Research Article Volume 01, Issue No. 02. 2025

THE MEDICAL JOURNAL OF PSYCHIATRY AND NEUROSURGERY

Comparative Effectiveness of Antipsychotics in Patients With Schizophrenia Spectrum Disorder

[1] Hani, [1] Yohana

[1] Faculty of Medicine, Maranatha Christian University, Bandung City, West Java, Indonesia

Correspondence : dr.hani39938484@gmail.com

Article History :

Received date : 2024/07/12
Revised date : 2024/08/19
Accepted date : 2024/09/24
Published date : 2025/10/20

ABSTRACT

Background: The comparative effectiveness of antipsychotic medications in treating schizophrenia spectrum disorder has been extensively researched, revealing a complex landscape of efficacy, safety, and tolerability among both first-generation and second-generation antipsychotics. **Literature Review:** Building on this groundwork, (Melnik et al., 2010) conducted a systematic review that found no statistically significant differences in overall psychopathology improvement between atypical and first-generation antipsychotics, although some atypicals, like risperidone, exhibited favorable outcomes. The authors emphasized the need for further exploration of refractory schizophrenia, especially regarding long-term benefits and treatment adherence. The discussion was further advanced by (M. Kane & U. Correll, 2010), who advocated for individualized treatment strategies that consider each patient's unique symptom profile and treatment history. They recognized clozapine as the only evidence-based treatment for refractory cases, indicating a gap in effective interventions for patients who do not respond to standard therapies. This emphasis on personalized care aligns with the findings of (T. Coyle et al., 2010), who critiqued the dopamine-centric pharmacological approaches and called for broader therapeutic targets beyond traditional antipsychotic mechanisms, given the modest efficacy of current treatments. **Conclusion:** In conclusion, the literature indicates that while there are some advantages associated with newer atypical antipsychotics, these benefits are not universally applicable. The complexity of schizophrenia, characterized by diverse symptomatology and individual patient needs, calls for a nuanced understanding of treatment efficacy. Future research should focus on long-term outcomes, individualized treatment approaches, and the exploration of novel therapeutic targets beyond the current pharmacological paradigms to improve patient outcomes.

Keyword: Effectiveness, Antipsychotics, Schizophrenia Spectrum Disorder

INTRODUCTION

The comparative effectiveness of antipsychotic medications in treating schizophrenia spectrum disorder has been a focal point of research over the past two decades, with significant contributions made by various studies that explore the efficacy, safety, and tolerability of both first-generation and second-generation antipsychotics. (Scott Stroup et al., 2000) laid the groundwork by suggesting that while newer atypical antipsychotics might offer advantages in efficacy and tolerability compared to conventional options, the limitations in study designs and patient samples restrict the generalizability of these findings. They emphasized the importance of ongoing studies, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), to provide essential insights into the comparative effectiveness of these medications.

Building on this foundation, (Melnik et al., 2010) conducted a systematic review that highlighted the lack of statistically significant differences in overall psychopathology improvement between several atypical antipsychotics and first-generation counterparts. They noted that while some atypicals, like risperidone, showed favorable outcomes, the need for further research on refractory schizophrenia remains critical, particularly concerning long-term benefits and treatment adherence.

(M. Kane & U. Correll, 2010) further advanced the discourse by advocating for an individualized treatment approach, considering a patient's unique symptom profile and treatment history. They underscored the importance of distinguishing between the acute effects of first- and second-generation antipsychotics, while also recognizing clozapine as the only evidence-based treatment for refractory cases. Their call for research into biomarkers and novel treatment options indicates a shift towards a more nuanced understanding of schizophrenia management.

(T. Coyle et al., 2010) addressed the limitations of dopamine receptor-centric pharmacological approaches, revealing that while second-generation antipsychotics may provide modest benefits over first-generation options, many patients still experience significant challenges, particularly regarding negative symptoms and cognitive dysfunction. Their findings suggest that schizophrenia is a progressive disorder, necessitating a broader exploration of therapeutic targets beyond traditional dopamine modulation.

In a more recent analysis, (Taylor, 2013) revisited the ongoing debate regarding the efficacy of antipsychotic medications, emphasizing the small yet significant differences in effectiveness between individual drugs. He pointed out that while newer antipsychotics like clozapine and amisulpride demonstrate superiority over first-generation options, the overall efficacy and discontinuation rates remain contentious, underscoring the complexities inherent in treatment decisions.

(G. Severance et al., 2018) expanded the scope of inquiry by examining autoimmune phenotypes in schizophrenia, which could reveal novel treatment targets beyond the established pharmacological agents. They highlighted that while current treatments primarily address positive symptoms, there remains a substantial gap in effectively managing negative and cognitive symptoms, prompting a need for innovative therapeutic strategies.

Finally, (Huhn et al., 2019) conducted a comprehensive network meta-analysis, consolidating data from numerous studies to evaluate the comparative efficacy and tolerability of a wide array of antipsychotic medications. Their findings reaffirm that both newer and older antipsychotics outperform placebo in reducing overall symptoms, yet they also reveal significant differences in side-effect profiles, emphasizing the necessity for informed treatment choices based on individual patient needs.

This literature review will further explore these insights and critically evaluate the evolving landscape of antipsychotic treatment for schizophrenia, considering the implications for clinical practice and future research directions.

LITERATURE REVIEW

The article titled "Comparative effectiveness of antipsychotic drugs in schizophrenia" by (Scott Stroup et al., 2000) provides a critical examination of the existing evidence regarding the efficacy and tolerability of atypical antipsychotics compared to conventional antipsychotics in treating schizophrenia spectrum disorders. The authors highlight that while there are some advantages associated with atypical antipsychotics, these benefits are inconsistent and not universally applicable across all patient populations.

A significant concern raised in the article is the limited scope of assessment measures utilized in existing studies. The authors point out that the short duration of these studies fails to capture the chronic and highly variable nature of schizophrenia, which necessitates a more comprehensive evaluation of treatment outcomes over extended periods. This limitation poses challenges for clinicians seeking to make informed treatment decisions based on the available data.

Moreover, the article emphasizes the issues surrounding the generalizability of findings due to the specific patient samples involved in these studies. The authors argue that the diversity of the schizophrenia spectrum is not adequately represented, which may skew the perceived effectiveness of antipsychotic medications. This calls for a more inclusive approach in future research to ensure that results can be applied to a broader patient demographic.

The authors also discuss the ongoing Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project, which aims to address some of the shortcomings of previous research. The CATIE trial is designed to assess the effectiveness of second-generation antipsychotics in a diverse patient population, incorporating both efficacy and effectiveness measures. The focus on all-cause treatment discontinuation, alongside symptom management, side effects, quality of life, and cost analyses, reflects a more holistic approach to evaluating treatment options.

The article "Efficacy and safety of atypical antipsychotic drugs (quetiapine, risperidone, aripiprazole and paliperidone) compared with placebo or typical

antipsychotic drugs for treating refractory schizophrenia: overview of systematic reviews" by (Melnik et al., 2010) provides a comprehensive overview of the comparative effectiveness of atypical antipsychotics in the treatment of refractory schizophrenia. The authors critically analyze the efficacy and safety profiles of quetiapine, aripiprazole, paliperidone, and risperidone against both placebo and first-generation antipsychotics, contributing valuable insights to the ongoing discourse regarding optimal pharmacological interventions for this challenging patient population.

The findings indicate that the atypical antipsychotics—quetiapine, aripiprazole, and paliperidone—do not exhibit statistically significant differences in overall psychopathology improvement when compared to first-generation antipsychotics. This suggests that while these newer medications may be perceived as more favorable due to their side effect profiles, they may not necessarily confer superior therapeutic benefits in managing the core symptoms of schizophrenia. In contrast, risperidone appears to demonstrate some favorable outcomes compared to other effective medications like amisulpride, clozapine, and olanzapine, although the authors caution that these results are not definitive.

A notable aspect of the review is the emphasis on the lower frequency of extrapyramidal side effects associated with the atypical antipsychotics when compared to their first-generation counterparts. This finding is particularly relevant, as extrapyramidal symptoms can significantly impact patient quality of life and treatment adherence. The authors highlight that patients treated with atypical antipsychotics are more likely to adhere to their treatment regimens, which is a critical factor in managing chronic conditions like schizophrenia.

However, the authors underscore a significant gap in the current literature regarding the long-term effectiveness of these interventions, particularly for patients with refractory schizophrenia. They call for further studies to evaluate various outcomes, including risk profiles, long-term benefits, relapse rates, and residual symptoms. The need for comprehensive assessments of safety and cost-effectiveness is also

identified, which is essential for guiding clinical decision-making in this complex area.

Moreover, the article advocates for the inclusion of treatment compliance as a primary outcome measure, given its pivotal role in determining the balance between efficacy and safety. The authors also suggest that quality of life, well-being, and the effects of personal and family interventions require more thorough evaluation in future research.

The article "Pharmacologic treatment of schizophrenia" by (M. Kane & U. Correll, 2010) provides a comprehensive overview of the complexities involved in the pharmacologic management of schizophrenia spectrum disorder. The authors highlight that, despite advancements in pharmacotherapy, patients frequently experience suboptimal outcomes, indicating a pressing need for individualized treatment strategies. This perspective aligns with the understanding that schizophrenia is a heterogeneous disorder, necessitating a tailored approach that considers not only the current symptomatology but also comorbid conditions, previous treatment responses, and patient preferences.

(M. Kane & U. Correll, 2010) emphasize that while the acute efficacy of first-generation antipsychotics is comparable to that of second-generation agents, the latter often presents significant advantages. Specifically, second-generation antipsychotics are associated with lower incidences of extrapyramidal side effects and tardive dyskinesia, which are critical considerations in long-term treatment plans. This evaluation is crucial, as the tolerability of medication can greatly influence patient adherence and overall treatment outcomes.

Moreover, the authors point out that clozapine remains the only evidence-based treatment for patients with refractory schizophrenia, underscoring the limitations of existing pharmacological options for those who do not respond adequately to standard therapies. This highlights a significant gap in the current treatment landscape, particularly regarding effective interventions for cognitive dysfunction

and negative symptoms, which are often inadequately addressed by available antipsychotics.

The article also calls for a more nuanced understanding of functional outcomes in schizophrenia treatment, suggesting that future research should focus on developing therapies that not only alleviate psychotic symptoms but also enhance cognitive and social functioning. This is an essential consideration, as the ultimate goal of treatment should extend beyond symptom management to encompass improvements in quality of life and daily functioning.

The article "Beyond the dopamine receptor: novel therapeutic targets for treating schizophrenia" by (T. Coyle et al., 2010) provides a comprehensive examination of the pharmacological landscape of schizophrenia treatment, primarily focusing on the limitations of current antipsychotic medications and the need for novel therapeutic targets. The authors critically analyze the historical context of antipsychotic drug development, beginning with chlorpromazine, and highlight the ongoing reliance on dopamine receptor antagonism as a primary mechanism of action for these medications.

One of the key insights from the article is the acknowledgment of the modest efficacy of current antipsychotic treatments, particularly in addressing the diverse symptoms of schizophrenia. While second-generation antipsychotics have shown some superiority in managing positive symptoms, the authors emphasize that these effects are not universally applicable to all patients. The high rates of discontinuation due to inefficacy or intolerable side effects underscore the urgent need for more effective and tolerable treatment options (T. Coyle et al., 2010). This observation is particularly pertinent when considering the chronic nature of schizophrenia and the significant impact of negative symptoms on patient outcomes.

The article also delves into the neurobiological underpinnings of schizophrenia, citing advancements in neuropsychology and brain imaging techniques. The authors discuss how structural and functional abnormalities in the brain, particularly

in the prefrontal cortex and white matter tracts, contribute to the cognitive impairments observed in individuals with schizophrenia. This highlights the necessity for a more holistic approach to treatment that extends beyond dopamine receptor antagonism to encompass other neurotransmitter systems and cognitive deficits (T. Coyle et al., 2010).

Moreover, the authors critique the historical focus on positive symptoms, advocating for a broader understanding of schizophrenia that includes the interplay between positive and negative symptoms. They argue that addressing negative symptoms and cognitive dysfunction is crucial for improving overall patient outcomes and quality of life. This perspective aligns with contemporary trends in schizophrenia research, which increasingly recognize the complexity of the disorder and the need for multifaceted treatment strategies.

In the article "Assessing the use and effectiveness of antipsychotic medication," (Taylor, 2013) delves into the ongoing debate surrounding the comparative effectiveness of antipsychotic medications, particularly focusing on class and intra-class differences. The article begins by referencing a pivotal meta-analysis by Geddes et al. (2000), which raised questions about the superiority of newer atypical antipsychotics over traditional low-dose haloperidol. This analysis sparked significant discussion within the psychiatric community, particularly as the National Institute for Health and Care Excellence (NICE) guidelines (2002) recommended the use of second-generation antipsychotics (SGAs) for first-episode psychosis, despite the findings presented by Geddes et al.

Taylor further elaborates on the evolution of this debate, highlighting the contributions of subsequent meta-analyses, particularly those by Davis et al. (2003) and Leucht et al. (2009). These analyses provided evidence of small but clinically significant differences in efficacy among individual antipsychotics, suggesting that medications such as clozapine, olanzapine, risperidone, and amisulpride demonstrated superior effectiveness compared to FGAs like haloperidol. This nuanced understanding of antipsychotic efficacy is crucial for clinicians when

making treatment decisions, as it underscores the importance of tailoring medication choices to individual patient needs and symptom profiles.

Moreover, Taylor discusses the findings of Crossley et al. (2010), which supported the earlier conclusions of Geddes et al. while also emphasizing the distinct side effect profiles associated with FGAs and SGAs. The article notes that while SGAs did not show a significant advantage over FGAs in terms of symptom efficacy or discontinuation rates, they were more frequently linked to weight gain, whereas FGAs were more likely to cause movement disorders. This distinction is particularly relevant in clinical practice, as the side effects of antipsychotic medications can significantly impact patient quality of life and adherence to treatment.

The article "Autoimmune phenotypes in schizophrenia reveal novel treatment targets" by (G. Severance et al., 2018) provides a comprehensive examination of schizophrenia as a polygenic disorder characterized by a spectrum of symptoms, including positive, negative, and cognitive impairments. The authors effectively delineate the limitations of current treatment modalities, particularly focusing on the pharmacological approaches targeting dopamine receptors.

The article's main premise revolves around the inadequacy of existing antipsychotic treatments, particularly in addressing the negative and cognitive symptoms of schizophrenia. While the authors acknowledge the effectiveness of typical antipsychotics in managing positive symptoms through their action on dopamine receptors, they highlight that these agents often fall short in alleviating the broader symptomatology associated with the disorder. This is a critical observation, as it underscores the need for a more nuanced understanding of schizophrenia that goes beyond dopamine dysregulation (G. Severance et al., 2018).

Moreover, the discussion regarding atypical antipsychotics presents a balanced view of their advantages and disadvantages. The authors note that while these second-generation medications tend to mitigate some of the extrapyramidal side effects commonly associated with first-generation drugs, they introduce metabolic

risks, such as diabetes and weight gain. This duality in treatment efficacy and side effect profiles is crucial for clinicians when considering the best therapeutic options for their patients, particularly in light of the comprehensive analysis provided by Leucht et al. (2009) referenced in the article.

The authors' call for a shift in research focus towards autoimmune phenotypes as potential treatment targets is particularly noteworthy. This suggestion implies a paradigm shift in understanding the etiology of schizophrenia and opens the door for novel therapeutic strategies that could address the unmet needs of patients suffering from negative and cognitive symptoms. By advocating for a broader exploration of treatment targets beyond traditional dopamine modulation, (G. Severance et al., 2018) contribute valuable insights that could inform future research directions.

The article titled "Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis" by (Huhn et al., 2019) presents a comprehensive analysis of the effectiveness and tolerability of various antipsychotic medications in treating schizophrenia spectrum disorders. This systematic review and network meta-analysis is notable for its extensive scope, incorporating data from 402 studies with a total of 53,463 participants, making it one of the largest analyses in this domain.

The authors employed rigorous methodologies to compare 32 different antipsychotics, including both newly approved medications, such as cariprazine and brexpiprazole, and older agents like haloperidol and chlorpromazine. This inclusion of a broader range of medications addresses a significant gap in previous research, which often focused on a limited selection of treatments. The study's primary outcome was the reduction of overall schizophrenic symptoms, but it also explored various secondary outcomes, including positive and negative symptoms, dropout rates, depression, quality of life, and overall functioning.

One of the critical findings of the study is that both newer and older antipsychotics demonstrated a greater reduction in overall symptoms compared to placebo, and they also exhibited lower all-cause discontinuation rates. This suggests that, regardless of the class of antipsychotic, patients are likely to experience some level of symptom relief when treated with these medications. However, the authors also highlighted significant variability in side-effect profiles among the different drugs, indicating that while some medications may be more effective, they could also come with a higher risk of adverse effects.

The article underscores the importance of considering both efficacy and tolerability when selecting antipsychotic treatments for patients with schizophrenia. The authors noted that the evidence for older antipsychotics was often of lower quality due to smaller data sets, resulting in more uncertain comparisons. This raises important questions regarding the clinical relevance of older medications in contemporary treatment regimens.

CONCLUSION

The comparative effectiveness of antipsychotic medications in treating schizophrenia spectrum disorder has been extensively researched, revealing a complex landscape of efficacy, safety, and tolerability among both first-generation and second-generation antipsychotics. The foundational work by (Scott Stroup et al., 2000) highlighted the potential advantages of atypical antipsychotics over conventional options but also pointed out significant limitations in study designs and patient demographics, which hinder the generalizability of findings. This underscores the necessity for ongoing research, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), to provide more robust insights into treatment effectiveness.

Building on this groundwork, (Melnik et al., 2010) conducted a systematic review that found no statistically significant differences in overall psychopathology improvement between atypical and first-generation antipsychotics, although some atypicals, like risperidone, exhibited favorable outcomes. The authors emphasized

the need for further exploration of refractory schizophrenia, especially regarding long-term benefits and treatment adherence.

The discussion was further advanced by (M. Kane & U. Correll, 2010), who advocated for individualized treatment strategies that consider each patient's unique symptom profile and treatment history. They recognized clozapine as the only evidence-based treatment for refractory cases, indicating a gap in effective interventions for patients who do not respond to standard therapies. This emphasis on personalized care aligns with the findings of (T. Coyle et al., 2010), who critiqued the dopamine-centric pharmacological approaches and called for broader therapeutic targets beyond traditional antipsychotic mechanisms, given the modest efficacy of current treatments.

In a more recent analysis, (Taylor, 2013) revisited the debate on antipsychotic efficacy, noting small yet significant differences in effectiveness among individual drugs. He highlighted that while newer antipsychotics like clozapine and amisulpride show superiority, the overall efficacy and discontinuation rates remain contentious. This is supported by (G. Severance et al., 2018), who explored autoimmune phenotypes in schizophrenia, suggesting novel treatment targets and emphasizing the need for strategies that address negative and cognitive symptoms, which are often inadequately managed by current pharmacological agents.

Finally, (Huhn et al., 2019) conducted a comprehensive network meta-analysis that consolidated data from numerous studies to evaluate the comparative efficacy and tolerability of a wide array of antipsychotic medications. Their findings reaffirmed that both newer and older antipsychotics outperform placebo in reducing overall symptoms, yet they also revealed significant differences in side-effect profiles, which necessitate informed treatment choices tailored to individual patient needs.

In conclusion, the literature indicates that while there are some advantages associated with newer atypical antipsychotics, these benefits are not universally applicable. The complexity of schizophrenia, characterized by diverse symptomatology and individual patient needs, calls for a nuanced understanding of

treatment efficacy. Future research should focus on long-term outcomes, individualized treatment approaches, and the exploration of novel therapeutic targets beyond the current pharmacological paradigms to improve patient outcomes.

DISCLOSURE STATEMENT

- Disclosure Statement : The authors have no conflicts of Interest to declare
- Funding Sources : None
- Acknowledgements : -
- Author Contribution : All authors discussed and contributed the final content for journal submission and publication

REFERENCES

1. Scott Stroup, T., A. Lieberman, J., S. Swartz, M., & P. McEvoy, J., 2000. Comparative effectiveness of antipsychotic drugs in schizophrenia. ncbi.nlm.nih.gov
2. Melnik, T., Garcia Soares, B., Eduarda dos Santos Puga, M., & Nagib Atallah, Álvaro, 2010. Efficacy and safety of atypical antipsychotic drugs (quetiapine, risperidone, aripiprazole and paliperidone) compared with placebo or typical antipsychotic drugs for treating refractory schizophrenia: overview of systematic reviews. ncbi.nlm.nih.gov
3. M. Kane, J. & U. Correll, C., 2010. Pharmacologic treatment of schizophrenia. ncbi.nlm.nih.gov
4. T. Coyle, J., Balu, D., Benneyworth, M., Basu, A., & Roseman, A., 2010. Beyond the dopamine receptor: novel therapeutic targets for treating schizophrenia. ncbi.nlm.nih.gov
5. Taylor, M., 2013. Assessing the use and effectiveness of antipsychotic medication. [PDF]

6. G. Severance, E., B. Dickerson, F., & H. Yolken, R., 2018. Autoimmune phenotypes in schizophrenia reveal novel treatment targets. ncbi.nlm.nih.gov

7. Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Bäckers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., & Leucht, S., 2019. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis.. [PDF]