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Prevalence of Drug-Induced Movement Disorders in Mental Disorders using AI-Powered Data Extraction: A Meta-analysis and Systematic Review

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ABSTRACT

This meta-analysis systematically examines the global prevalence of extrapyramidal symptoms (EPS) among patients with mental disorders taking antipsychotic medication. A comprehensive search of databases such as PubMed, MEDLINE, EMBASE, PsycInfo, and Google Scholar was conducted for literature from 2018 to 2024 using predefined keywords. Observational studies reporting antipsychotic-induced EPS were included. Data extraction was performed using an artificial intelligence (AI) based retrieval-augmented generation (RAG) tool. Our proposed tool does not require any data-specific fine-tuning to extract data for meta-analysis studies. Meta- analysis was conducted using SPSS and R software. Subgroup analysis was performed based on geographical location. Nine studies, with a total of 15,332 patients, met the specified criteria for inclusion. The pooled prevalence of EPS was 26.70%, with drug-induced Parkinsonism being the most common (16.51%). Subgroup analysis revealed higher effect sizes in Asia (0.28) and Africa (0.27) compared to Europe and America (0.13).

Our study shows that antipsychotic-induced EPS are prevalent globally, with regional population-specific variations. Drug-induced Parkinsonism was the most frequent EPS. Further research on demographic and clinical factors influencing EPS is needed to optimize patient care.

Keywords: Extrapyramidal Symptoms, Schizophrenia, Movement Disorders, Antipsychotic Medication, Motor Abnormalities, Mental Health

INTRODUCTION

Antipsychotic medications are the cornerstone in the treatment regimen for psychosis-related disorders, offering relief from debilitating symptoms[1]. However, one significant disadvantage linked with their use is the incidence of extrapyramidal side effects (EPS), which are common with typical and atypical antipsychotics[2]. These EPS, including tardive dyskinesia, parkinsonism, akathisia,

and dystonia, significantly impact medication adherence and the overall quality of life for patients[3]. Understanding the prevalence of EPS is important for clinicians to engage in informed discussions with patients before initiating antipsychotic treatment[4]. These treatments, categorized as first-generation antipsychotics (FGAs) or conventional (typical) drugs, and second-generation antipsychotics (SGAs), generally referred to as atypical agents, have both positive and negative effects[5]. According to a recent study, more than 20% of patients who were prescribed atypical antipsychotics experienced extrapyramidal symptoms (EPS) within the first year of starting therapy. Specifically, drug-induced Parkinsonism and akathisia were observed in around one out of every seven individuals[6]. The likelihood of developing EPS is influenced by a variety of factors, including gender, age, the type of antipsychotics used, physical illness, and concurrent medication use[7].

Furthermore, the significant prevalence of substance use, particularly tobacco, among patients presents more challenges to the management of antipsychotic medication adverse effects[8]. The prevalence of drug-induced movement disorders among patients reaches 44%, encompassing pseudo-Parkinsonism, akathisia, tardive dyskinesia, and tardive dystonia[9]. Gender disparities exist, with females more prone to certain EPS like pseudo-Parkinsonism and tardive dyskinesia, whereas males exhibit a higher likelihood of tardive dystonia. The complexity of EPS management is further exacerbated by clinical factors, such as the duration of treatment, co-morbid psychiatric and chronic medical conditions, and a familial history of movement disorders[8]. Acute EPS may manifest shortly after initiating or increasing antipsychotic doses, while tardive EPS may emerge after prolonged treatment. Although SGAs offer a reduced risk of EPS compared to FGAs, concerns remain regarding tardive dyskinesia[10]. Recent research that employs meta-analysis techniques in real-world therapeutic settings provides valuable insights into the prevalence and scope of EPS.

The objective of this study is to conduct a meta-analysis to determine the prevalence of EPS across different populations systematically. With the help of existing research findings, we aim to provide comprehensive insights into the occurrence of EPS associated with antipsychotic medications. We developed a retrieval-augmented generation (RAG) tool to perform efficient data extraction from the literature. Our tool combines machine learning and natural language processing to perform a fast, reliable, automated data extraction for meta-analysis studies. We demonstrate the application of a proposed RAG tool to automate data extraction in our meta-analysis study on EPS.

Evaluation of the RAG tool

To evaluate the performance of our RAG tool, we used the manually verified and corrected extraction results for the 9 studies included in our meta-analysis, as the ground truth. 16 fields were extracted from each study, hence we had a total of 144 instances. For each example, we compared the ground truth with the prediction of the RAG tool. Out of 144 total instances, our solution gave correct predictions for 106 instances, giving an overall accuracy of 73.61%. In future work, further improvements can be made by incorporating advanced chunking strategies and use of knowledge graphs.

MATERIALS AND METHODS

Protocol and Registration

PRISMA criteria were followed for this study [12] with the help of the PRISMA checklist that comprehensively reports the content of this systematic review and meta-analysis[13].

Databases and Search Strategy

From 2018 to April 2023, PubMed, MEDLINE, EMBASE, Google Scholar, and PsycInfo were searched extensively. The search used predefined keywords including ("antipsychotic agents" OR "antipsychotic" OR" antipsychotic agents" OR "dopamine agonists") AND ("extrapyramidal side effects" OR "extrapyramidal symptoms" OR "EPS" OR "drug-induced movement disorders" OR "movement disorders" OR "Parkinsonism" OR "dystonia" OR "akathisia" OR "tremors" OR "rigidity") AND ("schizophrenia" OR "bipolar disorder" OR "major depressive disorder" OR "substance-induced disorder") as shown in **Figure 1.**

Inclusion and exclusion criteria

The screening and eligibility methods followed predetermined inclusion and exclusion criteria. Observational studies (cross-sectional, cohort, case-control, longitudinal studies) on antipsychotic-induced EPS were included. These studies were conducted in various parts of the world. The authors have adequate information about the screened population and details of diagnostic criteria for psychiatric disorders. The study includes prevalence data from various global studies, providing a comprehensive overview of EPS occurrences across different populations. Restrictions were placed on publication years (2018-2023) and language (English) to account for methodological changes, temporal sensitivity, and study consistency. By focusing on recent years, the study aims to capture the latest advancements in diagnostic methods, treatment protocols, and the prevalence of EPS. Titles and abstracts were screened to eliminate irrelevant articles, review papers, editorials, commentaries, opinions, qualitative research, and case reports. The selection procedure eliminated papers on drug-induced EPS in preclinical and experimental animal models. We rejected studies with missing information and mixed or non-specific outcome measures during the eligibility evaluation.

Data Extraction using Retrieval-Augmented Generation (RAG) tool

The methodological parameters and outcome variables in **Table 1** include the first author, publication year, study design, population, country, age, and sample size. To extract values corresponding to these fields from the selected 49 studies, we developed a RAG tool that utilizes a pre-trained, open-source large language model (LLM) and a sentence embedding model[14]. The RAG tool operates in several steps. At first, it reads each document text using a PDF reader, organizes it in reading order, and divides it into smaller intact text chunks[15]. Next, an embedding vector is generated for each text chunk using a pre-trained sentence embedding deep learning model, and both the text chunks and their corresponding embedding vectors are stored in a vector database [16]. The approach utilizes a natural language query as input to retrieve information for each field. The

query is transformed into an embedding vector using the identical embedding technique employed for text chunks, as shown in **Figure 2.**

A cosine similarity comparison is then carried out between the query embedding vector and the embedding vectors of text chunks, retrieving the most similar chunks. These retrieved text chunks are used to construct the prompt for the LLM to generate the final response[17]. Further, post- processing guardrails ensure that the resulting response adheres to the expected JSON format. Finally, the extracted data for each study was written into an Excel document.

Risk of Bias (Quality) Assessment

Following the assessment of eligible articles, two authors independently evaluated the methodological validity and analysis of outcome measures. The assessment tool included ten questions for the studies to evaluate study quality. The article quality was assessed using 10 questions, and the articles were given values based on how well they met the requirements. Critical evaluation was done to assess studies' internal (systematic error) and external (generalizability) validity and reduce biases. Our study included only articles with a score of 50% or higher, and the selection was based on the two authors' average score.

Statistical analysis

The analysis was performed using R version (4.3.1) [18]. The data were exported from Excel to SPSS software for meta-analysis and subgroup analysis. Meta-analysis was conducted using a random effects pooling model with a 95% confidence level, [19] and the heterogeneity of studies was evaluated using I^2 statistic[20]. The leave-one-out sensitivity analysis was used to identify outliers that could significantly alter the overall effect magnitude and study heterogeneity[21]. To identify publication bias, we used funnel plot asymmetry and Egger's regression test[22]. To find publication bias, we employed the methods of funnel plot asymmetry and Egger's regression test. The statistical tests were conducted with a significance level set at $p < 0.05$ (two-sided).

RESULTS

Study Selection

A comprehensive search of reputable electronic databases, indexing services, search engines, and repositories yielded a total of 585 studies. Using Excel, a total of 248 duplicate studies were identified and eliminated, which was subsequently followed by a meticulous visual examination. Subsequently, 337 recordings were preserved for further assessment. Based on the assessment of their abstract and title, a total of 288 documents were eliminated. The eligibility of the remaining 49 papers was extensively scrutinised by analysing their entire texts. The RAG instrument was employed to acquire the requisite data from all 49 research studies. Approximately 40 studies were excluded as a result of factors such as inadequate information, failure to submit the study outcome, and ambiguous or contradictory findings. Ultimately, the systematic review and meta-analysis included a total of nine studies. The extractions for these nine studies were manually verified and corrected to rectify any

erroneous or absent data. Various factors, including the author, publication year, study design, population, study locations, nation, sample size, and EPS symptoms, are included in the methodological characteristics and outcome measures.

Study characteristics

A comprehensive review and meta-analysis included nine studies. Studies published between 2018 and 2023 were selected. The review included four Asian, three African, one European, and one North American studies. Study sample sizes ranged from 92 to 11,642. These investigations included 15,332 individuals with schizophrenia, bipolar disorder, and other psychotic diseases, with 26.70% having Extrapyramidal Symptoms (EPS) as shown in Figure 5.

Meta-analysis and sensitivity analysis

An examination of outcome measures and a sensitivity analysis were conducted using meta-analytical techniques. 26.70% of patients receiving these drugs experienced extrapyramidal symptoms (EPS) caused by antipsychotics. The incidence rates of akathisia, dystonia, tardive dyskinesia, and Parkinsonism were 4.96%, 2.05%, 3.17%, and 16.51%, respectively. Nine studies that reported outcome measures were included in the meta-analysis to estimate the total extent of antipsychotic-induced extrapyramidal symptoms (EPS). The analysis yielded a pooled estimate of 0.24 effect size (95% confidence interval: 0.14 – 0.32). In order to evaluate the consistency of effect sizes among the studies that were included, we performed a homogeneity test using the Q- statistic. The findings revealed substantial variation among the studies, as seen by the statistical test results ($Q = 22.8$; $df = 8$; $p < 0.004$).Furthermore, the analysis uncovered significant variability among the studies included, as indicated by the I^2 value of 65.1.

Subgroup analysis and risk factors

Subgroup analyses based on geographical location were conducted to investigate potential variations in effect sizes across different populations. A geography-wise analysis of EPS was conducted to explore potential regional variations in the prevalence and characteristics of these symptoms. This approach is essential because factors such as genetic diversity, healthcare infrastructure, socio-economic conditions, and cultural practices can significantly influence the reporting of EPS across different populations. The effect sizes (standardized mean differences) and corresponding 95% confidence intervals (CI) for each area are summarized in **Table** 2 Notably, Asia and Africa demonstrate larger effect sizes (0.277 and 0.267) compared to Europe and the Americas (effect size = 0.131). The overall p-value for the meta-analysis is < 0.001, indicating that the observed effect size across all subgroups is statistically significant (see **Figure 3**). The final model revealed that drug-induced Parkinsonism was significantly associated with factors such as female sex, age, and the type of antipsychotic used, physical illness, and the use of anti-cholinergic medications. Elderly patients were particularly prone to tardive dyskinesia, while the duration and severity of illness were linked to both Parkinsonism and akathisia.

Publication bias

Egger's regression test, together with the analysis of funnel plot asymmetry, was used to verify the presence of a small-study effect bias. The results indicated that the data do not strongly suggest the presence of publication bias in the studies, as shown in Figure 4. The intercept from Egger's regression was 0.05 (95% CI: -0.091, 0.195), there is no strong evidence of publication bias.

DISCUSSION

This study aims to provide an effective method for data extraction in meta-analysis, while enhancing our current knowledge on the prevalence and severity of extrapyramidal symptoms (EPS). We adopted an AI-driven RAG tool to accelerate the data extraction phase for meta- analysis. Our proposed RAG solution incorporates pre-trained deep learning models that do not require fine-tuning, yet provide high accuracy in data extraction. We have demonstrated that our approach is highly generic and robust. Our work underscores the potential of RAG as a versatile and scalable tool for enhancing the efficiency of meta-analysis studies on a larger scale. The use of this tool helped in speeding up our meta-analysis, as it significantly reduces the time required for data extraction.

Our comprehensive meta-analysis sheds light on the prevalence of EPS induced by antipsychotic medications across different geographic regions, providing valuable insights for clinicians and researchers. This study conducted a systematic review and meta-analysis to determine the overall proportion of extrapyramidal symptoms (EPS) associated with antipsychotic medicines in patients with mental disorders. Antipsychotic drugs have demonstrated effectiveness in treating schizophrenia and other significant psychiatric disorders. Most antipsychotics have their effects on the transmission of dopamine and serotonin neurotransmitters[23]. The effectiveness of antipsychotic medications depends on the activity and the specific location of these neuronal receptors[24]. The effectiveness of traditional antipsychotic medicines is strongly linked to their ability to bind to the dopamine (D2) receptor, hence inhibiting the action of naturally occurring dopamine in several dopaminergic pathways[25].

Antipsychotic-induced EPS was found in 26.70% of patients who were taking antipsychotic medications. We observed variations in EPS prevalence akathisia, dystonia, tardive dyskinesia, and parkinsonism were 4.96%, 2.05%, 3.17%, and 16.51%, respectively. Socioeconomic factors, cultural differences, genetic predispositions, healthcare infrastructure, and prescribing practices could all play a role in EPS outcomes. For instance, differences in healthcare services and availability of medication may impact treatment adherence and monitoring, thereby influencing EPS outcomes[26]. Additionally, genetic factors and variations in pharmacogenomics could contribute to differential drug responses and susceptibility to side effects across populations[27]. These findings have important clinical implications for the management of EPS in patients receiving antipsychotic treatment. Additionally, efforts to enhance patient education and medication adherence are crucial for minimizing the impact of EPS on quality of life[28]. By including observational studies in this work, we have demonstrated a comprehensive understanding of existing key findings on EPS. Moreover, the geographical diversity of the included data offers insights into the safety of these drugs across diverse populations and settings, increasing the generalizability of our findings.

The limitations of our study include the inability to perform subgroup analysis based on

demographic and clinical characteristics due to significant variation in diagnosis and drug usage (typical, atypical, mixed). This heterogeneity prevented further meta-analysis, limiting the depth of insight into specific subgroups. Future research may explore the underlying mechanisms contributing to regional variations in EPS prevalence, such as genetic polymorphisms, environmental factors, and healthcare disparities. Longitudinal studies investigating the trajectory of EPS development over time and its association with clinical outcomes could provide further insights into risk factors and prognostic indicators.

CONCLUSION

In summary, our meta-analysis shows the significant prevalence of antipsychotic-induced EPS, with drug-induced Parkinsonism emerging as the most common EPS, followed by akathisia. Addressing the paradoxical nature of tardive and Parkinsonian symptoms is crucial in treatment planning to minimise adverse effects. Early prevention and management strategies targeting these EPS effects can optimise the overall benefits of antipsychotic therapy. Furthermore, we integrated advanced AI-based tools such as RAG, which helped to optimise our data extraction methodology for meta-analysis. Our work suggests that RAG technologies can facilitate data extraction and synthesis, enabling more comprehensive and efficient reviews of the studies of interest. Moving forward, efforts towards developing EPS treatment guidelines, alongside considerations for antipsychotics with minimal side effects and enhanced psychoeducation, are important to improve clinical outcomes in patients receiving antipsychotic treatment.

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Figures

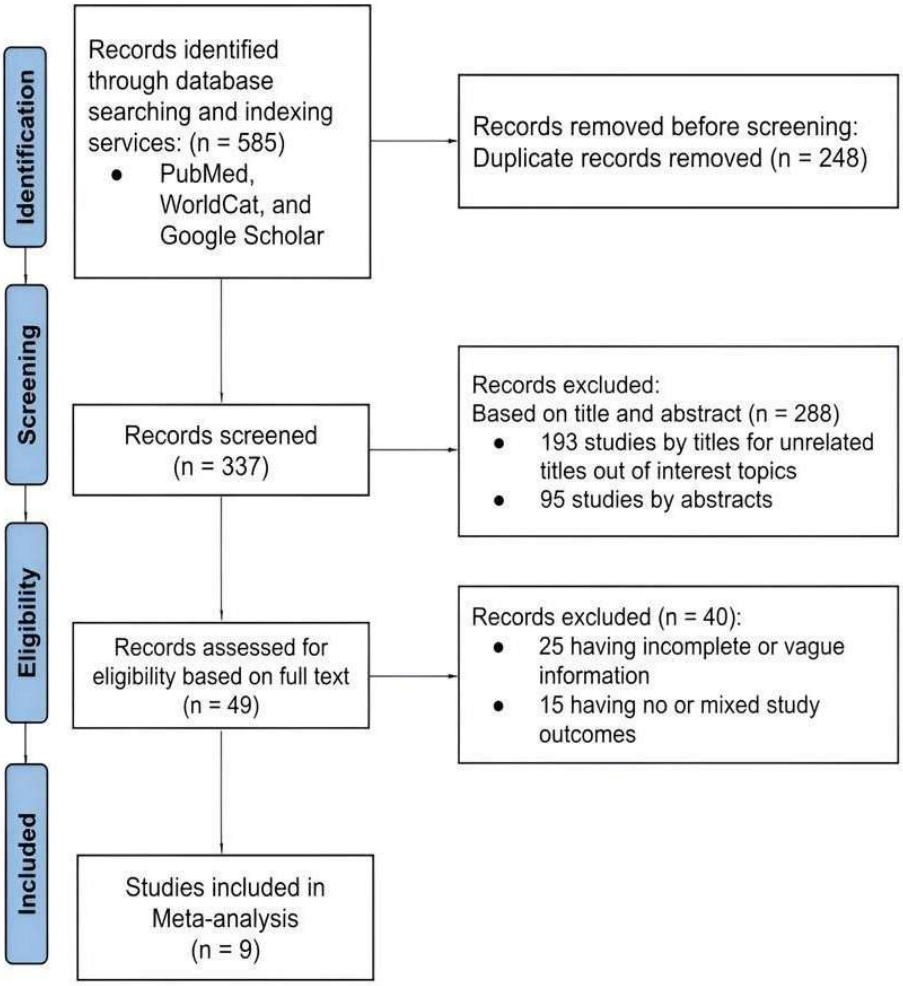


Figure 1. PRISMA flowchart illustrating the selection process of studies included in our meta-analysis. This flowchart outlines the systematic search and screening process, detailing the identification, screening, eligibility, and inclusion of studies according to PRISMA guidelines.

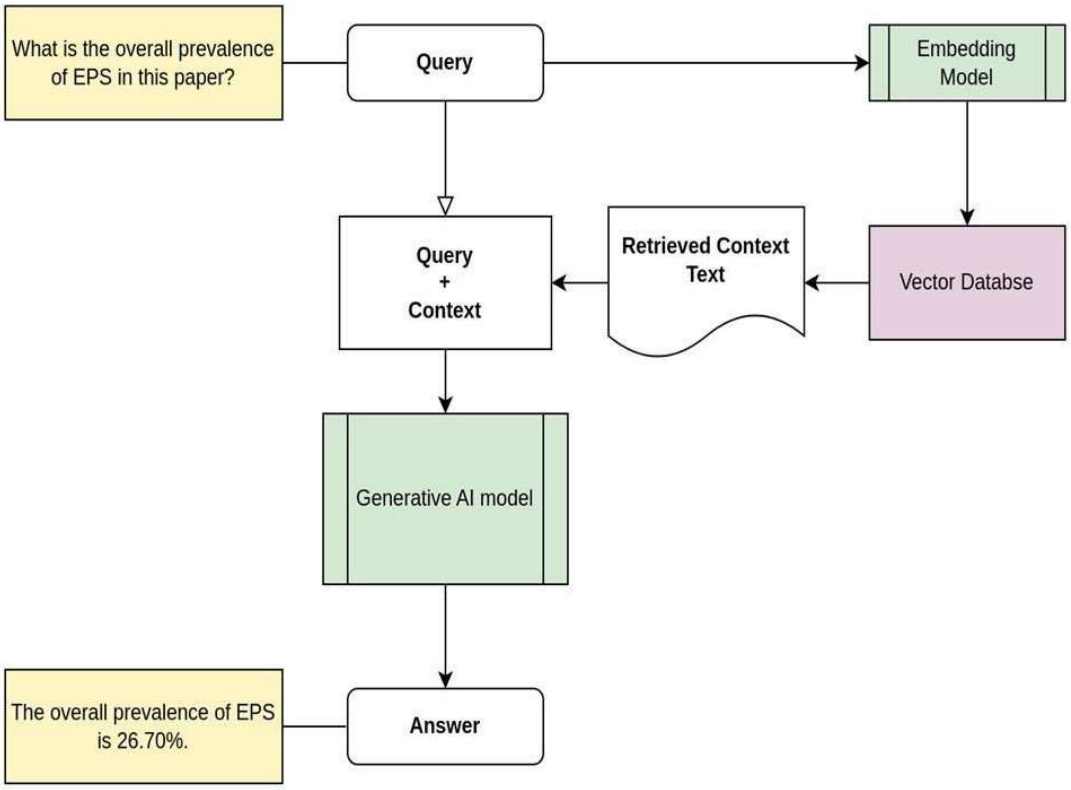
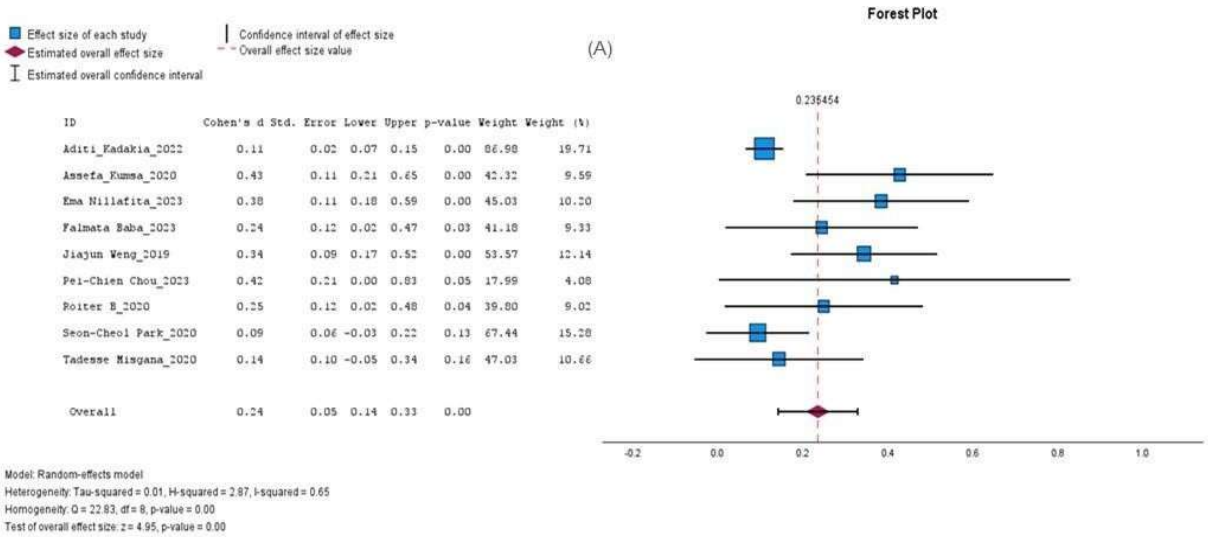


Figure 2. Flowchart illustrating the workflow of the RAG tool. The sequential process of query embedding, context retrieval, and response generation from the Gen AI model.



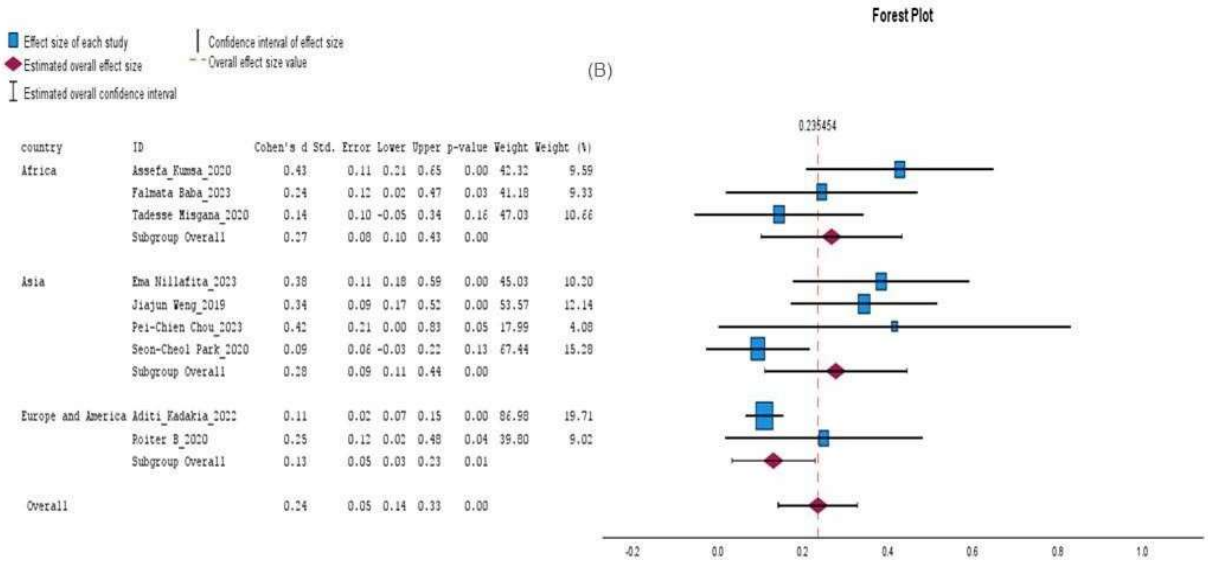


Figure 3. Forest Plots of Antipsychotic-Induced EPS. (A) Forest plot depicting the overall antipsychotic-induced EPS, **(B)** Forest plot shows subgroup analysis of the overall EPS estimate based on geographical distribution.

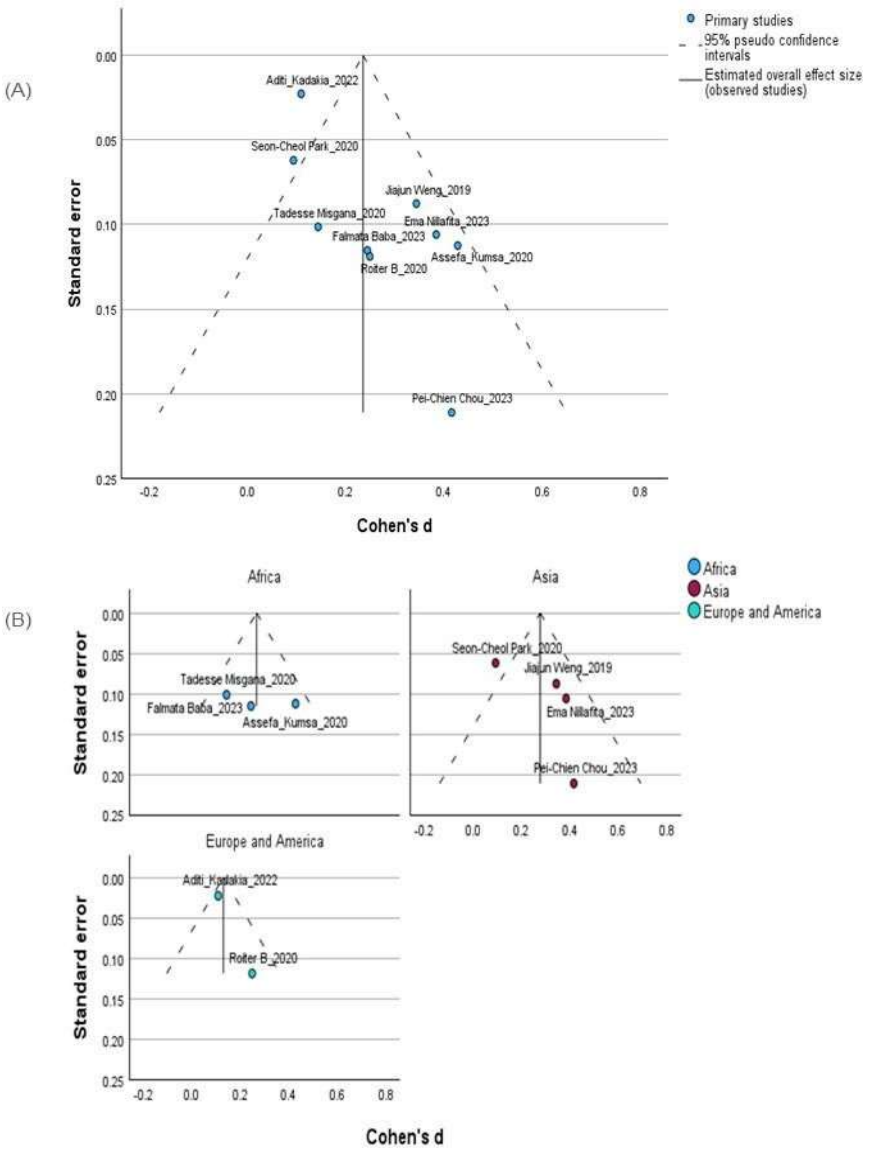


Figure 4. Funnel Plots Illustrating Publication Bias. (A) Funnel plot depicting publication bias in overall EPS **(B).** Funnel plot for assessing publication bias in the subgroup analysis.

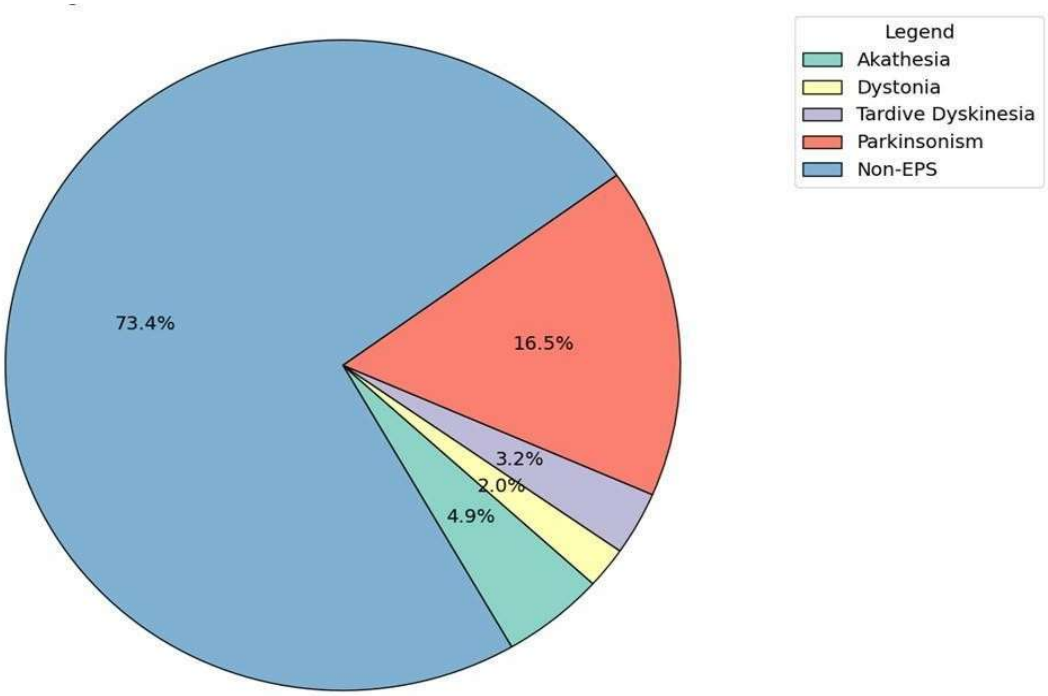


Figure 5. Shows the distribution of extrapyramidal symptoms (EPS) vs non-EPS in the study.

Table 1. Summary of studies included in the systematic review and meta-analysis.

SCZ, Schizophrenia; MDD, Major Depressive Disorder; BD, Bipolar Disorder, SD; Substance use Disorders

Study	Country	Participants diagnosis	Age in yrs (mean)	Total sample size (n)	EPS sample size (n)
Aditi_Kadakia et al., 2022[29]	USA	SCZ	39.5	11642	2468
Assefa_Kumsa et al.,2020[30]	Ethiopia	SCZ, MDD, BP	33.3	410	110
Tadesse Misgana et al.,2020[31]	Ethiopia	SCZ, MDD, BP, Other psychotic disorders	44.73	411	252

Pei-Chien Chou et al.,2023[32]	Taiwan	Delusional disorder, Organic delusional disorder, SCZ	53.4	92	49
Roiter B et al.,2020[33]	Italy	SCZ, BP, MDD, SD	46	285	144
Seon-Cheol Park et al.,2020[34]	India,Indonesia, Japan,Malaysia, and Taiwan	SCZ	38.7	1064	610
Ema Nillafita Putri Kusuma et al.,2023[35]	Indonesia	SCZ	40	446	126
Jiajun Weng et al.,2019[36]	China	SCZ	40.8	679	182
Falmata Baba Shettima et al.,2023[37]	Nigeria	SCZ	37.29	303	152

Table 2. Comparison of subgroups with the overall studies included in the systematic review and meta-analysis.

Comparison	No. of studies	Sample Size	SMD (95% CI)	p-value (overall)	p-value (homogeneity)	p-value (publication bias)	I^2 (heterogeneity)
Asia	4	2281	0.277	0.002*	0.025*	0.312	44
Africa	3	1124	0.267	0.001*	0.169	0.547	64
Europe and America	2	11927	0.131	0.009*	0.249	-	24.8
Overall	9	15332	0.235	<0.001*	0.004*	0.25	65.1

*p<0.05 is significant