Systematic Review / Meta-analysis

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# Risk of Parkinson's disease among users of alpha-adrenergic receptor antagonists: a systematic review and meta-analysis

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**Background:** Recent studies have tried to establish an association between the use of alpha-1-adrenergic receptor antagonists (A1ARAs) used in benign prostatic hyperplasia (BPH) and the risk of PD. The objective of the study is to compare the risk of Parkinson's disease (PD) between terazosin/alfuzosin/doxazosin (TZ/AZ/DZ) users and tamsulosin users.

**Methods:** PubMed, Google Scholar, and Embase were systematically searched from inception to April 2023. Observational studies comparing the risk of PD among patients using different types of A1ARAs were included in the meta-analysis. The primary outcome was the hazard ratio (HR) with a 95% CI for the risk of occurrence of PD among A1ARAs users of two different classes.

**Results:** This study was based on a total of 678 433 BPH patients, out of which 287 080 patients belonged to the TZ/AZ/DZ cohort and 391 353 patients belonged to the tamsulosin cohort. The pooled incidence of PD was higher in tamsulosin users (1.28%, 95% CI: 1.04–1.55%) than in TZ/AZ/DZ drug users (1.11%, 95% CI: 0.83–1.42%). The risk of occurrence of PD was significantly lower in patients taking TZ/AZ/DZ than tamsulosin ($n$ = 610,363, HR = 0.82, 95% CI = 0.71–0.94, $P$ = 0.01; $I^2$ = 87.4%).

**Conclusion:** This meta-analysis demonstrated that patients with BPH who take TZ/AZ/DZ have a lower risk for developing PD than those who take tamsulosin.

**Keywords:** alpha antagonists, alfuzosin, benign prostatic hyperplasia, doxazosin, Parkinson's disease, tamsulosin, Terazosin

## Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, mostly occurring in the elderly population[1,2]. It is mainly characterized by a classic triad of bradykinesia, tremors, and rigidity. PD is the result of a lack of dopamine production owing to the early death of dopaminergic neurons in the substantia nigra pars compacta (SNPC) of the human brain[2,3]. Apart from motor symptoms, patients with PD can have cognitive issues such as depression and dementia[1,3,4]. Likewise, autonomic features such as orthostatic hypotension, erectile dysfunction, and gastrointestinal disturbances are fairly common as well.

### HIGHLIGHTS

- The pooled incidence of Parkinson's disease (PD) was higher in tamsulosin (1.2%) users than in terazosin, doxazosin, alfuzosin (TZ/DZ/AZ) (1.11%) users, numerically.
- The risk of occurrence of PD was significantly lower in patients taking TZ/DZ/AZ than tamsulosin.
- There is a need of large-scale clinical trials which can determine the efficacy of alpha antagonists on PD.

The number of cases of PD is increasing worldwide, and the frequency of PD increases sharply with age. PD is rare before the age of fifty, and its incidence increases greatly after the age of sixty. The incidence of PD among the age group of 50–59 years is 107 per 100 000 population, and it rose to 428 per 100 000 population in the age group of 60–69 years[5]. The incidence of PD is between 10 and 50 per 100 000 person-years, while the prevalence of PD is 100–300 per 10 000 people[5,6]. PD is considered to be caused by the cumulative effects of various factors, mainly genetic and environmental factors. Most of the PD cases are sporadic, and genetic factors only contribute to a few of the cases[6,7]. Various environmental factors, either protective or causative, have been considered in the aetiology of PD. Studies have suggested that smoking cigarettes, drinking coffee or tea, and exercising have protective effects[6–9]. However, dairy products and exposure to pesticides have been found to increase the risk of the disease[6–8].

Till now, the mainstay of the treatment of PD has been symptomatic management with medications, which either

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increase dopamine concentrations or directly stimulate dopamine receptors in the SNPC. Disease-modifying and disease-protective drugs have not been used clinically in the treatment of PD yet. A revolution in the preventive and curative pharmacological treatment of PD needs a deeper understanding of the disease pathogenesis[2]. Although multiple studies have been conducted to identify the exact mechanism of death of dopaminergic neurons in PD, the underlying pathogenesis is still obscure. Few studies have postulated a theory of impaired energy metabolism in the SNPC neurons arising due to mitochondrial dysfunction and oxidative stress[9,10]. The dysfunction in mitochondria encompasses biochemical abnormalities in complex I, which is mainly responsible for electron transport during oxidative phosphorylation. The resulting disruption in electron flow subsequently decreases ATP production and generates reactive oxygen species that increase oxidative stress in the neurons of SNPC[11]. The SNPC neurons are highly vulnerable to these insults owing to their huge metabolic burden arising from highly branched and unmyelinated axons, multiple neurotransmitter release sites, and their rhythmic firing patterns[12]. The core reason behind the deranged mitochondrial function is not completely understood; however, the advancing age has been hypothesized to play a major role in reduced mitochondrial biogenesis and increased stress-induced apoptosis. Hence, all of these factors suggest impaired brain metabolism as the common pathology of PD[13–15]. Hence, enhancing energy metabolism and increasing ATP production in the SNPC of the brain might be an effective preventive strategy for PD.

Terazosin, doxazosin, alfuzosin (TZ/DZ/AZ) and tamsulosin are the alpha-1-adrenergic receptor antagonist (A1ARA) drugs widely used in the symptomatic management of benign prostatic hyperplasia (BPH). TZ, DZ, and AZ are non-selective A1ARAs, whereas tamsulosin is a selective A1ARA with specific actions at α1A and α1D[16]. Cai and colleagues hypothesized that drugs like TZ with an independent phosphoglycerate kinase 1 (PGK1) enzyme-activating property can enhance glycolysis to increase ATP production in dopaminergic neurons. The increase in ATP production can counter the ineffective energy metabolism of SNPC neurons, which lies at the core of the pathogenesis of PD. Terazosin has been shown to have neuroprotective properties in cellular and animal models in a number of studies[3,17]. Unlike TZ/AZ/DZ, tamsulosin lacks the PKG1 activating property. A number of recent studies have compared the neuroprotective effects of TZ/DZ/AZ against tamsulosin in BPH patients. Hence, we conducted a meta-analysis to compare the risk of occurrence of PD between patients taking TZ/DZ/AZ and tamsulosin.

## Methods

This systematic review and meta-analysis were conducted in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), using the PRISMA flow diagram and PRISMA checklist, Supplemental Digital Content 1, http://links.lww.com/MS9/A457[18]. In accordance with the guidelines, the systematic review protocol was registered in PROSPERO. The ethical clearance was not obtained owing to the nature of the study. The AMSTAR2 checklist, Supplemental Digital Content 2, http://links.lww.com/MS9/A458 was used to assess the overall quality of the review[19]. The study was rated to be of moderate quality. The initial step in conducting the review was to formulate the research topic. The main aim of the study was to determine the risk of occurrence of PD in patients taking two different classes of A1ARAs. Next, we developed a search strategy and eligibility criteria for the selection of the studies.

### *Search strategy*

Our literature search included databases; PubMed, Google Scholar, and the Scopus, for studies published in English till April 2023. The studies of interest were identified using the following keywords: "Parkinson's disease" "Alpha antagonists" "Alpha blockers" "Benign prostatic hyperplasia" "Benign prostatic enlargement" "Alfuzosin" "Doxazosin" "Terazosin" and "Tamsulosin". We used boolean logic to conduct the database search, and boolean search operators "AND" and "OR" to link the search terms. Additionally, we combed through reference list of included studies for original articles and previous reviews were also scanned for more relevant studies. The details of the search strategy is provided in the Appendix 1 of the Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A459.

### *Study selection*

All shortlisted studies were then imported to the Mendeley library, and duplicates were removed appropriately. We also performed an additional manual check of the library to remove remaining redundant studies. The titles, keywords, and abstracts were screened, and then the full text of papers that met the inclusion criteria were obtained. Two reviewers independently screened for the articles from the databases. Any dilemma regarding the selection of the studies in the systematic review was resolved through the discussion among a group of reviewers. When two different studies with the same set of study populations were found, the study with a bigger sample size or superior quality was selected for the systematic review.

### *Eligibility criteria*

Studies were included if the full text was published in English, and if they were observational studies that compared the risk of PD among patients using different types of A1ARA. However, studies investigating drugs other than alpha-receptor antagonists, animal studies, case reports and series, reviews, letters, and editorials were excluded from the analysis. Further, the articles with insufficient information, irrelevant full texts, and those that did not meet the eligibility criteria were also excluded.

### *Data extraction and data synthesis*

Two independent reviewers carried out the data extraction process. The data extraction was performed using a standardized data extraction form in Microsoft Excel 2019 spreadsheet program. If they did not reach an agreement, a small group of reviewers discussed disagreements to reach a final consensus. The relevant data extracted from the selected studies were the first author, study title, year of publication, study design, study site, sample size of cases and control, and outcomes (incidence and risk of occurrence of PD in both groups). A systematic narrative synthesis was performed to summarize the included studies in the text and tables. The corresponding authors of the individual studies were contacted via e-mail to provide clarification if essential data were missing, not included in the publication, or

presented in an unusual manner. Supplementary material relating to the main publication was also reviewed in certain cases.

### Statistical analysis

The primary outcome of the meta-analysis was the hazard ratio (HR) with a 95% CI for the risk of occurrence of PD among A1ARA users of two different classes. The data were pooled using either a random-effects or fixed-effect model. The heterogeneity between the included studies was determined with the $I^2$ test (0–40%: not important; 30–60%: moderate heterogeneity; 50–90%: substantial heterogeneity; 75–100%: considerable heterogeneity), which quantifies the percentage of overall discrepancy due to variations in the study[20]. When $I^2$ was greater than 50%, meta-analysis was performed using DerSimonian and Laird's random-effects model[21]. To illustrate the overall weighted mean estimations with 95% CIs, forest plots with 95% CIs were generated. A sensitivity analysis was performed by omitting each individual study sequentially to check the stability and robustness of the pooled outcomes. All statistical analyses were performed with STATA version 16.0 (Stata Corp). A $p$ value less than 0.05 was regarded as significant.

### Quality assessment

The quality of studies was evaluated using the Newcastle–Ottawa Scale (https://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf). The scale was used to assess the quality of studies under three major headings: selection, comparability, and exposure. Studies that obtained a score of five or more qualified for inclusion, while those obtaining more than seven were labelled as high-quality studies. Further, the quality of each included study was independently assessed by the two reviewers.

## Results

### Study characteristics

Our literature search revealed 168 articles, out of which four articles[15,16,22,23] exploring the risk of PD in BPH patients using different A1ARAs were included in this systematic review and meta-analysis. The process of selection of the included articles is shown in Figure 1. This study was based on a total of 678 433 patients, out of which 287 080 patients belonged to the TZ/AZ/DZ cohort and 391 353 patients belonged to the tamsulosin cohort. All of the studies were retrospective in nature. The studies were conducted in Canada, USA and Denmark. The details of each four studies are given below in the Table 1.

Gros *et al.*[22] conducted a retrospective cohort study conducted in Canada among men above 66 years who were taking either TZ/AZ/DZ or tamsulosin for their urological indications. The mean age of patients in TZ/AZ/DZ and tamsulosin cohorts was 74.2 years and 74.7 years, respectively. The participants were included in the study by the date of their prescription of any of these drugs. The main outcome of the study was the incidence of PD (new occurrence) after starting the use of A1ARAs. Simmering *et al.*[15] analyzed secondary data from Danish nationwide health registries from 1996 to 2017 for men over 40 years taking A1ARAs. They studied 52,365 propensity score-matched pairs of TZ/DZ/AZ and tamsulosin users, of which the mean age was $67.9 \pm 10.4$ years. Likewise, two studies; Sasane *et al.*[23] and Simmering *et al.*[16], analyzed the secondary data from Optum Research database and Truven Health Analytics Marketscan database from the USA, respectively. These studies had an average follow-up duration of 5 years and 10 years, respectively. Sasane *et al.*[23] Enroled patients $\geq 18$ years of age taking A1ARAs for BPH and who had no evidence of PD during the baseline period. On the other hand, Simmering *et al.*[16] studied patients over 40 years old using A1ARAs for at least one year for BPH. All of the studies excluded individuals who switched from one drug category (e.g. TZ/AZ/DZ) to another (e.g. tamsulosin) during the observation period.

The quality assessment of the studies is provided in Appendix 2 of the Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A459. According to quality assessment tools, the methodological quality score ranged from 7 to 8. None of the selected studies were of low quality. All the studies were included in the systematic review and meta-analysis.

### Incidence of PD in A1ARA users

All four selected studies have measured the incidence of PD in A1ARA users. All of the studies have reported a higher incidence of PD in tamsulosin users compared to TZ/AZ/DZ users. About 1.16–1.78% of tamsulosin users and 0.83–1.52% of TZ/AZ/DZ users developed PD in the study duration. Two studies[16,23] observed a statistically significant lower incidence of PD in tamsulosin users compared to TZ/AZ/DZ drug users. The pooled incidence of PD in tamsulosin users was 1.28% (95% CI: 1.04–1.55%). The pooled incidence of PD in TZ/AZ/DZ drug users was 1.11% (95% CI: 0.83–1.42%). Hence, the pooled incidence of PD was higher in tamsulosin users than in TZ/AZ/DZ drug users numerically.

### Risk of PD in A1ARA users

Three out of four studies included in the systematic review had reported a risk of occurrence of PD in two different classes of A1ARAs. The risk of occurrence of PD was significantly lower in patients taking TZ/AZ/DZ than tamsulosin (n = 610,363, HR = 0.82, 95% CI = 0.71–0.94, $P = 0.01$). The heterogeneity given by the $I^2$ statistic was 43.39%, which falls under considerable heterogeneity. The forest plot showing the pooled estimate of hazard ratio of occurrence of PD is depicted in Figure 2.

### Sensitivity analysis

Sensitivity analysis was performed using the leave-one-out method in a total of three studies that reported on the association between the risk of occurrence of PD and drug users. None of the studies had a major influence on the pooled HR. The details of sensitivity analysis is provided in the Appendix 3 of Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A459.

## Discussion

To the best of our knowledge, this is the first meta-analysis to study the association between the risk of PD and the use of A1ARA drugs. Our study incorporated 678 433 patients, who were taking A1ARA drugs for BPH symptoms. Between the two patient groups, those under TZ/AZ/DZ drugs showed a lower incidence of PD than those who were under tamsulosin during years of follow-up. The pooled incidence in tamsulosin users and

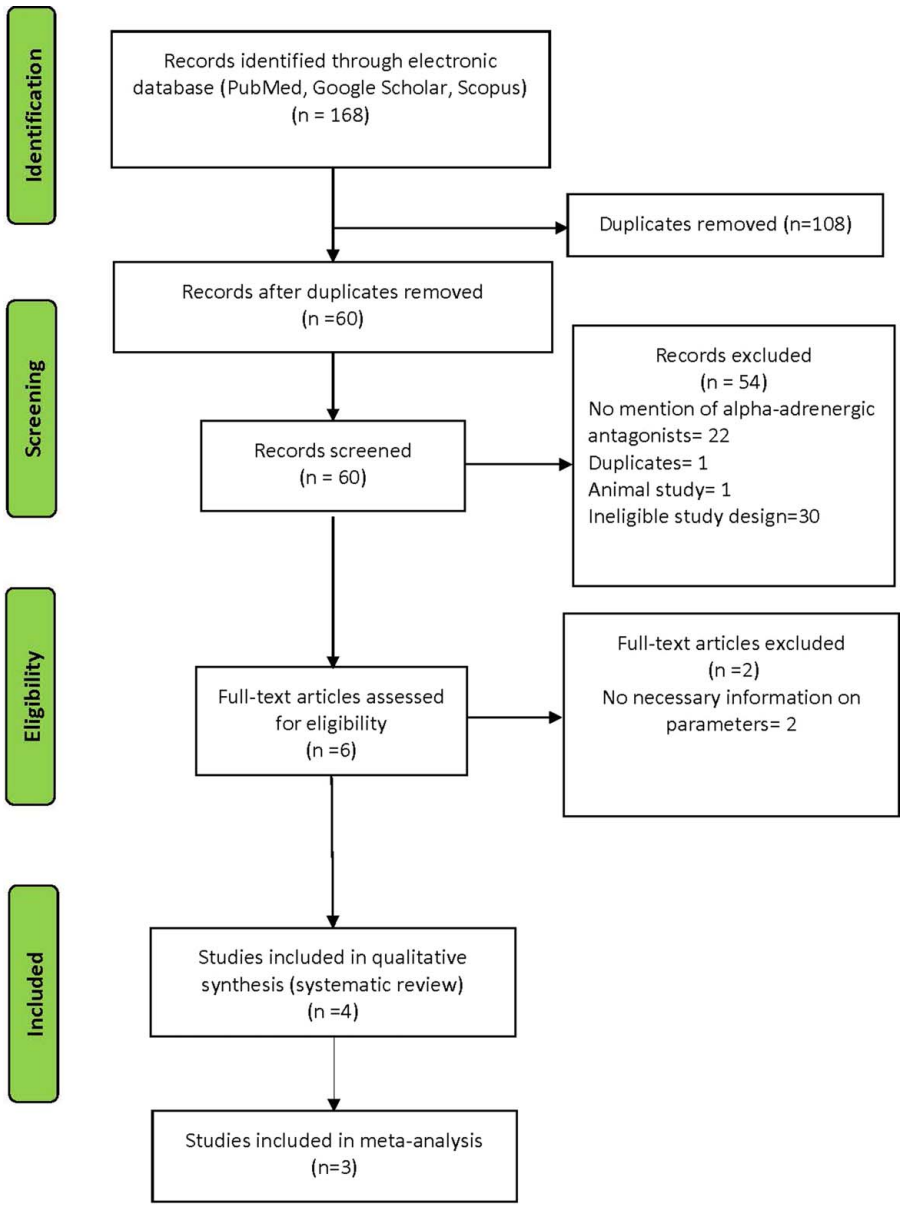


**Figure 1.** PRISMA flow diagram.

**Table 1**

**Characteristics of included studies.**

| Study | Study year | Study design | Study country | Sample size | No. zosin (TZ/AZ/DZ) drug users | No. tamsulosin drug users | Incidence of PD (T = tamsulosin) (Z = zosins) | Follow-up duration (Y = years) |
|---|---|---|---|---|---|---|---|---|
| Gros *et al.* | 2021[22] | Retrospective, Cohort | Canada | 265 745 | 92 081 | 173 664 | T = 2141 (1.23%)<br>Z = 958 (1.04%) | 3.75 Y for Z<br>4.16 Y for T |
| Simmering *et al.* | 2021[15] | Retrospective, Cohort | Denmark | 104 730 | 52 365 | 52 365 | T = 939 (1.78%)<br>Z = 798 (1.52%) | 4.99 Y for Z<br>5.35 Y for T |
| Sasane *et al.* | 2021[23] | Retrospective, Observational | USA | 68 070 | 22 690 | 45 380 | T = 693 (1.53%)<br>Z = 249 (1.10%) | 5 Y for both groups |
| Simmering *et al.* | 2022[16] | Retrospective, Cohort | USA | 239 888 | 119 944 | 119 944 | T = 1391 (1.16%)<br>Z = 991 (0.83%) | 10 Y for both groups |

PD, Parkinson's disease.

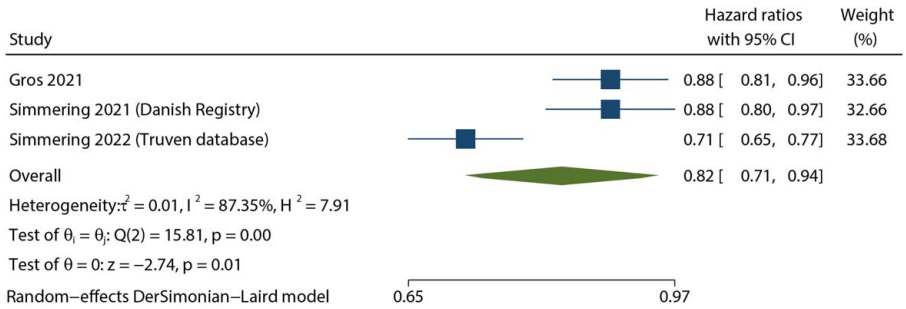


**Figure 2.** Forestplot of meta-analysis of risk of Parkinson disease.

TZ/AZ/DZ users was 1.28% and 1.11%, respectively. Additionally, the risk of occurrence of PD was significantly lower in patients taking TZ/AZ/DZ than tamsulosin (HR = 0.82, 95% CI = 0.71–0.94).

None of the available therapies till date have been successful to prevent neurodegeneration in human beings[24]. Since neurodegeneration lies at the core of the pathogenesis of PD, prevention of neurodegeneration or retardation of its progression shall serve as a curative treatment[25]. However, no medical treatment has been able to achieve such outcomes till date. Numerous experimental models and drugs have been tested to have a beneficial effect on the PD yet there has been no clear benefit from any drug so far. According to a wealth of studies, in patients with PD, glycolysis and overall mitochondrial function of the neurons are also drastically reduced[26–28]. Additionally, mitochondrial toxins such as rotenone and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) are known to induce PD-like models[3,25]. Genetic mutations in PINK1, PARKIN, DJ-1, LRRK2 gene that lead to disturbed mitochondrial function are found to be associated with an increased risk of familial PD[29]. These findings have strongly supported the theory of impaired energy metabolism in mitochondria of dopaminergic neurons as the pathogenesis of the disease.

A couple of recent studies have tried to explore the effect of AAs on the PD through toxin-induced and genetic models. It began with the discovery that TZ binds and activates PGK1 enzyme, which is an essential enzyme to catalyze the reaction to produce first ATP molecule in the glycolysis pathway. This was followed by a hypothesis that TZ crosses the blood-brain barrier and could alleviate impaired energy production in dopaminergic neurons of SNPC which is considered one of the important reasons behind the apoptotic neurodegeneration in PD[3,29]. The crystal structure of TZ implied that related drugs with quinazoline motifs like AZ and DZ could also enhance PGK1 enzyme activity and have a similar beneficial effect on the disease[30].

Cai *et al.*[3] discovered when TZ activates PGK1 enzyme, the end product of glycolysis; pyruvate was increased. Since pyruvate us the major substrate of citric acid cycle, the overall production of ATP through oxidative phosphorylation was increased in the cells. Additionally, TZ was found to increase the citrate synthase activity and provided mitochondrial protection against toxins. These mechanisms are considered to contribute to an increased ATP content in the cells in the presence of TZ. In-vivo studies have found that the administration of TZ even after the onset of neurodegeneration, halted cellular death, and increased dopamine content while elevating motor performance. Human genetic model studies of PD with PINK1 and LRRK2 mutations also demonstrated partial reversibility of low dopamine production and motor deficits with the use of TZ. Moreover, a pilot study in humans had demonstrated an increased ATP levels in the brain with use of TZ[31].

Tamsulosin can serve as a control for TZ. Tamsulosin has served as a powerful protection against confounding by indication since the users of both drug categories have similar characteristics at the baseline. In contrast to TZ/AZ/DZ, tamsulosin does not have a quinazoline motif that binds to and enhances PGK1 activity. Tamsulosin did not produce beneficial effects on animal models of PD in experimental studies either[3]. Another potential beneficial effect of TZ, which is the retardation of the progression of PD was observed in the small population of Parkinson's Progression Markers Initiative (PPMI) database. This database enrols patients with PD shortly after diagnosis and follows their motor function as determined by the Movement Disorder Society's Unified Parkinson's Disease Rating Scale Part 3. Compared with the controls, the patients who used TZ had a slower rate of motor function decline[32].

Simmering *et al.*[15] reported that TZ/AZ/DZ drug users had 12% to 37% lower hazards of developing PD compared to tamsulosin users. Additionally, prolonged use of TZ/AZ/DZ was associated with a greater reduction in the hazard ratio compared to using tamsulosin for a similar time period. Another similar study by Sasane *et al.*[23] reported a higher risk of PD in individuals using tamsulosin (1.53%) compared with TZ/AZ/DZ users (1.10%). Likewise, a higher risk of PD was also reported in the tamsulosin cohort compared with matched controls (1.01%). Similarly, there was no difference in the incidence of PD when compared between TZ/DZ/AZ drug users and the matched cohort. Therefore, they concluded that the decreased risk of PD among TZ/AZ/DZ users versus tamsulosin users was due to tamsulosin increasing the risk of developing PD. This proposition is substantiated by Duan *et al.*[33], revealing that the likelihood of developing dementia was increased among tamsulosin users, when compared to a control group that did not take any medication for BPH, as well as separate groups who were prescribed TZ/DZ/AZ. This association was significant even after adjusting for the burden of comorbidities and the usage of chronic drugs that are known to elevate the chance of acquiring dementia. Therefore, the utilization of tamsulosin seems to elevate the likelihood of cognitive side effects. However, this does not necessarily mean that tamsulosin directly leads to worsening of PD. Further, this finding by Sasane *et al.*[23] has been contradicted by another study by Simmering *et al.*[16] which also reported

possible neuroprotective role of TZ/DZ/AZ even when compared to tamsulosin users and a new comparison population of BPH patients taking 5-alpha reductase inhibitor drugs.

Gros *et al.*[22] found that both TZ/AZ/DZ and tamsulosin exposure were associated with a small reduced risk of incidence of PD. This finding is in direct contrast to the results reported by Simmering *et al.*[16] and Sasane *et al.*[23] Since both TZ/AZ/DZ and tamsulosin reduced the incidence of PD, Gros *et al.*[22] hypothesized that alpha-receptor antagonistic activity should be the common mechanism behind the reduction of disease risk. Further, they proposed that the alpha antagonism at the supporting cells like astrocytes could be involved in the protective effect on the neurons of basal ganglia. The differences in outcomes observed between these studies can be partly explained by the differences in their research question and methodologies. Gros *et al.*[22] answered whether an increased exposure to TZ/AZ/DZ or tamsulosin decreased the likelihood of developing PD. However, other studies, like Simmering *et al.*[16] and Sasane *et al.*[23] attempted to answer if TZ/AZ/DZ are better than any use of tamsulosin. The inherent limitations of Gros *et al.*[22] were the baseline confounding by indication of drug use. They also observed that the risk of developing PD before starting patients on any of the two drug categories was lower in TZ/AZ/DZ cohort compared to tamsulosin. One possible explanation for the discrepancy in baseline risk between TZ/AZ/DZ and tamsulosin in relation to the incidence of PD may be attributed to a common practice among physicians to refrain from prescribing TZ/AZ/DZ to individuals with hypotension due to their known capacity to reduce blood pressure.

Our systematic review and meta-analysis is not free of limitations. Since most of the data analyzed in our meta-analysis was extracted from the retrospective database, there might have been some unseen biases in the primarily collected data of selected studies. Likewise, the source of considerable heterogeneity observed in the risk of occurrence of PD could not be ascertained due to limited availability data for subgroup analysis. We utilized prescription-based data available in major health databases, which do not necessarily reflect compliance with the drugs. Likewise, even though all the drugs were prescribed for BPH, we cannot exclude the possibility that various factors might have influenced prescribing behaviour of the physicians. For instance, orthostatic hypotension is a complication of both the autonomic dysfunction in PD and of the drugs used in PD. However, physicians are likely to avoid prescribing TZ/DZ/AZ since the risk of orthostatic hypotension is less with the use of tamsulosin than TZ/DZ/AZ[16] Patients could have discontinued TZ/DZ/AZ or tamsulosin because of orthostatic effects or may never be prescribed them given physicians' awareness of their dysautonomia. Interestingly, the risk of hypotension and falls was reduced, not increased, for patients with PD taking TZ/DZ/AZ versus those on tamsulosin[34] Such a complex relationship of drugs and PD could have affected the prescription of drugs to the patients while introducing biases in the data. Another limitation of our analysis is that our findings are limited to men since they are the ones treated for BPH. This has affected the applicability and generalizability of our findings. Another important consideration is some of the studies included in our review had a short follow-up duration that may not be sufficient to estimate the risk of occurrence of PD.

## Conclusion

The outcome of our meta-analysis is only suggestive of the potential beneficial effect of alpha antagonists, especially TZ/AZ/DZ drugs in decreasing the risk of occurrence of PD. Considering the complex and heterogeneous pathophysiology of PD, it is essential to identify the subset of patients with impaired energy metabolism or those who might benefit from glycolysis-enhancing drugs. The differences in conclusions of studies included in our systematic review have also highlighted the need for randomized controlled trials to determine the efficacy of these drugs in PD.

## Ethical approval

Not applicable due to the nature of the review article.

## Consent

Not applicable for review article.

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No funding was received to complete the research work.

## Author contribution

Conceptualization: P.L., A.T., A.N.A., M.R., A.L., A.A. Methodology: P.L., A.L., A.A. Data curation and analysis: P.L., A.L., M.R. Software: P.L.. Original draft writing: P.L., A.T., A.N.A., A.L., M.R., A.A. Original draft-review and editing: P.L., A.T., A.N.A., A.L., M.R., A.A. Supervision: P.L.

## Conflicts of interest disclosure

None declared.

## Research registration unique identifying number (UIN)

1. Name of the registry: PROSPERO.
2. Unique Identifying number or registration ID: CRD42023429650.
3. Hyperlink to your specific registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=429650

## Guarantor

Dr Pratik Lamichhane.

## Data availability statement

The data used in the meta-analysis are available with the primary researcher.

## Provenance and peer review

Not commissioned, externally peer-reviewed.

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