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META-ANALYSIS

Effect of DOPA decarboxylase inhibitor supplements on the incidence of urinary tract infections in Parkinson's disease patients: A systematic review and meta-analysis of randomized controlled trials

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Summary

Objectives: *Parkinson's disease is the most common neurodegenerative disease. Combining levodopa with other drugs, including decarboxylase inhibitors (DCI) is its most effective treatment. Urinary tract infection (UTI) is the most common cause of hospitalization in Parkinson's patients, making it crucial to find an appropriate treatment to reduce the incidence of this complication. This study aimed to investigate UTIs in Parkinson's patients using levodopa with DCI supplements.*

Methods: *In this systematic review and meta-analysis, databases such as PubMed, Scopus, Embase, Cochrane, and Web of Science were searched up to March 2024. Only randomized controlled trials involving Parkinson's patients were included in the present study. Parkinson's patients who used levodopa along with carbidopa or benserazide were considered the intervention group, while those who used levodopa with another drug were considered the control group.*

Results: *Nine interventional studies were ultimately analyzed. The relative risk (RR) of UTI in patients taking DCI was 26% lower than those who did not (RR Treatment/Control = 0.74, 95% CI: 0.58-0.95, p = 0.019). Furthermore, observations at different times of follow-up showed that at 13-24 weeks and at > 24 weeks of treatment with DCI, there was a reduction in the incidence of UTI (RR = 0.68, 95% CI: 0.46-1.01 and RR = 0.77, 95% CI: 0.58-1.0, respectively). On the contrary, there was an increase of the risk of UTI in the first 12 weeks of treatment with DCI (RR = 1.11, 95% CI: 0.37-3.33).*

Conclusions: *The results of this study indicated that using DCI drugs is associated with a reduced relative risk of developing UTIs. The beneficial effect of the drug showed after 12 weeks of treatment after an initial negative effect on the risk of UTI.*

KEY WORDS: *Parkinson's disease; Urinary tract infections; Carbidopa; Beneserazide; Dopa-decarboxylase Inhibitors; Systematic review; Meta-analysis.*

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INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative diseases, primarily caused by the degeneration of dopamine-producing neurons and α-synuclein accumulation in the substantia nigra and the formation of Lewy bodies. However, various mechanisms and pathway dysfunctions contribute to Parkinson's disease pathogenesis, including oxidative stress, malfunctioning mitochondria, cellular calcium imbalance, neuroinflammation, and other neurotransmitter system abnormalities (1, 2). The main symptoms of this disease include bradykinesia, rigidity, tremors, and postural instability (3). The risk of PD increases almost exponentially with age, with most patients being over 65 years old. Globally, the incidence and prevalence of this disease from 1990 to 2019 have been reported to be 13.43 and 106.28 per 100.000 population, respectively, with a rising global trend in the burden of PD (4).

Since there is currently no definitive cure for PD, symptom control – primarily through dopamine agonists and dopamine replacement therapy – remains the only treatment approach (5). Levodopa is one of the most effective drugs, having been used in PD treatment for over five decades (6). The metabolism of this drug occurs through four pathways: decarboxylation, O-methylation, transamination, and oxidation (7). Seventy percent of oral levodopa is metabolized by the enzyme AAAD (aromatic amino-acid decarboxylase) in the gut and liver (8). To increase the drug's half-life and concentration levels, DOPA *decarboxylase inhibitors* (DCI) such as carbidopa and benserazide are prescribed alongside levodopa (9). The main side effects of PD medications include gastrointestinal issues like nausea and psychiatric disorders such as psychosis and dyskinesia (10). A recent retrospective study by *Gremke et al.* indicated that the incidence of *urinary tract infection* (UTI) during one year of treatment with DCI drugs exceeds ten percent (11). *Urinary tract infection* (UTI) is a common factor in worsening the neurological status of patients with PD. UTI can be one of the leading causes of delirium, decreased functional-

ity, falls, and hospitalizations in these patients (12). Various clinical features of PD, including autonomic dysfunction, urodynamic changes, weakness, cognitive impairment, and the need for bladder catheterization, contribute to the increased risk of UTI (13). Moreover, untreated UTI can lead to urosepsis, a major complication in PD. The use of clean methods for catheterization when requested, antibiotics, and supplements are among the preventive strategies for UTI in PD patients (13). Various studies have reported UTI as a side effect of DCI drugs in Parkinson's patients (14-16). However, given that this significant complication has not been addressed explicitly in different studies, we aimed to conduct a systematic review and meta-analysis to investigate and compare the incidence of UTI due to DCI drugs with other Parkinson's medications.

Materials and methods

Research design

This systematic review and meta-analysis were registered with PROSPERO (registration number: CRD42024560930) and were done according the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) guidelines (17). Additionally, this study was reported in compliance with the AMSTAR (*A Measurement Tool to Assess Systematic Reviews*) methodological quality guidelines.

Research question

Does the incidence of UTI in patients treatment with DCI drugs differ compared to patients on other Parkinson's medications?

Research criteria and study selection

Two researchers independently imported the search results from each database into EndNote software. Using EndNote, duplicates were identified and removed. Subsequently, two researchers screened all remaining articles to identify eligible studies. A third researcher reviewed and resolved any controversies between the two researchers.

This study's inclusion criteria were *randomized clinical trials* (RCTs) published as full articles. Exclusion criteria included reviews, book chapters, conference abstracts, in vivo and in vitro studies, cross-sectional, case-control, and cohort studies. Additionally, studies with a lack of full text and unclear data, including patients with prostate carcinoma or uncontrolled diabetes, patients with other urinary problems, or studies with small sample size ($n < 20$), were excluded. The *relative risk* (RR) was calculated as the effect size based on the reported incidence of UTI in the intervention and control groups.

The intervention group comprised PD patients who received DCI drugs (carbidopa or benserazide) alongside levodopa. The control group included PD patients who took levodopa with other medications (e.g., *Rotigotine*, *Safinamide*, or *Entacapone*). We labeled them as "*Other*" to indicate the use of drugs other than the intervention drugs.

Search strategy - Data sources

We researched the *PubMed/Medline*, *Scopus*, *Embase*, *Cochrane Library*, and Web of Science databases up to March 2024. Gray literature was also reviewed to identify additional relevant studies. The search was performed without any time or language restrictions. The MeSH (*Medical Subject Heading*) and non-MeSH keywords used included: "*Parkinson's Disease, Parkinson, Parkinsonism, Carbidopa, Benserazide, Aromatic Amino Acid Decarboxylase Inhibitors, DOPA decarboxylase inhibitor, DCI, Urinary Tract Infections, Cystitis, Pyelonephritis, lower urinary tract symptoms, urinary*, and *urosepsis*". A multi-stage process was employed to determine the search keywords and design the search syntax, utilizing common free-text keywords and MeSH terms.

Data extraction

The outcome was the incidence of UTI complications in the intervention and control groups. Data extracted from each study included the first author's name, publication date, start date of data collection, intervention or control designation, form of drug administration, collaborating countries in data collection, sample size, and incidence of UTI in both groups.

Quality Assessment (Risk of Bias assessment)

A systematic assessment of bias in the included RCTs was conducted using the Cochrane RoB 2.0 tool (introduced in 2016 and last revised on August 22, 2019) to assess the risk of bias in randomized trials (18). The following domains were used to evaluate each study: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Studies were categorized as low risk of bias, high risk of bias, or with some concerns. Two researchers independently performed screening, study selection, validation, data extraction, and methodological quality assessment, with any disagreements resolved by a third reviewer.

Publication Bias

Publication bias was assessed using funnel plots and Eggar's weighted regression (19). A p-value greater than 0.05 indicated no publication bias.

Subgroup and sensitivity analysis

Sensitivity analysis was conducted using a leave-one-out approach to assess the impact of individual studies on the overall effect size. Subgroup analysis was performed based on variables such as follow-up duration and type of treatment.

Statistical analyses

Data were entered into a statistical program and analyzed using STATA 17.0 (*Stata Corporation, College Station, TX*). A random effects model was used to account for heterogeneity between studies. Heterogeneity was assessed using Cochran's test and the Higgins I^2 test, and the differences between studies by the researchers were evaluated using qualitative evaluation. Forest plots were used to display the effect size of each study and pooled estimates. A p-value of less than 0.05 was considered statistically significant.

Results

Study selection and characteristics

After searching all international databases, 1407 articles

were found. After removing duplicate articles, 1328 were screened for title and abstract review. Following the screening phase, 150 articles were selected for the next phase, where full-text articles were assessed, and nine articles were included in the final analysis (20-28). Additionally, the references of the included articles were examined to identify and include related studies. The study selection process is illustrated in Figure 1.
The included studies were up to March 2024. Nine studies comprising 18 records within the time frame were eligible, and they specifically addressed UTI as a side effect of DCI use in Parkinson's disease patients. Descriptive data of these studies are presented in Table 1 (20-28).

Risk of Bias Assessment
Figure 2 shows the quality assessment results. Based on the quality evaluation checklist used, 7 articles were of good quality (low risk), 2 articles had some concerns, and none were of poor quality (high risk). It is noteworthy that all the reviewed studies were randomized trials. In 7 studies, blindness was double-masked, and five studies were phase 3 trials.

Heterogeneity
The results of the Chi-squared test and the I2 index indicated no heterogeneity regarding side effects among the studies (I^2 = 7.52%, Q-value = 14.07, p = 0.661). However, due to the inherent qualitative differences between the studies, a random effects model was used for the analyses. The results of the fixed effects model were also reported.

The relative risk of UTI side effects
Based on the random effects model, the *relative risk* (RR) of UTI in patients taking DCI (carbidopa) was 26% lower than in patients not taking it, and this reduction was statistically significant (RR Treatment/Control = 0.74, 95% CI: 0.58-0.95, p = 0.019) (Figure 3). Similarly, based on the fixed effects model, the results were consistent, showing a 25% lower relative risk of UTI in patients taking DCI (carbidopa) compared to those not taking it (RR Treatment/Control = 0.75, 95% CI: 0.60-0.94, p = 0.012) (Appendix 1).

Subgroup analysis
The subgroup analysis results based on the type of intervention (DCI group vs. Other groups) were consistent. In the DCI group, the relative risk of UTI was 26% lower (RR = 0.74, 95% CI: 0.54-1.03), and in the other group, it was 24% lower (RR = 0.76, 95% CI: 0.56-1.03) (Appendix 2). However, the results varied based on the follow-up duration. For follow-ups from 13 to 24 weeks and over 24 weeks, the relative risk was 32% lower (RR = 0.68, 95% CI: 0.46-1.01) and 23% lower (RR = 0.77, 95% CI: 0.58-1.02), respectively. For follow-ups up to 12 weeks, the relative risk was 11% higher (RR = 1.11, 95% CI: 0.37-3.33) (Appendix 3).

Sensitivity analysis
The sensitivity analysis showed that the effect size did not change significantly after excluding any individual study, and the results remained statistically significant (Appendix 4).

FIgure 1.
Preferred Reporting Items for a Systematic Review and Meta-Analysis (PRISMA) 2020 flow diagram for new systematic reviews, including database, registers, and other source searches.

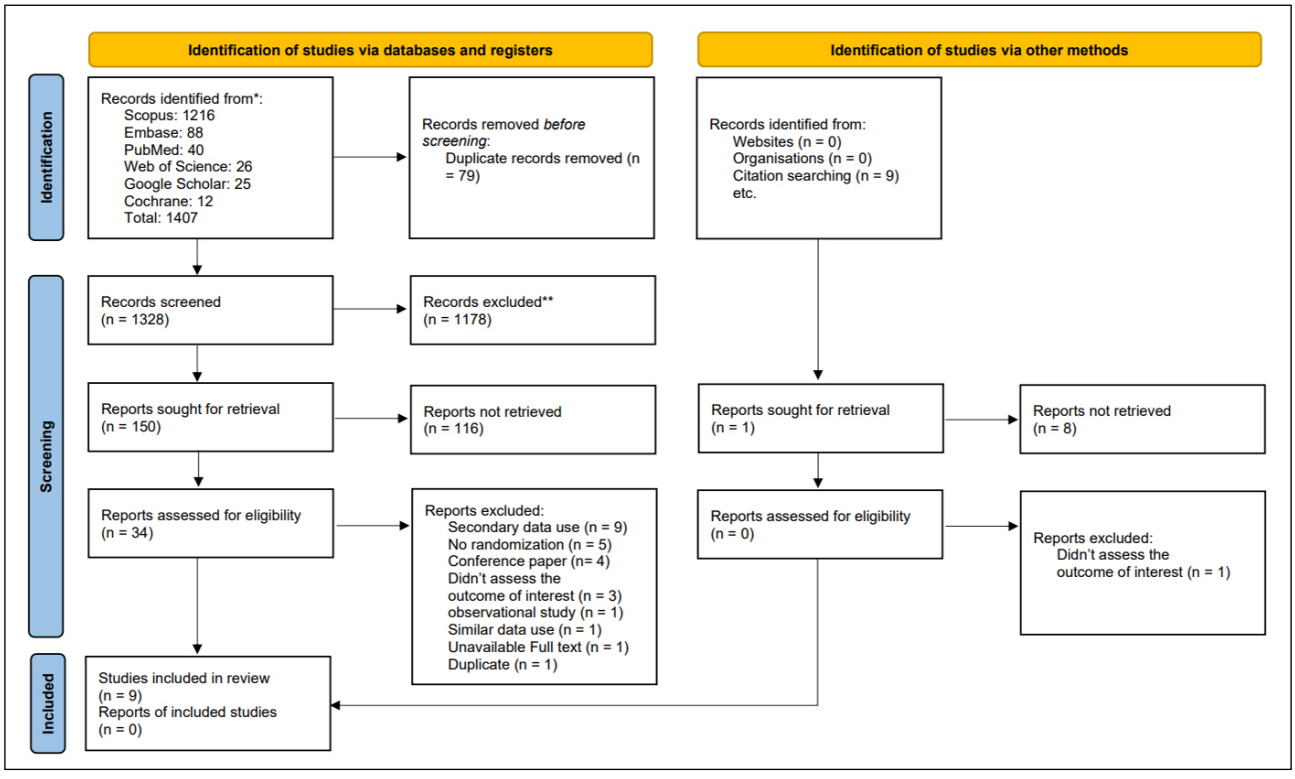


Table 1.
Demographic characteristics of the included studies in the systematic review.

D	Author	Year of publication	Year of starting data collection	Intervention or control	Consumption form	Country	Sample size	Follow-up time
1	Chung, et al (20)	2022	-	Levadopa+Carbidopa	Intestinal gel	9 sites in Spain, 8 sites in the United States, 7 sites in Italy, 4 sites in Australia, 3 sites in Canada, 3 sites in the Republic of Korea, 2 sites in Greece, 1 site in Germany, 1 site in Sweden	87	26 weeks
1	Chung, et al (20)	2022	-	Other	Tablet or capsule	9 sites in Spain, 8 sites in the United States, 7 sites in Italy, 4 sites in Australia, 3 sites in Canada, 3 sites in the Republic of Korea, 2 sites in Greece, 1 site in Germany, 1 site in Sweden	87	26 weeks
2	Fahn, et al (21)	2004	1998	Levadopa+Carbidopa	Tablet	33 sites in the United States and 5 sites in Canada	361	40 weeks
2	Fahn, et al (21)	2004	1998	Other	Tablet	33 sites in the United States and 5 sites in Canada	361	40 weeks
3	Freire-Alvarez, et al (22)	2021	-	Levadopa+Carbidopa	Intestinal gel	9 sites in Spain, 5 sites in Italy, 4 sites in Slovakia, 3 sites in Hungary, 3 sites in Greece, 2 sites in the United States, 2 sites in Finland	61	12 weeks
3	Freire-Alvarez, et al (22)	2021	-	Other	Tablet or capsule	9 sites in Spain, 5 sites in Italy, 4 sites in Slovakia, 3 sites in Hungary, 3 sites in Greece, 2 sites in the United States, 2 sites in Finland	61	12 weeks
4	Hauser, et al (23)	2013	2009	Levadopa+Carbidopa	Tablet (extended-release)	35 sites in the United States, 7 sites in Ukraine, 7 sites in Poland, 6 sites in Spain, 6 sites in Germany, 5 sites in France, 4 sites in Romania, 3 sites in Canada	393	22 weeks
4	Hauser, et al (23)	2013	2009	Levadopa+Carbidopa	Tablet (immediate release)	35 sites in the United States, 7 sites in Ukraine, 7 sites in Poland, 6 sites in Spain, 6 sites in Germany, 5 sites in France, 4 sites in Romania, 3 sites in Canada	393	22 weeks
5	Hauser, et al (24)	2023	2018	Levadopa+Carbidopa	Tablet (extended-release)	56 sites in the United States, 15 sites in Spain, 8 sites in Germany, 8 sites in Italy, 7 sites in Poland, 7 sites In Poland, 6 sites in Czechia, 6 sites in Germany, 5 sites in France, 3 sites in the United Kingdom	506	20 weeks
5	Hauser, et al (24)	2023	2018	Levadopa+Carbidopa	Tablet (immediate release)	56 sites in the United States, 15 sites in Spain, 8 sites in Germany, 8 sites in Italy, 7 sites in Poland, 7 sites In Poland, 6 sites in Czechia, 6 sites in Germany, 5 sites in France, 3 sites in the United Kingdom	506	20 weeks
6	Olanow, et al (25)	2004	-	Levadopa+Carbidopa	Tablet	multicenter	750	26 weeks
6	Olanow, et al (25)	2004	-	Other	Tablet	multicenter	750	26 weeks
7	Rascol, et al (26)	2016	2012	Levadopa+Carbidopa	Tablet	10 sites in the United States, 3 sites in Poland, 2 sites in Slovakia, 1 site in Germany	68	12 weeks
7	Rascol, et al (26)	2016	2012	Other	Tablet	10 sites in the United States, 3 sites in Poland, 2 sites in Slovakia, 1 site in Germany	68	12 weeks
8	Schapira, et al (27)	2017	2009	Levadopa+Carbidopa and/or Levadopa+ Benserazide	Tablet / Tablet	28 sites in the United States, 12 sites in Germany, 12 sites in Hungary, 8 sites in India, 6 sites in Israel, 6 sites in Slovakia, 6 sites in Canada, 6 sites in Belgium, 5 sites in Thailand, 5 sites in the United Kingdome, 5 sites in France, 4 sites in Spain, 3 sites in the Republic of Korea, 3 sites in Taiwan, 3 sites in New Zealand, 2 sites in Australia, 2 sites in Austria, 2 sites in Malaysia, 2 sites in Switzerland, 1 site in Estonia, 1 site in the Netherlands	549	24 weeks
8	Schapira, et al (27)	2017	2009	Other	Tablet	28 sites in the United States, 12 sites in Germany, 12 sites in Hungary, 8 sites in India, 6 sites in Israel, 6 sites in Slovakia, 6 sites in Canada, 6 sites in Belgium, 5 sites in Thailand, 5 sites in the United Kingdome, 5 sites in France, 4 sites in Spain, 3 sites in the Republic of Korea, 3 sites in Taiwan, 3 sites in New Zealand, 2 sites in Australia, 2 sites in Austria, 2 sites in Malaysia, 2 sites in Switzerland, 1 site in Estonia, 1 site in the Netherlands	549	24 weeks
9	Stocchi, et al (28)	2010	-	Levadopa+Carbidopa	Tablet	31 sites in the United States, 6 sites in Italy, 5 sites in Germany, 5 sites in Finland, 4 sites in Sweden, 4 sites in France, 4 sites in the United Kingdom, 4 sites in Canada, 2 sites in Greece, 2 sites in Belgium, 2 sites in Spain, 2 sites in Switzerland, 1 site in Australia, 1 site in Turkey	744	134 weeks
9	Stocchi, et al (28)	2010	-	Other	Tablet	31 sites in the United States, 6 sites in Italy, 5 sites in Germany, 5 sites in Finland, 4 sites in Sweden, 4 sites in France, 4 sites in the United Kingdom, 4 sites in Canada, 2 sites in Greece, 2 sites in the Belgium, 2 sites in the Spain, 2 sites in the Switzerland, 1 site in the Australia, 1 site in the Turkey	744	134 weeks

Figure 2.
Risk of Bias Assessment: (A) Risk of bias summary of all included randomized clinical trials (RCTs); (B) Detailed risk of bias.

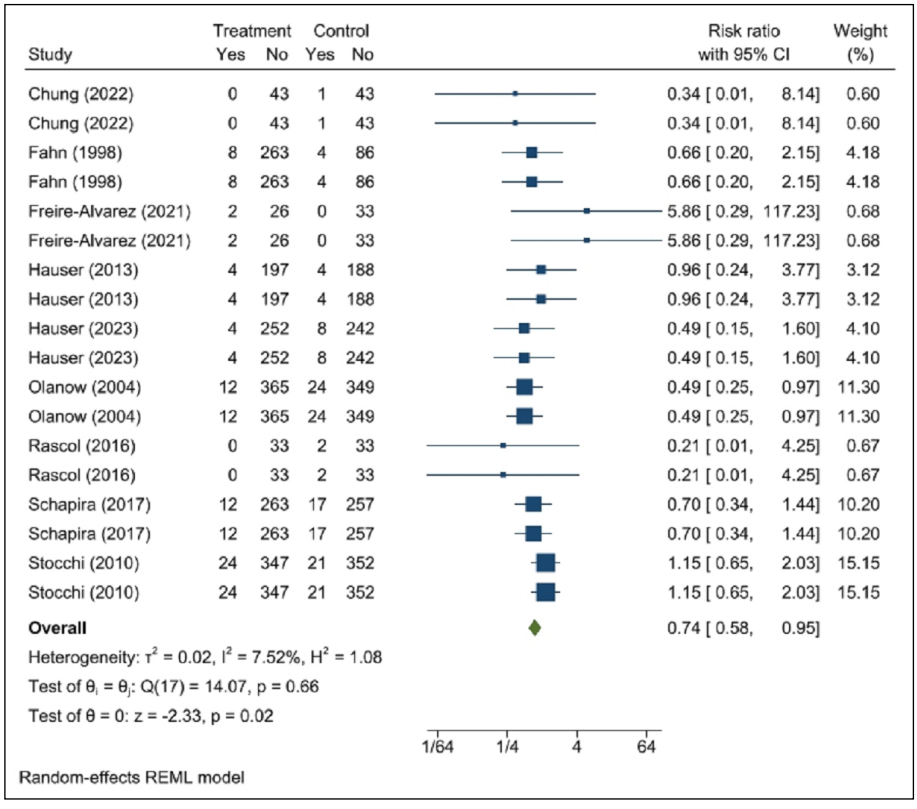
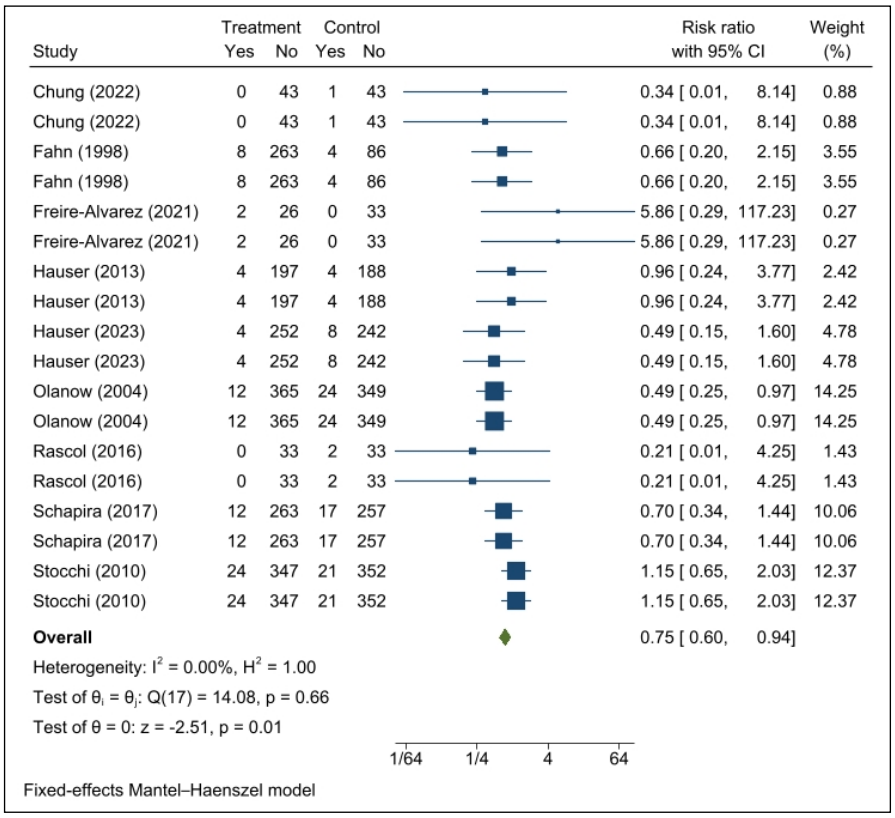
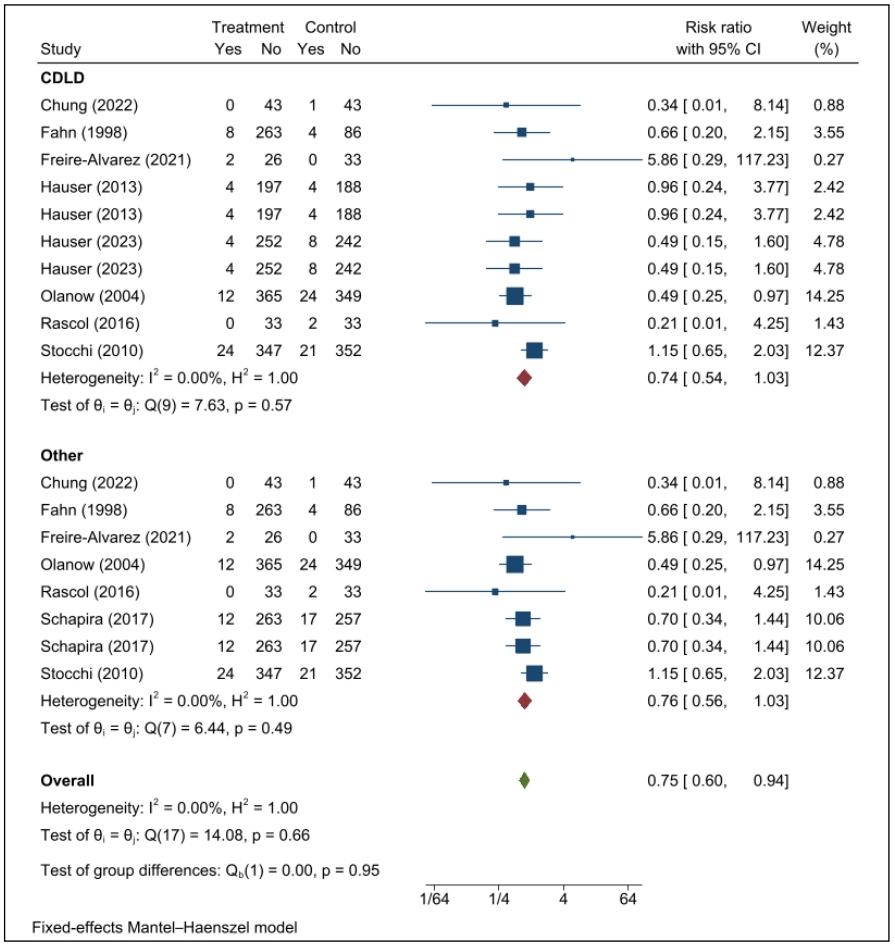


Figure 3.
Meta-analysis of the relative risk of urinary tract infection complications in Parkinson's disease patients;
CI: Confidence interval.

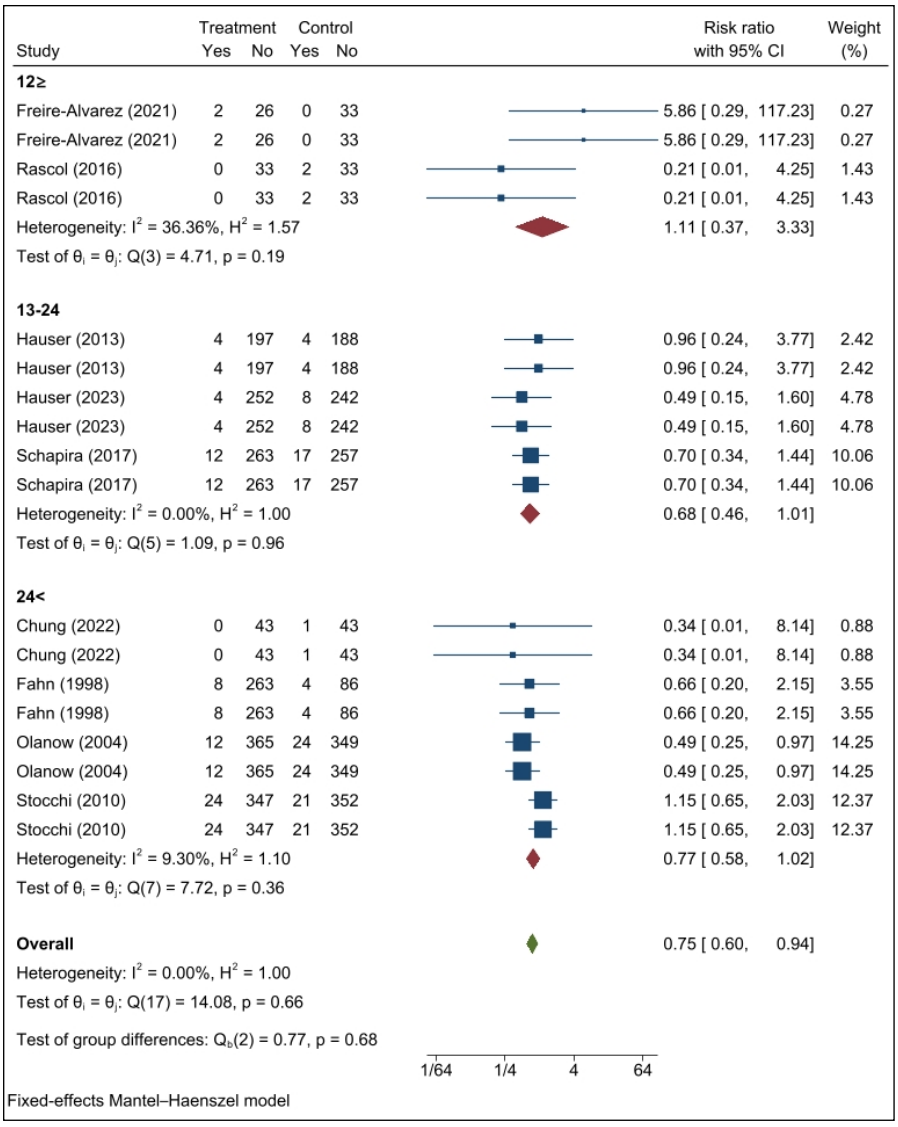
Appendix



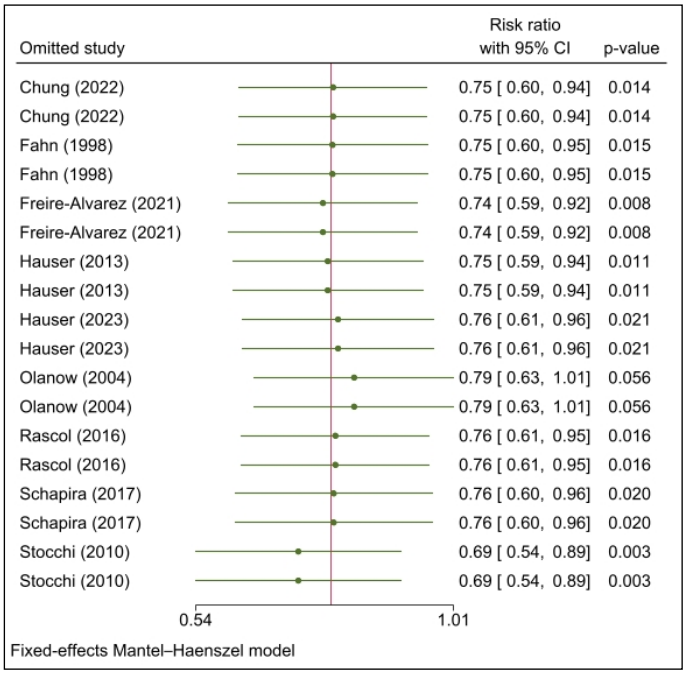
Appendix 1.
Meta-analysis of the relative risk of urinary tract infection in Parkinson's disease patients using decarboxylase inhibitors (Carbidopa); CI: Confidence interval.



Appendix 2.
Subgroup meta-analysis of the relative risk of urinary tract infection in Parkinson's disease patients using decarboxylase inhibitors (Carbidopa) based on type of intervention; CI: Confidence interval.



Appendix 3.
Subgroup meta-analysis of the relative risk of urinary tract infection in Parkinson's disease patients using decarboxylase inhibitors (Carbidopa) based on treatment duration; CI: Confidence interval.



Appendix 4.
Sensitivity analysis results of the studies included in the meta-analysis with the exclusion of one study; CI: Confidence interval.

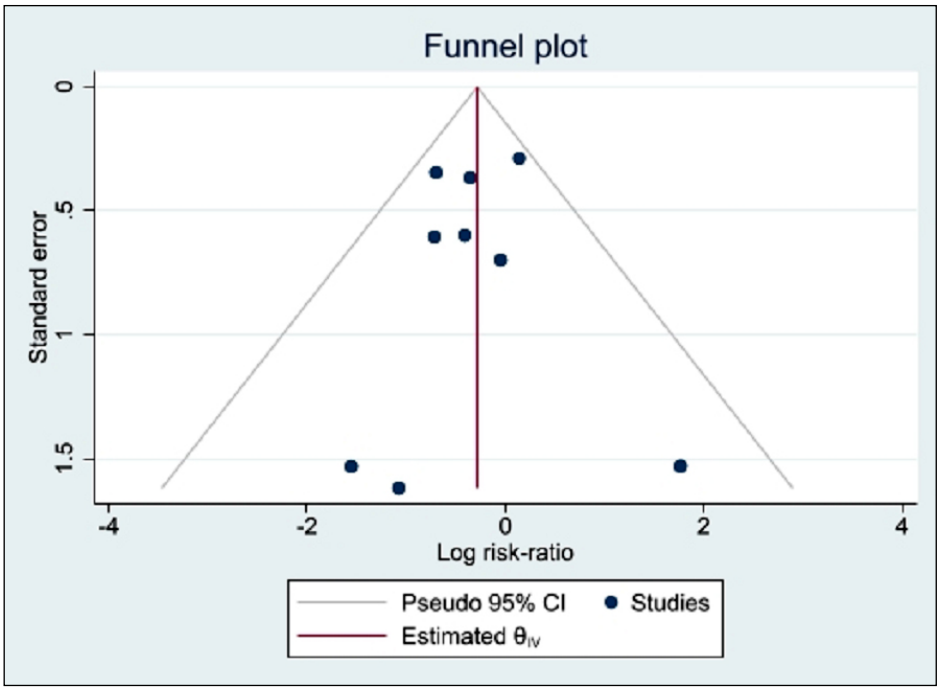


FIgure 4.
Funnel plot for the studies assessing urinary tract infection complication of carbidopa; CI: Confidence interval.

Publication bias

Finally, a funnel plot was created to assess publication bias for the UTI complication of DCI. Egger's test results did not confirm the presence of publication bias for UTI complications (bias: -0.19, SE = 0.48, p = 0.693) (Figure 4).

Discussion

Our study results indicated that the use of DCI drugs in PD patients is a protective factor against UTI. Furthermore, the duration of treatment is significantly essential, because DCI use for less than 12 weeks is associated with an increased relative risk of developing UTI in PD patients whereas long-term use has shown a protective effect against UTI.

Findings from a prospective cross-sectional study by Chaudhuri et al. indicated that the occurrence of UTI in PD patients using carbidopa gel is 3% (20). Additionally, a cross-sectional survey by *Fernandez et al.* reported a UTI incidence of 11.4% due to Levodopa-Carbidopa Intestinal Gel use in PD patients (21). Another study by *Fernandez et al.* reported that the occurrence of UTI in carbidopa users was 7.8% (29). Different results regarding UTI incidence have been obtained in randomized and controlled studies. A 134-week prospective double-blind trial by *Stocchi et al.* (28) reported that UTI occurrence in patients using levodopa and carbidopa was 1% higher than in the control group. Conversely, in a prospective, double-anonymized, placebo-controlled trial, *Olanow et al.* (25) reported that UTI occurrence was half as frequent in the levodopa and carbidopa group compared to the control group. Both studies compared entacapone in PD patients using levodopa and carbidopa, but differences in sample size, length of follow-up, and the duration of Parkinson's disease may explain the divergent results.

Our study demonstrated that although levodopa with DCI was associated with a reduced incidence of UTI, it did not significantly differ from other drugs used with levodopa in reducing UTI occurrence. Mechanistically, carbidopa increases the conversion of levodopa to dopamine in the *central nervous system* (CNS), reducing peripheral side effects during PD treatment (30). Although the effects of levodopa on urinary infections are not well-defined, some previous animal and human studies have shown that acute activation of D2 receptors worsens bladder function (31, 32). Conversely, a survey of Parkinsonian monkeys demonstrated that tonic activation of D1 receptors prevents bladder voiding (33). Residual urine can be associated with urinary infections (34, 35). Therefore, by preventing the peripheral conversion of levodopa, carbidopa causes a greater amount of levodopa to reach the brain, and as a result, the dose of levodopa consumed is reduced and its side effects are avoided (36).

Another mechanism suggests that inflammatory genes are expressed in PD, leading to immune cell infiltration into the brain and increased activated/memory T cells (37). In a laboratory study by *Zhu et al.* (30), carbidopa was shown to inhibit T cell responses and autoimmunity in two animal models of Parkinson's, potentially increasing infection risk. They concluded that this indicates the immunosuppressive activity of this DCI. Further studies are needed to better understand the relationship between carbidopa and urinary tract infection.

A cross-sectional study by *Gremke et al.* (11) used another DCI, benserazide, instead of carbidopa. The study (11) did not show a significant relationship between the two DCI drugs, but benserazide had better protective effects compared to carbidopa. Due to a lack of studies for comparison, we did not focus on benserazide, and most of our results pertain to carbidopa. Nonetheless, we recommend future studies to investigate urinary complications, particularly UTI, in PD patients using benserazide.

A phase 3 interventional study by *Freire-Alvarez et al.* (22) reported that UTI occurrence in PD patients was 7%

higher in the group treated with carbidopa-levodopa for 12 weeks compared to the control group. *Fernandez et al.* also noted an increasing trend in UTI occurrence up to week 13, followed by a decreasing trend until week 54 (29). Our study also found that treatment with levodopa and DCI (carbidopa) increased the risk of UTI within 12 weeks, while the risk decreased in the 13-24 week and ¬> 24-week periods. An open-label phase 3b study by Standaert et al., examining non-motor symptoms in PD patients using carbidopa gel over 60 weeks, reported a significant reduction in urinary symptoms up to week 12, but this reduction was not sustained. They used the *Non-Motor Symptoms Scale* (NMSS) scoring system, which only assesses urgency, frequency, and nocturia, whereas our study focused solely on UTI occurrence.

UTI is a significant cause of hospitalization and mortality in PD patients. Management strategies for UTI in PD patients mainly involve preventive measures, including vitamin supplements, estrogen supplements, prophylactic antibiotics, and hygiene practices in catheterization cases (38). Given our study's finding of a 32% relative risk reduction in UTI occurrence in PD patients using DCI (carbidopa) during weeks 13-24, we recommend future studies focus on DCI drugs in patients with Parkinson's disease who suffer from urinary symptoms, especially UTI, in this treatment period so that they can benefit from the maximum protective effects of DCI drugs, especially carbidopa. Further research is necessary to optimize PD treatment, considering the associated urological complications and infections.

Limitations and Strengths: This study is the first systematic review and meta-analysis examining UTI occurrence in PD patients using DCI drugs. However, it has some limitations. Firstly, many studies were excluded due to the need of randomization and control groups. Secondly, control groups in the studies were highly heterogeneous, potentially affecting the comparison of DCI drug effects. Thirdly, not all studies provided detailed information on specific variables, so the intended outcome in this study was not reported in terms of the dosage of the drugs used, and it was impossible to estimate the relative risk based on the dosage.

Conclusions

Our study showed that DCI use, along with levodopa in PD patients, is associated with a reduced relative risk of UTI occurrence. However, this reduction was not specific to DCI drugs, as other medications used with levodopa also reduced UTI occurrence. Subgroup analysis indicated that the relative risk of UTI significantly decreased starting from the 13 to 24-week treatment period with DCI. These findings can help researchers better manage the primary cause of hospitalization and mortality in PD patients that is UTI. Additionally, researchers can use these findings to design future studies more effectively, focusing on the type of drug and treatment duration with DCI drugs, especially carbidopa.

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