Review Article

Non-Steroidal Anti-Inflammatory Drugs and Parkinson's Disease: A Systematic Review and Meta-analysis

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Abstract

Background: Several studies have explored the impact of non-steroidal anti-inflammatory drugs (NSAIDs) and the hazard of Parkinson's ailment. However, the extent to which NSAID increases or reduces the hazard of PD remains unresolved. **Aim:** This work aims to determine the effect of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) on increasing the risk of Parkinson's Disease (PD). **Materials and Methods:** A systematic search was performed over different medical databases to identify Neurology studies, which studied the outcome of NSAIDs users versus Non-user patients. Using the meta-analysis process, either with fixed or random-effects models, we conducted a meta-analysis on the overall prevalence of Parkinson's disease as a primary outcome, and on the effect of type of NSAIDs (Aspirin or NSAID) on the prevalence of Parkinson's disease as secondary outcomes. **Results:** Five studies were identified involving 265919 patients, with 67502 patients in NSAIDs users, and 198417 patients were Non-users. The meta-analysis process revealed that the overall pooled prevalence of PD=6.6%. The meta-analysis process revealed a highly significant increase in the prevalence of PD in Aspirin users compared to Non-users (p=0.004), and a non-significant difference in the prevalence of PD in NSAIDs users compared to Non-users (p>0.05). **Conclusion:** To conclude, despite the neuroprotective potential of NSAIDs demonstrate in some experimental studies, our findings suggest that there is no association between NSAIDs and the risk of Parkinson's disease at the population level.

Keywords: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs); Parkinson's Disease

Introduction

Defined by James Parkinson in 1817, Parkinson's Disease (PD) is a chronic neurodegenerative process in which there is loss of dopamine-releasing neurons inside substantia nigra which leads to reduced stages of dopamine in the striatum and disrupted motor manages. Neuronal eosinophilic inclusions called Lewy our bodies and aggregation of alpha-syncline protein are hallmarks of the disorder. Many other neuronal cell populations are also affected and account for the presence of non-motor symptoms. The main pathophysiological mechanisms include mitochondrial dysfunction, abnormal aggregation of alpha-synuclein, and oxidative stress. [1]

Parkinson's disease (PD), the second most common age-related neurodegenerative disease, is characterized by way of dopaminergic (DA) neurons loss and the presence of α-synuclein-containing aggregates within substantia nigra pars compacta (SNpc). Postmortem analyses of PD patient's animals revealed that the activation of glial cells increases pro-inflammatory markers in the brain. [2]

One of the most commonly used agents, acetylsalicylic acid (aspirin), which may interrupt neurotoxic cascade. Aspirin exerts its effects at the anti-inflammatory cascades, irreversibly inhibiting cyclooxygenase COX-1, and editing enzyme interest of COX-2, suppressing the production of prostaglandins and thromboxane. These anti-inflammatory and anti-platelet mechanisms proved to have positive effects on the risk of strokes, atherosclerosis, heart disease, and potentially, some cancers. [3]

Several studies have explored the impact of NSAIDs and the hazard of Parkinson's ailment. However, the extent to which NSAID increases or reduces the hazard of PD remains unresolved. We, therefore, performed a meta-analysis of

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How to Cite this Article: Alharbi BA, et al. Non-Steroidal Anti-Inflammatory Drugs and Parkinson's Disease: A Systematic Review and Meta-analysis. Ann Med Health Sci Res. 2020;10: 1023-1028.

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relevant research to quantify the magnitude of the association among NSAID use and PD hazard in the aged population. [4]

This work aims to determine the effect of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) on increasing the risk of Parkinson's disease (PD).

Literature Review

Our review came following the (PRISMA) statement guidelines. [5]

Study eligibility

The included studies should be in English, a journal published article, and a human study describing Parkinson's disease patients. The excluded studies were non-English or animal studies or describing other types of drugs (e.g. Steroids and Parkinson's disease patients.

Study identification

Basic searching was done over the PubMed, Cochrane library, and Google scholar using the following keywords: Non-Steroidal Anti-Inflammatory Drugs, Parkinson's disease.

Data extraction and synthesis

RCTs, Case-control, and comparative studies, which studied the outcome of NSAIDs users versus Non-users of Parkinson's Disease patients, will be reviewed.

Outcome measures included the overall prevalence of Parkinson's disease (as a primary outcome), and on the effect of type of NSAIDs (Aspirin or NSAID) on the prevalence of Parkinson's disease (as secondary outcomes).

Study selection

We found 150 records, 90 excluded based on title and abstract review; 60 articles are searched for eligibility by full-text review; 24 articles cannot be accessed; 13 studies were reviews and case reports; 11 were not describing our outcome; the desired drug not used in 7 studies leaving 5 studies that met all inclusion criteria.

Statistical methodology

The pooling of data, Proportions (%), Odds Ratios (ORs), with 95% confidence intervals (CI) were done, using MedCalc ver. 18.11.3 (MedCalc, Belgium). According to heterogeneity across trials using the I^2-statistics; a fixed-effects model or random-effects model were used in the meta-analysis process.

Results

The included studies published between 2006 and 2020. Regarding the type of included studies, 3 studies (out of 5 studies) were case-control studies, while 2 studies were cohort studies [Table 1]. [6-10]

Regarding patients' characteristics, the total number of patients in all the included studies was 265919 patients, with 67502 patients in NSAIDs users, and 198417 patients were Non-users, while their average follow-up time was (10 years) [Table 1]. The mean age of all patients was (56.7 years) [Table 1].

A meta-analysis study was done on 5 studies that described and compared the 2 different groups of patients; with an overall number of patients (N=265919) [Table 2]. [6-10]

Each outcome was measured by:

Pooled proportion

- For the overall prevalence of Parkinson's disease (PD).

Odds Ratio (OR)

- For the prevalence of Parkinson's disease in Aspirin users.
- For the prevalence of Parkinson's disease in NSAIDs users.

Concerning the primary outcome measure, we found 5 studies reported an overall prevalence of PD with a total number of patients (N= 265919). I^2 (inconsistency) was 99.9% with a highly significant Q test for heterogeneity ($p<0.0001$), so random-effects model was carried out; with pooled prevalence=6.6%

Table 1: Patients and study characteristics.

N	Author	Type of study	Type of NSAID	Number of patients			Age (Average years)	Follow-up time (Average years)
				Total	NSAIDs users	Non-users		
1	Hernán, et al. [6]	Case-control	NSAID/Aspirin	10626	2730	7896	---	6
2	Becker et al. [7]	Case-control	NSAID/Aspirin	39990	17885	22105	60	14
3	Lin et al. [8]	Cohort	NSAID	33388	8164	25224	50	4
4	Sung et al. [9]	Cohort	NSAID	166105	33221	132884	53.9	12
5	Starhof et al. [10]	Case-control	NSAID/Aspirin	15810	5502	10308	63	14

#Studies arranged via publication year.

Table 2: Summary of outcome measures in all studies.

N	Author	Primary outcome	Secondary outcomes			
		Overall PD prevalence	PD prevalence in Aspirin users		PD prevalence in NSAIDs users	
		Total	Aspirin users	Non-users	NSAIDs users	Non-users
1	Hernán, et al. [6]	2730	678	179	301	1572
2	Becker et al. [7]	8052	2663	1363	2435	1591
3	Lin et al. [8]	32	---	---	11	21
4	Sung et al. [9]	2778	---	---	397	2381
5	Starhof et al. [10]	310	116	39	86	69

(95% CI=0.779 to 17.448). Using the random-effects model, the meta-analysis process revealed an overall pooled prevalence of PD=6.6% (p<0.001) [Figure 1].

Concerning the secondary outcome measures, we found 3 studies reported prevalence of PD in Aspirin users with a total number of patients (N=66426). I^2 (inconsistency) was 99% with a highly significant Q test for heterogeneity (p<0.0001), so random-effects model was carried out; with overall OR= 5.98 (95% CI=1.743 to 20.547). Using the random-effects model, the meta-analysis process revealed a highly significant increase in the prevalence of PD in Aspirin users compared to Non-users (p=0.004) [Figure 2].

We found 5 studies reported the prevalence of PD in NSAID users with a total number of patients (N= 265919).

I^2 (inconsistency) was 99.2% with a highly significant Q test for heterogeneity (p<0.0001), so random-effects model was carried out; with overall OR= 1.18 (95% CI=0.580 to 2.436). Using the random-effects model, the meta-analysis process revealed a non-significant difference in the prevalence of PD in NSAID users compared to Non-users (p>0.05) [Figure 3].

Discussion

This work aims to determine the effect of NSAIDs on increasing the risk of Parkinson's. The included studies published between

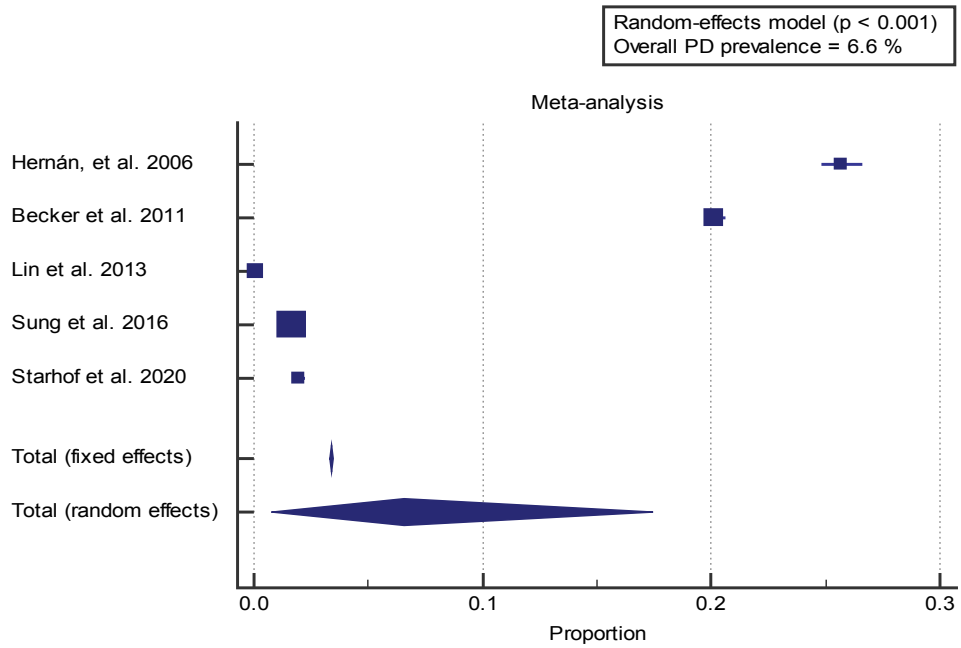

Figure 1: Forest plot demonstrating (Overall PD prevalence).

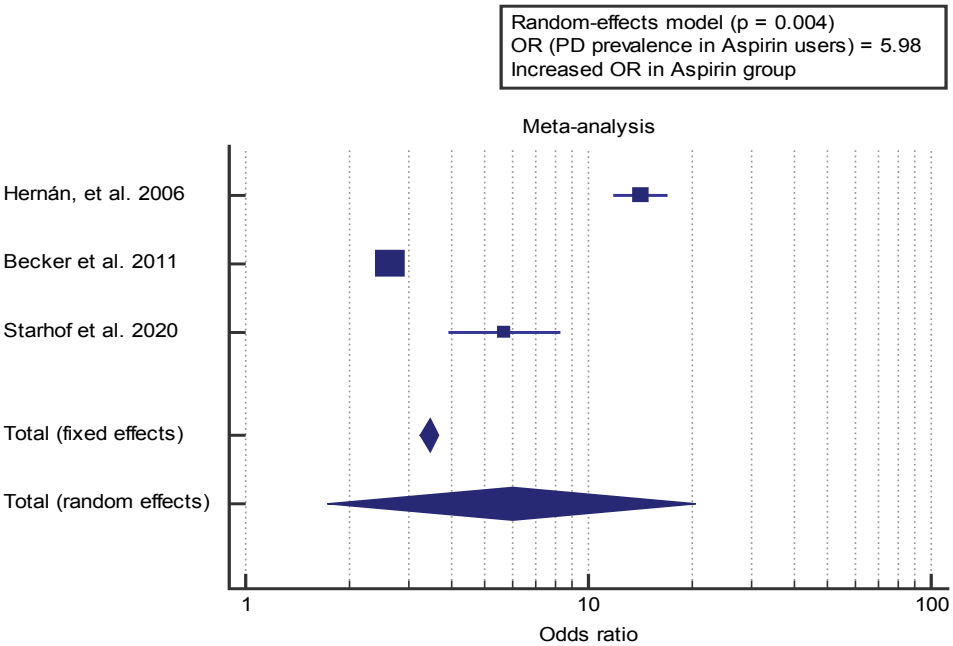

Figure 2: Forest plot demonstrating (OR of PD prevalence in Aspirin users).

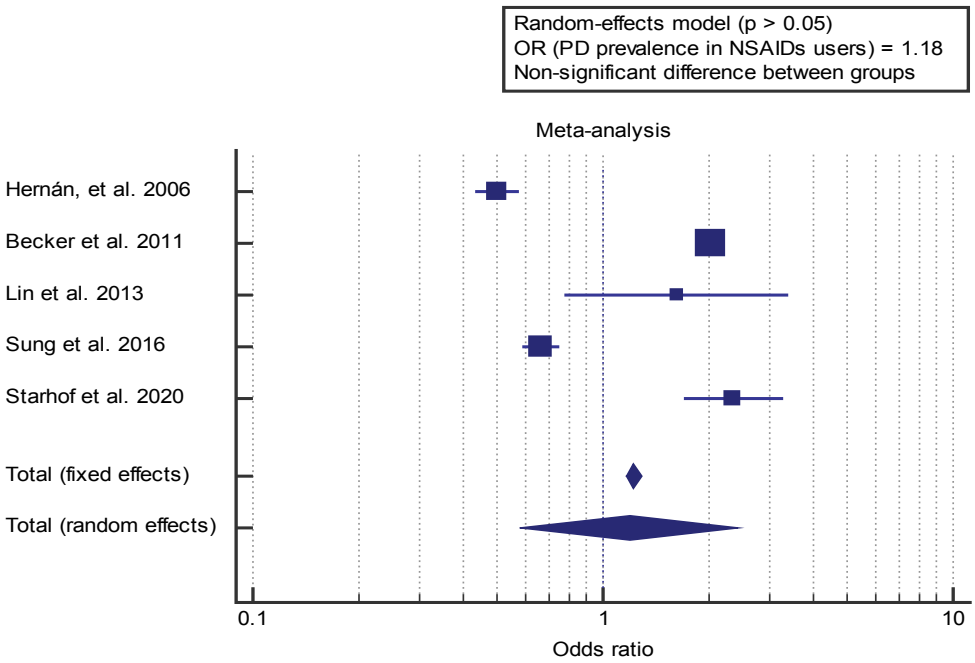

Figure 3: Forest plot demonstrating (OR of PD prevalence in Aspirin users).

2006 and 2020. Regarding the type of included studies, 3 studies (out of 5 studies) were case-control studies, while 2 studies were cohort studies.

Regarding patients' characteristics, the total number of patients in all the included studies was 265919 patients, with 67502 patients in NSAIDs users, and 198417 patients were Non-users, while their average follow-up time was (10 years). The mean age of all patients was (56.7 years).

A meta-analysis study was done on 5 studies that described and compared the 2 different groups of patients; with an overall number of patients (N=265919).

Concerning the primary outcome measure, we found 5 studies reported an overall prevalence of PD with a total number of patients (N= 265919). Using the random-effects model, the meta-analysis process revealed an overall pooled prevalence of PD=6.6% (p<0.001), which came in agreement with Delamarre and Meissner, [11] Elbaz et al., [1] Kieburtz and Wunderle, [12] Poly et al. [4]

Delamarre and Meissner reported that many kinds of research focused on the epidemiology of PD and associated problems. The prevalence and incidence range with the methodology of the studies and populations targeted. A recent meta-analysis showed an age-dependent incidence; from 41/100,000 between 40 and 49 years and the prevalence is 134 men and 41 women per 100,000 individuals. In the 70–79-yrs-old population, PD is much less common in Asia than in North America, Europe, and Australia. In every other meta-analysis, the incidence was 37.6 cases per 100,000 person-years in women older than 40 years and 61.2 in men older than 40 years 1903 per 100,000 inhabitants older than 80. [11]

Elbaz et al. reported that PD prevalence is usually comprised between 10 and 50/100,000 individual-years, and its occurrence between 100 and 300/100,000 populations. Although it is the second most common neurodegenerative disorder after Alzheimer's, PD remains relatively uncommon. However, because of the general aging of the population, the range of PD patients is expected to double by 2030. PD frequency increases sharply with age. It is uncommon earlier than age 50 years, and its prevalence and incidence both increase progressively after age 60; based on a meta-analysis of incidence studies. [1]

Kieburtz and Wunderle reported that they discovered that prevalence in men was about 50% higher than that in ladies and that PD was extremely uncommon earlier than the age of 40. Prevalence rates rise to as excessive as 150 in 100,000 in men at the age of 70, and 80 in 100,000 in women among the ages of 70 and 90. Even though this relationship of age to the prevalence of PD may seem self-evident, the underlying mechanism by which advancing age can also confer hazard for PD remains obscure. [12]

Poly et al. reported that a total of 17 studies with 2,498,258 participants and nearly 14,713 PD patients were included in the final analysis. The overall risk of PD was 0.95 (p<0.0001). In the subgroup analysis, the overall risk of PD was 0.90, 0.96, and 0.99 from the studies of North America, Europe, and Asia respectively. [4]

Concerning the secondary outcome measures, we found 3 studies reported prevalence of PD in Aspirin users with a total number of patients (N=66426). Using the random-effects model, the meta-analysis process revealed a highly significant increase in the prevalence of PD in Aspirin users compared to Non-users (p=0.004), which came in agreement with Bellou et al., [13] Elbaz et al. [1] and Ren et al. [14]

Bellou et al. reported that, 17 (23%) meta-analyses had large heterogeneity estimates (I2 <50% and I2>75%) and 16 (21%) meta-analyses had very huge heterogeneity estimates (I2>75%).

proof for small-examine effects was mentioned in 13 (17%) meta-analyses. Assuming that the effect size in the largest study was the true impact, 23 (31%) of the 75 Meta-analyses had a significant difference between the number of observed and expected positive studies. Aspirin cases were 2781 with 6 studies RR was 1.08. [13]

Elbaz et al. reported that because neuroinflammatory factors play a role in PD pathogenesis and NSAIDs exhibit neuroprotective effects in animal PD models. An inverse association was found for non-aspirin NSAIDs (OR: 0.85), including ibuprofen (OR: 0.75), but not for aspirin (OR: 1.08). [1]

Ren et al. reported that aspirin use was significantly related to Parkinson's disorder hazard decrement (RR: 0.91; P=.028) (desk 3). Furthermore, NSAID's use was not related to Parkinson's disorder hazard in women (RR: 0.99;P=.876) and male (RR: 1.01; P=.913). [14] On the other hand, our result came in disagreement with Fu, Zhen, and Lu [15] and Kieburtz and Wunderle. [12]

Fu, Zhen, and Lu reported that data reveals that the combination of DHA and ASA is a mechanism for improving PD. DHA affected PPARa through activating RXRa and promoting the expression of PPARa via inhibiting miR-21, and ASA could activate PPARa. The functions of ASA and DHA significantly increased heterodimer formation of PPARa and RXRa and improved their ability to enter the nucleus. [15]

Kieburtz and Wunderle reported that Use of aspirin and acetaminophen (APAP) appears to not affect PD risk. The effect is prominent in women but minimal in men. [12]

Using the random-effects model, the meta-analysis process revealed a non-significant difference in the prevalence of PD in NSAIDs users compared to Non-users (p>0.05), which came in agreement with Poly et al., [4] Bellou et al., [13] Delamarre and Meissner, [11] Kieburtz and Wunderle, [12] Pettit et al. [16] and Ren et al. [14]

Poly et al. reported that seventeen studies evaluated the association between NSAID therapy and the risk of PD. NSAID use was not significantly associated with increased risk of PD compared with non-users; pooled RR was 0.95. [4]

Bellou et al. reported that met analyses pertained to alcohol consumption, coffee drinking, energy intake, exposure to hydrocarbons, serum vitamin D, lutein intake, non-aspirin NSAIDs, organic solvents, pesticides, rural living, vitamin B6 intake, statins, and smoking. Assuming that the impact size in the largest has a look at changed into the true effect, 23 (31%) of the 75 met analyses had a significant difference between the number of discovered and expected positive research. NSAIDs cases turned into 3967 with 7 research and RR 0.85 and I2 become 0.1 with the non-significant difference in the incidence of PD. [13]

Delamarre and Meissner reported that, in a meta-analysis, ibuprofen was shown to reduce PD risk, with no effect of NSAID as a class. Ibuprofen is a ligand of PPARg and may thereby exert anti-apoptotic and anti-oxidative effects. Another meta-analysis showed a protective effect of non- aspirin NSAID and a negative effect of aspirin use. [11]

Kieburtz and Wunderle reported that similar modest reductions in PD risk have been observed with the use of non-steroidal anti-inflammatory drugs (NSAIDs). Results from more than one group suggest that the benefit regarding PD is observed in those who regularly use non-aspirin NSAIDs and that the effect is larger with a longer duration of use. [12]

Pettit et al. reported that Epidemiological studies have shown an inverse relationship between NSAID intake and the development of Alzheimer's and Parkinson's illnesses. NSAIDs are also proposed to affect the inflammatory component of Multiple Sclerosis and Amyotrophic Lateral Sclerosis. [16]

Ren et al. reported that fifteen eligible researches had been included in this meta-analysis. NSAIDs' use was not related to Parkinson's disorder threat [relevant risk (RR): 0.06]. Subgroup analysis confirmed that aspirin use (RR: 1.14) or ibuprofen use (RR: 1.01) was not related to Parkinson's disorder hazard. [14-16]

Conclusion

To conclude, despite the neuroprotective potential of NSAIDs demonstrate in some experimental studies, our findings suggest that there is no association between NSAIDs and the risk of Parkinson's disease at the population level.

Competing Interests

The authors declare that they have no competing interests. All the listed authors contributed significantly to the conception and design of study, acquisition, analysis, and interpretation of data and drafting of the manuscript, to justify authorship.

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