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ORIGINAL RESEARCH ARTICLE

Chronic Use of β-Blockers and the Risk of Parkinson's Disease

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Abstract

Background Most patients with Parkinson's disease exhibit intracellular accumulation of the α-synuclein protein encoded by the α-synuclein gene. It was recently shown that β_2-adrenoreceptor agonists downregulate this gene, decreasing the apparent risk of Parkinson's disease by up to 40%. In contrast, exposure to β-blocking drugs increases production of the α-synuclein protein.

Objective The aim of this study was to examine whether chronic exposure to β-blockers is associated with an increased risk for Parkinson's disease.

Patients and Methods From the electronic charts of Maccabi Health Services, we identified all patients receiving their first β-blocker treatment between 1998 and 2004, and followed them up, for a diagnosis of Parkinson's disease, between 2005 and 2016. We calculated the morbidity hazard of Parkinson's disease diagnosis in users of β-blockers compared with non-users, as well as users of angiotensin-converting enzyme (ACE) inhibitors for hypertension, after adjusting for sex, age, weight, smoking status, cholesterol levels and use of statins, employing the Cox proportional hazard model. We also conducted a Kaplan–Meier survival analysis.

Results Overall, 145,098 patients received β-blockers, and 1,187,151 patients did not. The adjusted hazard ratio for Parkinson's disease among β-blocker users was 1.51 (95% confidence interval 1.28–1.77; $p < 0.0001$). In contrast, the Parkinson's disease morbidity hazard for patients receiving ACE inhibitors was no different than for the general population. The morbidity risk showed the effect of cumulative dose response with low threshold levels.

Conclusions Chronic use of β-blockers confers a time- and dose-dependent increased risk for Parkinson's disease. In view of the available alternatives for β-blockers, their chronic use should be carefully reconsidered.

Key Points

Most patients with Parkinson's disease exhibit intracellular accumulation of the α-synuclein protein encoded by the α-synuclein gene. It has recently been shown that β2-adrenoreceptor agonists downregulate this gene, decreasing the apparent risk of Parkinson's disease by up to 40%.

The adjusted hazard ratio for Parkinson's disease among β-blocker users was 1.51 (95% confidence interval 1.28–1.77; $p < 0.0001$).

Chronic use of β-blockers confers a time- and dose-dependent increased risk for Parkinson's disease. In view of available alternatives for β-blockers, their chronic use should be carefully reconsidered.

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1 Introduction

Parkinson's disease affects between 0.6 and 2.6% of people over 65 years of age, and, although its etiology is not yet clear, most patients exhibit intracellular accumulation of the α-synuclein protein (Lewy Bodies), encoded by the wild-type α-synuclein gene (SNCA) [1–3]. The α-synuclein is an abundantly expressed neuronal protein, and synucleinopathies are characterized by the appearance of aggregated α-synuclein inside cells. In a 2017 study, Mittal et al. showed that β2-adrenoreceptor agonists downregulate this gene, decreasing the apparent risk of Parkinson's disease by up to 40% among exposed people in Norway. In contrast, exposure to the β-blocking agent propranolol was associated with an increased morbidity hazard for Parkinson's disease [4]. There are scores of other β-blockers in clinical use that are widely employed on a chronic basis for the management of hypertension, congestive heart failure post-myocardial infarction, and for primary tremor [5]; however, it is not clear whether a similar effect is caused by these β-blockers in regulating the synuclein gene.

A recent study confirmed the use of propranolol increased the risk of Parkinson's disease [6], while another

study found no such effect of propranolol after adjusting for primary tremor [7]. None of the existing studies have addressed a possible threshold effect in terms of cumulative dose and time of exposure to β-blockers.

There are several recognized risk factors for Parkinson's disease, including age, male sex, and family clustering [6]. In contrast, cigarette smoking and lower total and low-density lipoprotein (LDL)-cholesterol have been shown to confer an apparent protective effect against Parkinson's disease [7]. The objective of the present study was to evaluate the potential association between chronic use of β-blockers and the risk of Parkinson's disease and its threshold levels, after adjustment for potential confounders.

2 Methods

2.1 Study Population

To select patients for inclusion in this study, we used the electronic medical records (EMRs) of Maccabi Health Services, the second largest health fund in Israel, insuring over 2 million persons (or one-quarter of the country's population), from 1998 to 2016 [8].

2.1.1 Case Ascertainment

We identified all patients receiving their first β-blocker treatment between 1 January 1998 and 31 December 2004 for cardiovascular indications, and followed them up, for a diagnosis of Parkinson's disease, after 360 days, 600 days, 1000 days, and 1500 days. A diagnosis of Parkinson's disease was only included if it occurred longer than 365 days following the first β-blocker prescription. Patients with a diagnosis of Parkinson's disease between 1998 and 2005 were excluded. Follow-up continued until death, discontinuation of insurance in Maccabi, or until 31 December 2016, whichever was first.

The following coded, anonymized data were extracted for each patient: age, sex, body weight, body mass index (BMI), smoking status, all International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes, and all dates and amounts of drug purchases. A diagnosis of Parkinson's disease, as well as the date of diagnosis, was based on more than one diagnostic code extracted by a neurologist.

The dates of diagnosis and the diagnostic codes were extracted. Smoking status was obtained from the information recorded in the patient chart by the treating physicians. As drug costs were covered by Maccabi Health Services, the record of chronic, continuous drug purchases accurately reflects actual drug use [9]. To be included, patients would have had to have purchased at least one prescription of a β-blocker. From the list of patients who purchased β-blockers, we excluded those receiving these drugs following an ICD-9 diagnosis of essential tremor made by a neurologist, to obviate potential misdiagnosis of Parkinson's disease as essential tremor. We also excluded all other cases of essential tremor, not receiving β-blockers.

2.2 β-Blocker Dose

From the electronic medical files, for each patient receiving β-blockers for cardiovascular indication we recorded the mean dose per year and the mean cumulative purchased dose, and transformed the data into a defined daily dose (DDD) to standardize the different β-blockers used, according to their equivalent reference values [10]. The reference values are based on the DDD, bringing all the different β-blockers and their different doses to one common denominator. For example, one DDD of atenolol is 50 mg, equivalent to 80 mg of propranolol.

2.3 Matching

We recorded the time that had elapsed between the commencement of β-blocker therapy, from 1998 to 2005, and the subsequent diagnosis of Parkinson's disease between 2005 and 2016. Each patient receiving a β-blocker was matched with a patient not receiving either a β-blocker or a β-mimetic drug based on known confounders, including age (± 1 year), sex, smoking status (never/ever), LDL levels (above the normal range) and statin use (any dose level). The random allocation of matching was confirmed by propensity scoring.

2.4 Statistical Analysis

Applying the Cox proportional hazard model and Kaplan–Meier survival analysis, the adjusted hazard ratio (HR) for developing Parkinson's disease among β-blocker users was calculated. The threshold mean dose and cumulative dose associated with β-blocker risk for Parkinson's disease were calculated by identifying the mean daily and cumulative doses below which the HR for β-blockers was not statistically different than for patients not receiving β-blockers. In parallel, we also calculated the HR for Parkinson's disease among users of ACE inhibitors, to address a potential effect of hypertension. We regarded ACE exposure as any dose purchased for more than 2 months. All statistical analyses were performed using SPSS version 25 (IBM Corporation, Armonk, NY, USA).

3 Results

Table 1 displays the characteristics of β-blockers in the exposed and unexposed groups. Overall, 145,098 patients received β-blockers but did not receive β-agonists in the drug administration period, and 1,187,151 patients did not receive either of these drug classes. The vast majority of β-blocker use was for hypertension (92.9%), followed by acute myocardial infarction (4.7%) and congestive heart failure (2.5%). Our dataset included 4644 patients diagnosed with Parkinson's disease. After matching for age, sex, body weight, smoking, cholesterol, and use of statins, we created a group of 132,484 matched pairs. Applying the Cox proportional hazard model, the adjusted morbidity hazard for Parkinson's disease among β-blocker users was 1.51 (95% confidence interval [CI] 1.28–1.77; $p < 0.0001$) (Fig. 1). The mean defined daily dose of β-blockers was 1.43, with a median DDD of 0.55. The Parkinson's disease morbidity hazard of patients receiving a DDD under 0.15 was not significantly different from those not receiving β-blockers. The mean total cumulative DDD was 12.9, with a median DDD of 3.37. The Parkinson's disease morbidity hazard of patients receiving a cumulative DDD under 0.9 was not statistically different from those not treated with β-blockers. Furthermore, patients receiving angiotensin-converting enzyme (ACE) inhibitors were no different in their Parkinson's disease morbidity hazard than those not receiving β-blockers (HR 1.13, 95% CI 0.54–2.35; $p = 0.37$) (Fig. 2).

The Cox model-fitting shows that β-blocker consumption ($p < 0.000001$), DDD ($p < 0.04$), and cumulative DDD ($p = 0.01$) are significantly associated with Parkinson's disease, in addition to age ($p < 0.000001$) and sex ($p < 0.00001$). The significant association between β-blockers and Parkinson's disease was stable, with gaps of either 365, 1000, or 1500 days between β-blocker initiation and Parkinson's disease diagnosis. Patients receiving ACE inhibitors were no different in their Parkinson's disease morbidity hazard than the whole cohort ($p = 0.37$) (Fig. 2).

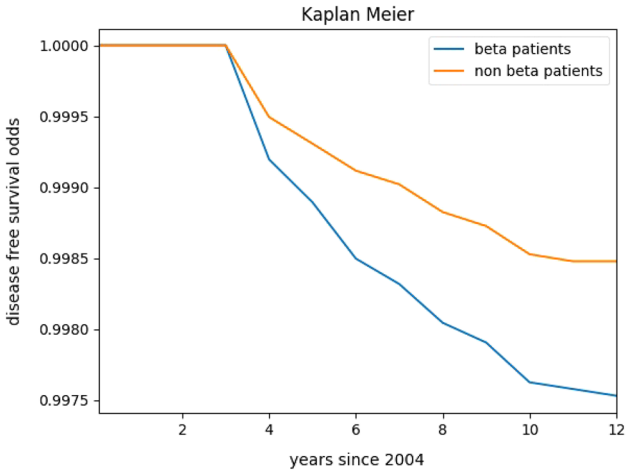

Fig. 1 Disease-free survival odds among patients exposed to β-blockers, compared with unexposed controls matched for age, sex and cigarette use

The lag time from exposure to a β-blocker to diagnosis of Parkinson's disease did not affect the HR (Table 2).

4 Discussion

Our study shows a statistically significant increased morbidity hazard for Parkinson's disease among patients exposed to β-blockers during the years prior to a diagnosis of Parkinson's disease. This risk appears to be dose- and time-dependent, strongly supporting a cumulative toxic effect and consistent with the biological accumulation of the Lewy bodies [1–3]. We adjusted for factors known to increase (age, sex) [6] or decrease (smoking, cholesterol, statins) the risk of Parkinson's disease [9, 11]. Because β-blockers are also used

Table 1 Demographics of the two cohorts

Characteristic	Beta users	Non-users of beta
Mean age, years [median (SD)]	53.84 [51 (19.49)]	53.3 [50 (19.5)]
Sex, males	59.6%	59.5%
Mean weight, kg [median (SD)]	70.94 [70 (14.13)]	70.8 [70 (14.18)]
Mean BMI, kg/m^2 [median (SD)]	25.07 [24.89 (4.92)]	24.72 [24.6 (5.13)]
Smoker, *n*	565	544
Past smoker, *n*	2732	2605
Never smoker, *n*	18,651	17,660
Unknown, *n*	2259	2143
LDL > 150, mg/dL	491	449
Mean number of years of statin use [median (SD)]	0.52 [0 (1.9)]	0.52 [0 (1.9)]

BMI body mass index, *LDL* low-density lipoproteins, *SD* standard deviation

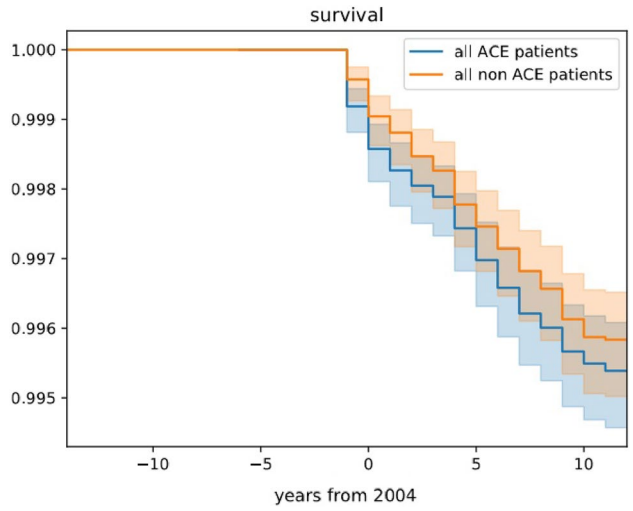

Fig. 2 Morbidity hazard for Parkinson's disease among patients receiving ACE inhibitors versus those not receiving any therapy for hypertension (differences are non-significant; $p=0.37$). *ACE* angiotensin-converting enzyme

in the treatment of essential tremor, which may be confused with or misdiagnosed as Parkinson's disease, we elected to exclude patients using β-blockers in relation to a diagnosis of benign tremor. To account for the possible effect of hypertension on the occurrence of Parkinson's disease, we also calculated the morbidity ratio of patients receiving ACE inhibitors for hypertension, ruling out bias by indication and documenting the specificity of the effect on β-blockers.

β-blockers are widely used worldwide in the treatment of hypertension and congestive heart failure, and are recommended for hypertension by several national guidelines (e.g. The European Society of Hypertension and Cardiology). Other guidelines, including the National Institute for Health and Care Excellence (NICE) and American Society of Hypertension/International Society of Hypertension (ASH/ISH), only recommend β-blockers when other options have not been sufficiently effective [12]. This stems from studies claiming β-blockers to be less effective than other classes in preventing stroke or other cardiovascular events, and also causing multiple adverse effects such as fatigue, sexual dysfunction, reduced exercise tolerance, and increased incidence of new-onset diabetes [12, 13].

In a recent study from Taiwan, the association between different antihypertensive agents and Parkinson's disease was sought [14]. Because the focus of that study was on the effects of calcium channel blockers (CCBs), the authors, assuming that β-blockers do not confer an increased risk for Parkinson's disease, used β-blockers as a reference group. Of interest, the CCBs amlodipine and felodipine were interpreted to have a 'protective effect' compared with β-blockers. In the context of the present new data, the Taiwanese study indirectly supports our present results, suggesting an increased risk of Parkinson's disease with β-blockers. A recent study has also shown that β2-adrenoreceptor agonists downregulate this gene, decreasing the apparent risk of Parkinson's disease by up to 40% among exposed people in Norway. In contrast, exposure to the β-blocker propranolol was associated with an increased morbidity hazard for Parkinson's disease [4]; however, that study did not adjust for confounders known to affect the risk for Parkinson's disease, such as smoking status, cholesterol levels, and use of statins [4].

Another study confirmed the use of propranolol increased the risk of Parkinson's disease [6], while another study found no such effect of propranolol after adjusting for primary tremor [7]. None of the existing studies have addressed a possible threshold effect in terms of cumulative dose and length of exposure to β-blockers.

The emerging molecular genetic evidence on the mechanism of action of β-blockers in promoting the accumulation of Lewy bodies in Parkinson's disease [4] renders the association shown by us between β-blockers and the risk of Parkinson's disease a potential causative role in the pathogenesis of Parkinson's disease. Overall, an estimated 26.4% of Americans over 60 years of age are treated with β-blockers [15]. In 2012, 20–24% of Americans were older than 60 years of age, translating to approximately 70 million people [16].

Assuming the mean population incidence of Parkinson's disease at age 60 years is 1%, if β-blockers increase this rate by 50% then this would translate to an additional 350,000 new cases of Parkinson's disease per year in the US [17].

In an attempt to identify a cumulative dose safety threshold for β-blockers, as related to Parkinson's disease, it became apparent that the safe dose is extremely low, at a mean DDD of 0.15 and a mean cumulative DDD of 0.9. These doses are not effective for most patients with hypertension or congestive heart failure. Patients receiving ACE

Table 2 Hazard ratio of Parkinson's disease as a function of lag time[a]

PD starting in 2006 [nBB = 24,608, BB = 23,317]	PD starting in 2008 [nBB = 24,608, BB = 23,295]	PD starting in 2010 [nBB = 24,608, BB = 23,317]	PD starting in 2012 [nBB = 24,608, BB = 23,317]
HR 1.7 (95% CI 1.2–2.39; $p=0.03$)	HR 1.86 (95% CI 1.26–2.74; $p=0.003$)	HR 1.84 (95% CI 1.11–3.07; $p=0.02$	HR 1.7 (95% CI 1.05–2.8; $p=0.05$)

nBB non-β-blockers, *BB* β-blockers, *PD* Parkinson's disease, *HR* hazard ratio, *CI* confidence interval

[a]Matched over all parameters

inhibitors, but not β-blockers, were no different in their Parkinson's disease morbidity hazard than the general population (HR 1.13, 95% CI 0.54–2.35).

The limitations of our study need to be acknowledged. Patients may leave the data set before the end of the analysis period due to death, having left Maccabi Health Services, or for other reasons. We therefore employed two survival models in our analysis. The Kaplan–Meier model estimates a survival function based on matched data, while the Cox proportional hazard model is a regression model that can take into account additional covariates.

In our data, the diagnostic codes of Parkinson's disease and primary tremor were entered by neurologists after examining and following-up these patients. It is extremely unlikely that a diagnosis of primary tremor or other tremor would be sustained over time in patients with genuine Parkinson's disease. Even if, in a rare event, we excluded a genuine case of Parkinson's disease as being primary tremor, this would theoretically bias the results toward the null and would decrease the signal of Parkinson's disease caused by β-blockers. The accuracy of diagnosis is always an issue in these studies, however it is unlikely that there is bias in the sensitivity and specificity of Parkinson's disease diagnosis between the group receiving β-blockers and those not receiving this class of drugs. Because ACE inhibitors are widely used medication class for hypertension, in an attempt to examine an association between their use and the incidence of Parkinson's disease, the question of confounding by indication had been partially answered. Clearly, to fully answer this question more matching would be needed.

By excluding patients who took β-agonists, mainly patients with asthma, we may have enriched the sample of non-smokers; however, this should not create a bias as smoking status was a measured variable that was adjusted for in the analysis.

The lag time from exposure to a β-blocker to diagnosis of Parkinson's disease did not affect the HR, ruling out a reverse causation.

5 Conclusions

Chronic use of β-blockers confers an increased risk for Parkinson's disease. In view of the available alternatives for β-blockers, their chronic use should be carefully re-evaluated.

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Author Contributions GK and GN contributed to the conception and design of the study; GN, KR, VS, and GK contributed to the acquisition and analysis of the data; and GK and GN contributed to drafting the text and preparing the figures.

Compliance with Ethical Standards

Funding No sources of funding were used to conduct this study.

Conflict of interest Gideon Koren, Galia Norton, Kira Radinsky and Varda Shalev have no potential conflicts of interest to report.

Data availability Anonymized data will be shared upon reasonable request from any qualified investigator, pending approval from Maccabi Health Services and the Assuta Research Ethics Committee.

Ethical approval All procedures in this study were in accordance with the 1964 Helsinki declaration and its amendments, and the study was approved by the Assuta Ethics Committee.

Informed consent As this study is based on anonymous data, the committee waived informed consent.

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