the most commonly prescribed co-medications with antipsychotics, followed by antidepressants and benzodiazepines.

Sensitivity and Subgroup Analysis

Leave-1-out sensitivity analysis was done to examine influential studies. The analysis showed no change in the degree of heterogeneity, and the pooled estimate prevalence of APP when each study was excluded from the analysis was between the confidence interval of the pooled prevalence of APP.

Subgroup analysis based on study setting showed that the pooled prevalence of APP in the outpatient setting was higher than the inpatient setting (Figure 3).

Subgroup analysis was also performed based on publication year before and after 2013. The result showed that prevalence of APP was higher after 2013 than before 2013 (Figure 4).

Meta Regression

To detect the source of heterogeneity, meta regression analysis was conducted. Sample size and study quality score were significant at P = .003 and P = .044, respectively.

Publication Bias

The Egger’s publication bias funnel plots of standard error with logit effect size are around the line. This showed there was no publication bias for the prevalence of APP among schizophrenia patients in Africa (Figure 5).

Discussion

Ideally, antipsychotics are recommended to be used as monotherapy in countries where antipsychotic treatment guidelines exist (Gaebel et al., 2011). But APP prescriptions in the treatment of schizophrenia are increasingly common (Ranceva et al., 2010; Gallego et al., 2012). In this review, the prevalence of APP in schizophrenia patients was found to be 40.6%. It is higher than another review done in 4 continents (Asia, Europe, North America, and Oceania) in which the median prevalence of APP was 19.6% (Gallego et al., 2012). It is also higher than a review and meta-analysis of developed countries in which the prevalence of APP in adolescent studies was 12.0% ± 7.9% (Toteja et al., 2014). The high prevalence of APP in this study could be due to the fact that a combination of antipsychotics achieves greater therapeutic response when there is an unsatisfactory response to a single antipsychotic (CADTH, 2012). Clinicians prescribe a combination of antipsychotics to achieve a satisfactory response. They prescribe APP when they treat a schizophrenic patient to gain a better treatment outcome, especially in treatment-resistant cases (Kotler et al., 2004; Cipriani et al., 2009).

In this review and meta-analysis, socio-demographic, clinical, and antipsychotic treatment were significantly associated with APP. There was a wide variation in specific factors assessed and the way that associations were determined by some studies reporting univariate analysis alone and other studies reporting results of multivariate analysis. In this study, patients aged between 30 and 60 years and male gender were significantly associated with APP (Armstrong and Temmingh, 2017; Anozie et al., 2020). As mentioned by different studies, schizophrenia is mostly seen in males and the middle-aged group, which leads to antipsychotic binge taken by these groups and the increased likelihood of the occurrence of APP (Banerjee et al., 2013; Sushma et al., 2015).

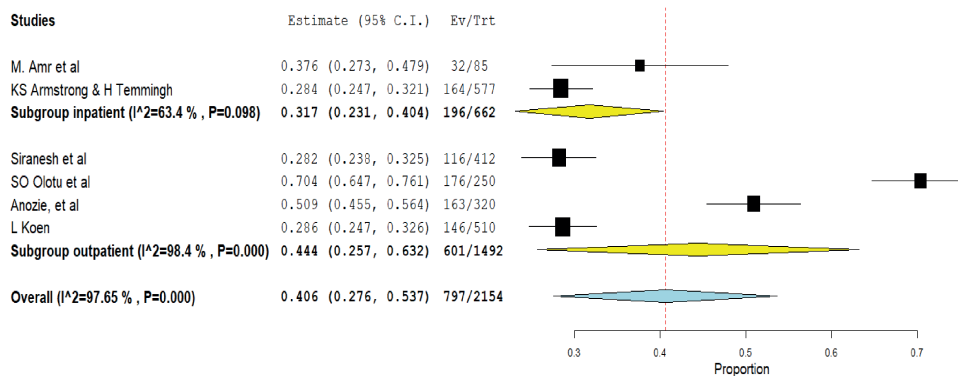


Figure 3. Subgroup analysis of the prevalence of antipsychotic polypharmacy (APP) based on study setting among patients with schizophrenia in Africa.

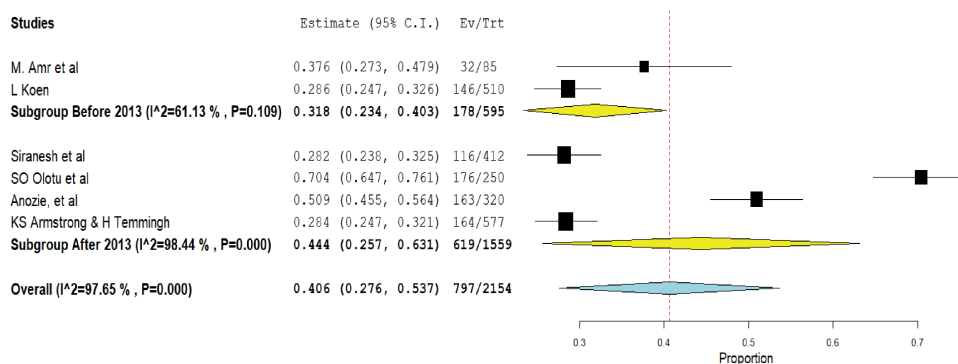


Figure 4. Subgroup analysis of the prevalence of antipsychotic polypharmacy (APP) based on publication year among patients with schizophrenia in Africa.

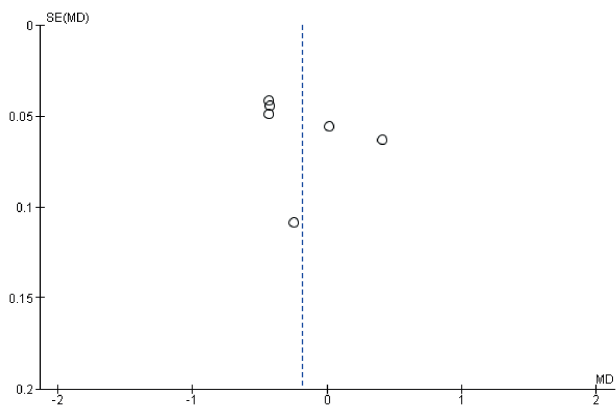


Figure 5. Funnel plot of the prevalence of antipsychotic polypharmacy (APP) among patients with schizophrenia in Africa.

Clinical characteristics such as diagnosis of schizophrenia, patients with longer duration of illness, increased relapse, and hospital admissions were also associated with APP. A meta-analysis done in 5 regions also showed that APP was associated with schizophrenia (Gallego et al., 2012).

Antipsychotic treatment-related factors such as high side effect burden, high dose prescribing combined with anticholinergic prescription, extrapyramidal side effects, longer antipsychotic treatment, and alcohol use were correlates of APP in this review (Amr et al., 2012; Tesfaye et al., 2016; Armstrong and Temmingh, 2017; Igbinomwanhia et al., 2017; Anozie et al., 2020). Those factors were also mentioned by different studies. For example, high total antipsychotic dosage was associated with APP, but this in turn

leads to the risk of dose-related antipsychotic adverse events such as extrapyramidal motor side effects and cognitive impairment (Suzuki et al., 2004; Procyshyn et al., 2010; Sakurai et al., 2012).

In this study, depot FGAs and oral FGAs were the most commonly prescribed APP combinations. Studies also showed that FGAs were as useful as SGAs with the exception of clozapine, which outperformed all (Jones et al., 2006).

In our study, FGAs were the preferred combinations as part of APP. This may be because SGAs cost more than FGAs (Gallego et al., 2012). Globally, the prevalence of SGAs APP is lower compared with FGAs. This may result from the higher cumulative cost of combining 2 SGAs. There is also high use of depot and oral FGAs combinations. This could be as a result of affordability, presumed higher effectiveness, and medication non-adherence (Bruggemann et al., 2008; Gallego et al., 2012).

When depot preparations are used in combination with oral agents, the result is often high-dose prescription and various challenges with clear drawbacks. Therefore, they should be prescribed with caution (Adesola et al., 2013).

Depot FGAs and oral SGAs and combinations of oral FGAs were also prescribed APP combinations in this study next to depot FGAs and oral FGAs. FGAs with FGAs were the most commonly prescribed antipsychotics in Ethiopia, followed by FGAs with SGAs. This study is consistent with a meta-analysis in which FGAs and SGAs were the most common APP combinations (Gallego et al., 2012).

Additional psychotropic medications were also co-prescribed with antipsychotics. Mood stabilizers and anticholinergic were the most commonly prescribed co-medications with antipsychotics followed by antidepressants and benzodiazepines in South Africa. In this study, co-prescription of anticholinergic

were significantly associated with APP. Studies also supported this study in which higher anticholinergic use had been significantly associated with APP. This shows prescribers run the risk of inducing clinically relevant extrapyramidal side effects in patients treated with APP (Hong and Bishop, 2010).

Most of the time, anticholinergics were co-prescribed with FGAs. They are added to reduce the extrapyramidal side effects of FGAs, especially the depot preparations (Haddad et al., 2009; Fusar-Poli et al., 2012).

This review and meta-analysis had a high degree of heterogeneity among the included studies. Subgroup analysis based on study setting and publication year could not identify the source of heterogeneity. Besides, sample size and study quality score were the source of heterogeneity.

In spite of our findings, this review and meta-analysis has limitations. We included articles which were published in English language. So, this is a limitation of our review and meta-analysis. The age category of the study participants in the included studies were different. Due to this, we could not standardize our results for age. There were 6 included studies with a high degree of heterogeneity. This considerable heterogeneity is also another limitation of this study.

Conclusions

In this review and meta-analysis, the prevalence of APP in schizophrenia patients was found to be 40.6%. This figure is rather high compared with other published reviews and meta-analysis. Therefore, the antipsychotic guidelines in Africa should be observed strictly. Socio-demographic (age and male gender), clinical, and antipsychotic treatments such as diagnosis of schizophrenia, relapse and hospital admission, side effects, high dose prescribing, and longer antipsychotic treatment were correlates of APP. Depot FGAs and oral FGAs were the most common prescribed APP combinations.

Acknowledgments

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Statement of Interest

There is no conflict of interest among authors.

Data Availability

All data produced and analyzed are available in this published article.

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