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ORIGINAL

An unusual adverse effect of the clozapine - appendicitis: A meta-analysis

Un efecto adverso inusual de la clozapina - apendicitis: Un meta-análisis

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Abstract

Objective: This meta-analysis aimed to compare the risk of appendicitis between clozapine and other antipsychotic medications.
Methods: Using the databases EMBASE, PubMed, SCOPUS, and Cochrane, we carried out a thorough literature search up to May 2023. Studies comparing Clozapine and Other antipsychotics in terms of occurrence of the appendicitis were included. We applied a random effect model using Rev-Man 5.4 software.
Results: Four studies were included in the analysis, involving a total of 4,685 patients on clozapine and 15,777 patients on other antipsychotics. Results consistently showed a higher incidence of appendicitis among patients treated with clozapine across all four studies, with incidence rates ranging from 2,086 to 2,726 per 100,000. A significantly higher incidence of appendicitis was observed in the clozapine group (OR: 45.76, 95% CI 8.03 to 260.75; P<0.0001), despite the considerable heterogeneity across the studies (I2=81%).
Conclusions: This meta-analysis highlights the importance of monitoring patients treated with clozapine for the occurrence of appendicitis. Clinicians should be aware of this potential risk and consider it when prescribing antipsychotic treatments.

Key words: Clozapine, appendicitis, schizophrenia, antipsychotics.

Resumen

Objetivo: Este meta-análisis tuvo como objetivo comparar el riesgo de apendicitis entre clozapina y otros medicamentos antipsicóticos.
Métodos: Utilizando las bases de datos EMBASE, PubMed, SCOPUS y Cochrane, se realizó una búsqueda bibliográfica exhaustiva hasta mayo de 2023. Se incluyeron estudios que comparaban Clozapina y Otros antipsicóticos en cuanto a la aparición de la apendicitis. Se aplicó un modelo de efectos aleatorios utilizando el software Rev-Man 5.4.
Resultados: Se incluyeron cuatro estudios en el análisis, con un total de 4.685 pacientes con clozapina y 15.777 pacientes con otros antipsicóticos. Los resultados mostraron sistemáticamente una mayor incidencia de apendicitis entre los pacientes tratados con clozapina en los cuatro estudios, con tasas de incidencia que oscilaban entre 2.086 y 2.726 por 100.000. La incidencia de apendicitis fue significativamente mayor entre los pacientes tratados con clozapina que entre los tratados con otros antipsicóticos. Se observó una incidencia significativamente mayor de apendicitis en el grupo de clozapina (OR: 45,76; IC 95%: 8,03 a 260,75; P<0,0001), a pesar de la considerable heterogeneidad entre los estudios (I2=81%).
Conclusiones: Este metaanálisis destaca la importancia de monitorizar a los pacientes tratados con clozapina para detectar la aparición de apendicitis. Los clínicos deben ser conscientes de este riesgo potencial y tenerlo en cuenta a la hora de prescribir tratamientos antipsicóticos.

Palabras clave: Clozapina, apendicitis, esquizofrenia, antipsicóticos.

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Introduction

Clozapine is an atypical antipsychotic medication that is primarily used to treat schizophrenia, especially in individuals who do not respond well to other antipsychotic medications. It is known for its efficacy in reducing both positive and negative symptoms of the disorder. However, despite its therapeutic benefits, clozapine has several adverse effects that can be concerning for patients and healthcare providers alike[1].

One of the most serious side effects of clozapine is agranulocytosis, a potentially life-threatening condition characterized by a significant reduction in the number of white blood cells, particularly neutrophils[2]. This can leave the patient susceptible to infections and sepsis. As a result, patients on clozapine are required to undergo regular blood tests to monitor their white blood cell count. Clozapine is associated with significant weight gain, which can lead to obesity, diabetes, and other metabolic disturbances. Clozapine can cause sedation, dizziness, and lightheadedness, especially during the initial phase of treatment or upon dosage adjustment. Orthostatic hypotension, a sudden drop in blood pressure upon standing, is another common side effect of clozapine[3-5].

Clozapine may cause constipation and other gastrointestinal issues, such as nausea, vomiting, and abdominal pain. These side effects can be managed with dietary adjustments, increased fluid intake, and over-the-counter laxatives, if necessary. In rare cases, severe constipation may lead to more serious complications, such as bowel obstruction or paralytic ileus and appendicitis[6].

In this meta-analysis, we investigate whether, in comparison to other antipsychotics, clozapine use is associated with an increased risk of appendicitis.

Materials and methods

Search strategy

We did a comprehensive literature search up to May 2023 using EMBASE, PubMed, SCOPUS, and Cochrane databases. The keywords used for the searches were "clozapine, clozapine and side effects, clozapine and appendicitis, clozapine and other antipsychotics". Moreover, manual searches of references and reviews were done for additional relevance.

Study selection

Studies comparing the incidence of appendicitis during clozapine and other antipsychotics treatment were included. The reviews, case reports, and irrelevant confounding articles were excluded.

Data extraction

Four authors independently reviewed the included studies (FBA, SIA, HŞB, HMA, and OG). We extracted information on sample size, study design, and year of publication. The studies' participants' ages and genders, the additional antipsychotic medications they took, their diagnoses, and the length of time they had been taking antipsychotics were all reviewed.

Risk of bias assessment

The Newcastle-Ottawa Scale (NOS), designed especially for observational studies, was chosen to assess the level of quality of the selected studies. Four authors (OG, SIA, HMA, and HŞB) independently analyzed the included studies, and any disagreements were resolved through discussion with the other reviewers. Thanks to the efforts of four different authors (OG, SIA, HMA, and HŞB), who used a predetermined meta-analysis form to extract pertinent data from each study, interobserver agreement was found to be high and satisfactory.

Statistical analysis

The Review Manager (RevMan) software, version 5.4, was used to analyze the statistical data. Risk ratios and measured mean differences were used to evaluate both continuous and dichotomous variables. The amount of statistical heterogeneity was assessed using the Chi-square test and the I2 statistic, which both quantify statistical heterogeneity. The significance level was set at $p<0.05$. To analyze the data, we used a model with random effects.

Reporting

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) was used to report the findings of this meta-analysis.

Results

Four studies comparing clozapine (n=4685) and other antipsychotics (n=15777) were determined to be appropriate for meta-analysis during the screening process of studies (PRISMA), as shown in **figure 1**. These four studies included three retrospective studies and one case series. The New-Castle Ottawa scores, type and year of the studies were summarized in **table I**.

The results presented in this article are based on four studies investigating the incidence and onset of appendicitis in patients treated with Clozapine and other antipsychotics (AP) (**Table II**).

In the study conducted by Kawakita et al.[7] (study period: 2009-2021), among 65 patients on Clozapine (21 males and 44 females, mean age 32.3 years, range 23.1-50.4 years), 5 cases of appendicitis were reported, yielding an incidence rate of 2,086 per 100,000. The average age at the onset of appendicitis in this group was 23 years (range 16.7-28.6 years). In the comparison group treated with other APs (400 patients, 171 males and 229 females), 5 cases of appendicitis were reported. The average age at the onset of appendicitis was 30.7 years (range 24.1-59.9 years).

Figure 1: PRISMA flow diagram of study selection.

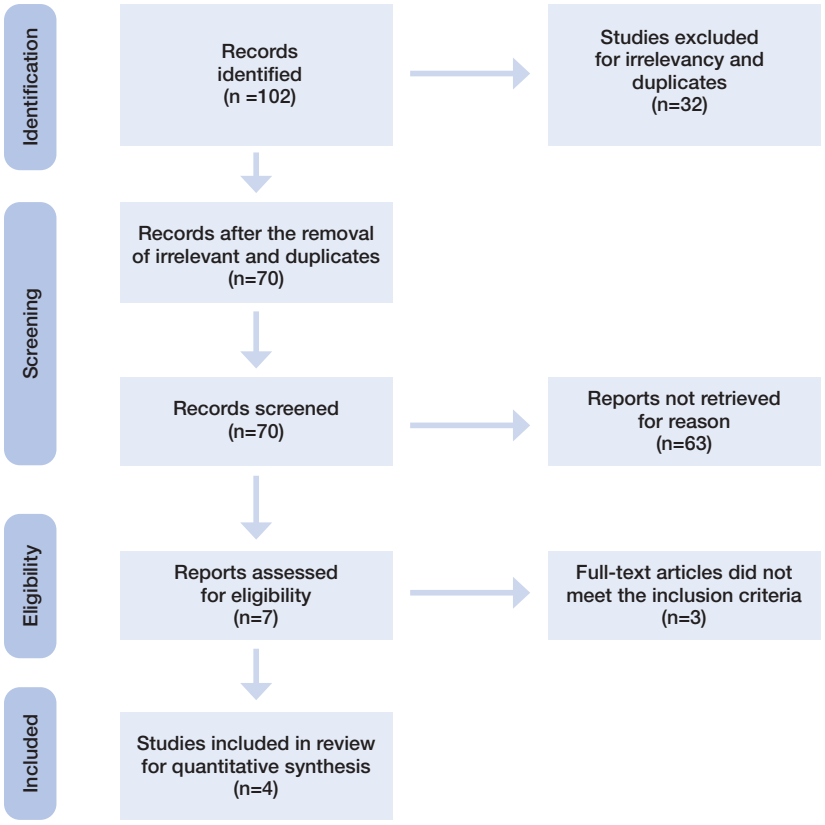


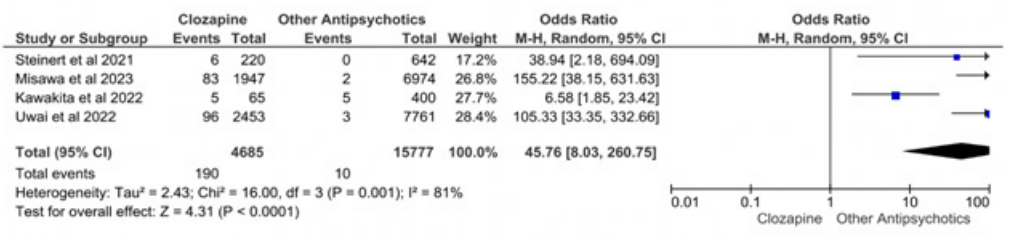
Table I: Summary of the included studies.

No	Author	Region	Year	Clozapine (n=4685)	Other antipsychotics (n=15777)	Type of Study	NOS score
1	Kawakita et al	Japan	2022	65	400	Retrospective	5
2	Uwai et al	Japan	2022	2453	7761	Retrospective	5
3	Misawa et al	Japan	2023	1947	6974	Retrospective	6
4	Steinert et al	Germany	2021	220	642	Case series	4

Table I: Characteristics of the studies.

No	Author	Study Period	Group	N	Sex, M/F	Age	Appendicitis (n)	Incidence (per 100,000)	Age at onset of appendicitis	Time to onset appendicitis
1	Kawakita et al	2009-2021	Clozapine Other AP	65 400	21/44 171/229	32.3(23.1-50.4) NA	5 5	2,086 NA	23(16.7-28.6) 30.7(24.1-59.9)	NA NA
2	Uwai et al	2004-2021	Clozapine Other AP	2453 7761	NA NA	NA NA	96 3	NA NA	NA NA	445(245-675) NA
3	Misawa et al	2004-2021	Clozapine Other AP	1947 6974	1086/835 3211/3763	NA NA	83 2	NA NA	NA NA	674(314-1096) NA
4	Steinert et al	NA (14 years)	Clozapine Other AP	220 642	NA NA	NA NA	6 0	2,726 130	NA NA	NA NA

Figure 2: Meta-analysis of the included studies in terms of occurrence of the appendicitis rate.



In the Uwai et al.[8] study (study period: 2004-2021), 96 cases of appendicitis were reported among 2,453 patients on Clozapine. The median time to the onset of appendicitis in this group was 445 days (range 245-675 days). In the comparison group of 7,761 patients treated with other APs, there were 3 cases of appendicitis.

The study by Misawa et al.[9] (study period: 2004-2021) involved 1,947 patients on Clozapine (1,086 males and 835 females). Here, 83 cases of appendicitis were reported, with a median time to onset of 674 days (range 314-1096 days). In the comparison group of 6,974 patients on other APs (3,211 males and 3,763 females), 2 cases of appendicitis were identified.

In the final study by Steinert et al. (10) spanning 14 years, 6 cases of appendicitis were reported among 220 patients on Clozapine, yielding an incidence rate of 2,726 per 100,000. In the comparison group of 642 patients on other APs, no cases of appendicitis were reported, and the incidence rate was estimated at 130 per 100,000.

Meta-analysis

Four studies[7-10] have discussed appendicitis rates in patients who received clozapine and other AP. The Clozapine group had a significantly higher incidence of appendicitis compared to other AP (I2=81%), (OR: 45.76, 95% CI 8.03 to 260.75; P<0.0001) (**Figure 2**).

Discussion

We will discuss the adverse effects associated with the use of clozapine and other antipsychotic medications. It is crucial to keep in mind that these medications, while effective in managing psychotic symptoms, also carry a risk of adverse reactions. Therefore, the benefits must be carefully weighed against these potential risks.

Clozapine, despite being one of the most effective antipsychotics for treatment-resistant schizophrenia, is associated with several adverse effects[6]. These range from relatively common but mild side effects such as salivation, sedation, and constipation to serious, potentially life-threatening conditions such as neutropenia, agranulocytosis, myocarditis, and seizures. The risk of agranulocytosis, in particular, has led to mandatory blood monitoring protocols for patients on clozapine. Additionally, the metabolic disturbances caused by clozapine, such as weight gain, hyperlipidemia, and diabetes mellitus, are concerning due to their long-term implications on patients' cardiovascular health[11-15]. In recent years, there have been publications suggesting an increased risk of appendicitis associated with the use of clozapine[7-10,16,17, 18]. This meta-analysis was conducted to compare the risk of appendicitis between clozapine and other antipsychotic medications.

The higher incidence of appendicitis among patients treated with Clozapine, compared to other APs, was consistently observed across all four studies. In the study by Kawakita et al.[7] the incidence rate among patients on Clozapine was remarkably high (2,086 per 100,000). This was corroborated by the findings of Steinert et al. (10) where the incidence rate for Clozapine patients was even higher (2,726 per 100,000), while no cases of appendicitis were reported in the comparison group.

Furthermore, Uwai et al.[8] and Misawa et al.[9] reported median times to onset of appendicitis of 445 days and 674 days, respectively, for patients treated with Clozapine. These figures suggest a relatively quick onset of appendicitis following the initiation of Clozapine treatment, as compared to other APs.

The results of the meta-analysis further substantiated these findings. A significantly higher incidence of appendicitis was observed in the Clozapine group (OR: 45.76, 95% CI 8.03 to 260.75; P<0.0001), despite the considerable heterogeneity across the studies (I2=81%). The reasons for this increased risk of appendicitis with Clozapine remain to be clarified[7]. It may be related to the unique pharmacological properties of Clozapine, which could potentially impact gut motility or the immune response. Further research is needed to elucidate the underlying mechanisms and to develop strategies for mitigating this risk.

Conclusions

The findings of this meta-analysis highlight the importance of monitoring for symptoms of appendicitis in patients treated with Clozapine. Clinicians should be aware of this potential risk and consider it in their decision-making when prescribing antipsychotic treatments.

Conflict of interest

No

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