

## Parkinson's disease, treatment choice and survival over time

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### ABSTRACT

**Objectives:** We compared Monoamine oxidase B (MAO-B) – and dopamine agonist (DA) monotherapy patients with respect to survival, considering gender, age, first prescriber's specialty and relevant co-morbidity, and compared their specialist health care contacts and hospitalizations.

**Methods:** With data from health registries, we considered 21,047 patients without redemptions for MAO-B, DA or levodopa 6 months prior to their first MAO-B or DA redemption in 2006 and followed them throughout 2016. We considered Cox proportional hazard regression models for comparing the risk of death among MAO-B and DA monotherapy patients.

**Results:** MAO-B-users had a higher mortality than DA-users, [HR: 1.587, 95% CI: 1.056; 2.384] for patients under 74 years. There was an increased mortality risk with increasing age, women had lower risk than men and previous diabetes-, antihypertensive-, and cardiac drug users had higher risk compared to patients without such history. Previous use of hypothyroid drugs and having a specialist as first prescriber were not significant risk factors.

Among patients without hospitalizations 13.7% died, while among patients who spent at least one night in hospital 36.73% died. The median duration of a hospitalization among those who died and not were 17.5 and 7 days. Among the small proportion with specialist health care contacts circulatory- and respiratory-system diseases were the most frequent cause of contact.

**Conclusions:** DAs were most frequently given when initiating Parkinson's treatment. DA-users had a lower mortality risk compared to MAO-B-users and less specialist health care contact.

### 1. Introduction

Parkinson's disease is a progressive neurodegenerative disorder with decreased dopamine production in the basal ganglia due to degeneration of dopamine-secreting neurons. After Alzheimer's Parkinson's is the second most common neurodegenerative disease [1]. Treatment, aimed to improve symptoms, usually involves use of monoamine oxidase-B inhibitors (MAO-B), dopamine agonists (DA) and levodopa, alone or in combination. Previous analyses provided a ranking of these drugs with respect to effect and side effects, but there is not one standard treatment guideline [2–6]. Levodopa is regarded the most effective drug, but long-term use often results in disabling fluctuations and dyskinesias [7] and may wear off after long-term use [8]. Levodopa treatment can be delayed by starting monotherapy with MAO-B- or DA treatment [9], and neurologists advocate such strategies [10]. This is especially relevant for younger patients with slower disease progression and at risk for earlier levodopa-induced motor complications [11].

This study was part of the project "Pharmacotherapy – comparative effects and new targets". We have previously studied when newly initiated MAO-B (selegiline, rasagiline or safinamide) and DA (cabergoline, pramipexole, rotigotine or ropinirole) monotherapy patients add

on levodopa to their treatment [12].

The aim of this study was to examine Norwegian patients initiating MAO-B inhibitor and dopamine agonist treatment as monotherapy during the 10 years period from 2006 to 2016 and assess their survival over time with the use of national data from official health registries. We also considered how the patients differed with respect to age, gender, geographic localization, co-morbidity and co-medication. Hospitalizations and contacts with specialist health care during treatment was also assessed.

### 2. Methods

#### 2.1. Primary research questions

The primary focus was to compare newly initiated MAO-B- and DA monotherapy patients with respect to survival, adjusting for relevant risk factors such as gender, age, first prescriber's specialty and relevant co-morbidity, and compare the specialist health care contacts for the two groups. A secondary goal was to examine patients who added levodopa to MAO-B- or DA treatment with respect to survival and specialist health care contacts.

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## 2.2. Data collection

This was an observational prescription registry study. We extracted data on prescription fulfillments from The Norwegian Prescription Registry (NorPD) [13] and linked these with specialist health care contact information from The Norwegian Patient Registry (NPR) [14].

## 2.3. Study population

We considered patients without any redemptions for MAO-B, DA or levodopa 6 months prior to their first redemption of MAO-B or DA (index date) in 2006, making the first possible index date July 1, 2006. We included these patients, 50 years or older at index date, and followed them until death or through 2016; altogether 21,047 patients of whom 3618 (17.2 %) died during the study period. In an additional analysis, we also considered the 1911 MAO-B-and DA-monotherapy patients who initiated levodopa treatment during follow-up. In the latter group, 21.4 % (408) died during the study period.

We obtained information regarding redemptions for diabetes-, -hypothyroid, antihypertensive-, and cardiac drugs as markers of relevant diseases. We considered age, gender and prescribers' specialty (general practitioner or specialist). We obtained information on benzodiazepines-, antidepressants-, and opioids-redemptions to study the patient's general well-being throughout the study period. For details on the data preparation procedure, see supplementary Table A1. The Anatomical Therapeutic Chemical (ATC) Classification codes for drugs redeemed are given in supplementary Table A2.

We considered the International Classification of Diseases (ICD)-10-codes for all specialist health care contacts and hospitalizations. As NPR only contain data from 2008 all findings relating to specialist health care contacts, including cause of death, is therefore given for those patients initiating MAO-B- and DA-treatment in 2008 or later.

## 2.4. Protocol approval

NorPD and NPR released the data by approval from the Regional Committee for Medical and Health Research Ethics [15], project number 2017/1833.

## 2.5. Statistical analysis

In an exploratory analysis we found the proportional hazards assumption satisfied for the optimal models for the three cohorts: 1) all patients below 74 years old, 2) men 74 years or older and 3) women 74 years and older, see Table A3 in the supplementary material.

We drew Kaplan-Meier plots displaying patients' survival within risk factor groups. We conducted Cox proportional hazard regression analyses for time to death. We specified a model including all risk factors, applied an automatic model selection procedure based on the Akaike information criterion for model evaluation [16,17], for optimal model

fitting always including the monotherapy specification, and obtained hazard ratios for different risk factor levels applying a 5% significance level. We conducted the analysis in the statistical software R [18].

We tested the proportional hazards assumption for our fitted cox regression models. For those who died during the study period we examined their cause of death based on specialist health care contact information. We also examined hospitalizations with corresponding length of stay and diagnoses.

## 3. Results

Table 1 displays cohort features with respect to gender, age, previously redeemed drugs, first prescribers' specialty and Parkinson's drug treatment for the three cohorts. More patients initiated DA-treatment compared to MAO-B-treatment. In the younger age group, the MAO-B-users encompasses 1.7% (228) of the patients, while 98.3% (13,490) were DA-users, and among those who died and survived during the study period, 2.3 and 1.6% were MAO-B-users respectively. Among those who died, 48.9% were men while the survival group encompassed 38.8% men. The survival group encompassed generally younger patients. A greater proportion of patients had previously used diabetes drugs, antihypertensive drugs and cardiac drugs in the group who died compared to the survival group, with 17.8, 20.0 and 44.4% compared to 9.5, 11.0 and 28.5%. Proportions with previous hypothyroid drug use were 10.5 and 11.7% in the dead and survival group, respectively. Among those who died, only 0.4% had a specialist first prescriber, while the corresponding number among those who survived was 1.2%. The median number of observed days on MAO-B- or DA monotherapy among those who died was 1,295 compared to 1,948 for those who survived the observation period. In the two elder cohorts the proportion of MAO-B-users were 2.8% (69) (men) and 1.1% (55) (women). These cohorts had a smaller difference between the survival and non-survival groups with respect to previous diabetic, antihypertensive and cardiac drug use, and the group of women was somewhat older than the group of men.

In the study period the median number of observed days for the MAO-B-users was 924 days and the median time to death was 903 days, while the corresponding numbers for DA-users were 1,737 and 1,288 days, respectively. All over the number of deaths per 1000 patient years was 72.98 among MAO-B-users and 34.43 among DA-users. A density plot of days under observation for the two user groups for all patients and a separate plot for those who died are given in Fig. S1 in the supplementary material. This shows the clear difference in observational time for the two groups, but also a more similar profile for the observational time among those who died. Considering the fraction of new users in the years 2006–2016 we found relatively few new MAO-B users the first years. During the first two years only 12.1% of all the MAO-B users initiated their treatment, while the corresponding number for the DA users was 21%. Considering the last two years 2015 and 2016 we found that 35.2% of the new MAO-B users then initiated their treatment, while the corresponding number for new DA users was only 19%.

**Table 1**

Cohort features with respect to gender, age, previously redeemed drugs, first prescribers' specialty and Parkinson's drug treatment for the three cohorts, summary statistics, percentages for those who survive and die during the study period.

	Both genders, <74 years		Men, ≥74 years		Women, ≥74 years	
	Survived (n = 12656)	Died (n = 1062)	Survived (n = 1451)	Died (n = 1026)	Survived (n = 3322)	Died (n = 1530)
Men	38.8	48.9	100	100	0	0
Age*	61.9(6.6)	65.3(6.1)	79.7(4.5)	82.7(5.2)	80.5(5.1)	83.8(5.5)
Diabetes drugs	9.5	17.8	11.8	13.5	8.4	9.8
Hypothyroid drugs	11.7	10.5	7.8	7.9	19.5	17.3
Antihypertensive drugs	11.0	20.0	21.2	26.4	18.3	25.7
Cardiac drugs	28.5	44.4	65.1	70.0	50.3	60.7
First prescriber specialist	1.2	0.4	0.9	1.1	0.7	0.5
MAO-B monotherapy users	1.6	2.3	2.3	3.5	0.9	1.7
Days observed*	1946(1171)	1410(967)	1600(1120)	1242(892)	1771(1139)	1480(931)

\* mean (standard deviation).

Kaplan-Meier plots display the surviving fraction of patients over time for men versus women, age groups (age at index date), MAO-B versus DA users, previous use of diabetes-, hypothyroid-, antihypertensive- and cardiac-drugs versus no such use and first prescriber being a specialist versus general practitioner for the younger age group (Fig. 1). Similar plots for the two elder age groups are given in the supplementary material (Figs. S2 and S3).

Considering the results from the fitted Cox proportional hazard regression models, Table 2, MAO-B-users had a higher mortality risk compared to DA-users with a hazard ratio (HR) of 1.587 [95% confidence interval (CI): 1.056;2.384], 1.863 [CI:1.335;2.599] and 2.505 [CI:1.696;3.699] for the younger (<74 years), elder (≥74 years) men and elder women age groups, respectively. In the younger age group women had lower mortality risk compared to men [HR: 0.6492 CI:0.612;0.782]. There was an increased mortality risk with increasing age for the younger, elder men and elder women age groups [HR:1.08, CI:1.069;1.091, HR:1.11, CI:1.097;1.123, HR:1.11, CI:1.1;1.12], respectively.

Previous diabetes-, antihypertensive-, and cardiac drug users had all higher risk of dying compared to patients without such history (younger age group [HR:1.659, CI:1.405;1.959, HR:1.427, CI:1.215;1.678, HR:1.462, CI:1.282;1.667], elder men [HR:1.461, CI:1.217;1.754, HR:1.322, CI:1.146;1.525, HR:1.227, CI:1.07;1.408] elder women [HR:1.429, CI:1.203;1.697, HR:1.525, CI:1.355;1.716, HR:1.406, CI:1.265;1.563], respectively).

Previous use of hypothyroid drugs was not a significant risk factor. Having a specialist as first prescriber indicated a reduced mortality risk among the younger patients [HR:0.338, CI:0.126;0.903].

Considering all patients; among MAO-B-users, 23.0% (18) used benzodiazepines, 9.7% (34) used antidepressants and 8.2% (29) used opioids during the study period, while the corresponding numbers for DA-users were larger: 37.6% (7776), 16.1% (3330) and 12.3% (2546)

respectively. Comparing the proportion using these drugs among those who died gave similar results; among MAO-B-users 55.3, 19.2 and 25.5% used benzodiazepines, antidepressants and opioids respectively and the corresponding numbers for the DA-users who died were 54.8%, 17.7% and 27.5% respectively.

Among patients who initiated Parkinson-treatment from 2008 and onwards (16793 patients) we found that 354 patients had at least one specialist health care contact and 196 had at least one hospitalization during the observation period, the latter of whom 28.1% (55) were MAO-B-users of whom 65.5% (36) survived, and 71.9% (141) were DA-users of whom 62.4% (88) survived.

Among patients without hospitalizations (16597 patients) 13.67% died, while among patients who spent at least one night in hospital (196 patients) 36.73% died. Among patients with hospitalizations the average percentage of days in the observation period hospitalized were 1.5% (median 0.7%) among MAO-B-users and 2.502 (median 0.845%) among DA-users. Among surviving patients (14,452) only 0.9% (124) were hospitalized one day or more, while the corresponding proportion of patients among those who died (2,341) was 3.1% (72). The average number of days hospitalized during the observation period were 11.4 (median 7) among those who did not die and 27.3 (median 17.5) among those who died. A small percentage of the patients had specialist healthcare contacts (Table 3), with diseases of the circulatory and respiratory system and Injury and external causes of morbidity and mortality as frequent causes. If we also consider patients adding-on levodopa treatment, the numbers in Table 3 become quite higher, see supplementary Table A4.

Altogether 92 patients died in 2006 or 2007, prior to the initiation of NPR, and hence we do not know their cause of death. To indicate cause of death among those who died during 2008 or later we examined hospitalizations 30 days prior to death. This encompassed 69 patients, where 21 died of lung disease, 12 of cancer, 10 of cardiovascular

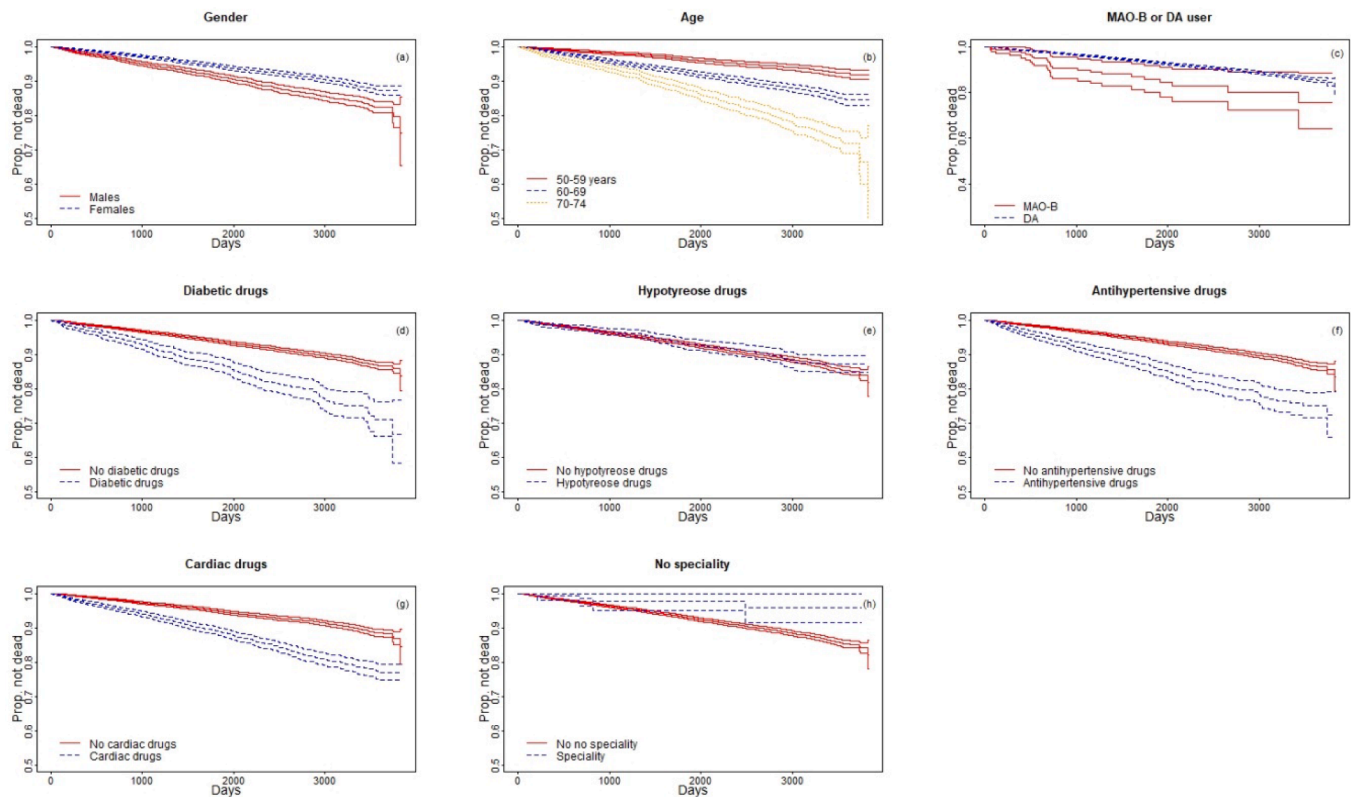


Fig. 1. Kaplan-Meier-plots: The surviving fraction of patients over time for men versus women, age groups (age at index date), MAO-B versus DA users, previous use of diabetes-, hypothyroid-, antihypertensive- and cardiac-drugs versus no such use and first prescriber being a specialist versus general practitioner for the younger age group (all patients <74 years). Similar plots for the two elder age groups are given in the supplementary material (Figs. S2 and S3).

**Table 2**

The results fitting the Cox proportional hazard regression models, time to death (baseline in parenthesis).

	Both genders, <74 years		Men, ≥74 years		Women, ≥74 years	
	HR (CI)	P-value	HR (CI)	P-value	HR (CI)	P-value
Women (men)	0.692 (0.612,0.782)	<0.001				
Age*	1.08 (1.069,1.091)	<0.001	1.11 (1.097,1.123)	<0.001	1.11 (1.1,1.12)	<0.001
Diabetes drugs (none)	1.659 (1.405,1.959)	<0.001	1.461 (1.217,1.754)	<0.001	1.429 (1.203,1.697)	<0.001
Hypothyroid drugs (none)		<0.001			0.904 (0.791,1.032)	0.134
Antihypertensive drugs (none)	1.427 (1.215,1.678)	<0.001	1.322 (1.146,1.525)	0.004	1.525 (1.355,1.716)	<0.001
Cardiac drugs (none)	1.462 (1.282,1.667)	<0.001	1.227 (1.07,1.408)		1.406 (1.265,1.563)	<0.001
First prescriber specialist (GP)	0.338 (0.126,0.903)	0.031				
MAO-B monotherapy users (DA)	1.587 (1.056,2.384)	0.026	1.863 (1.335,2.599)	<0.001	2.505 (1.696,3.699)	<0.001

\* linear age.

**Table 3**

A summary of the number of patients with registered ICD-10 codes for each specialist health care contact; percentage (number) of MAO-B- and DA monotherapy patients who initiated Parkinson treatment from 2008 and onwards and had ICD-10 code registrations A-X in their study period (out of 307 and 16,486 patients respectively).

ICD-10	Description	All contacts resulting in hospitalization		All specialist health care contacts	
		MAO-B	DA	MAO-B	DA
ABU	Infections, Resistance*	0.65 (2)	0.1 (17)	0.65 (2)	0.1 (17)
C	Cancer	2.28 (7)	0.11 (18)	2.28 (7)	0.11 (18)
D	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	0.65 (2)	0.05 (8)	0.65 (2)	0.05 (8)
E	Endocrine, nutritional and metabolic diseases	0.65 (2)	0.05 (9)	0.65 (2)	0.05 (9)
F	Mental and behavioral disorders	0.98 (3)	0.05 (9)	0.98 (3)	0.05 (9)
G	Diseases of the nervous system	3.26 (10)	0.18 (30)	3.26 (10)	0.18 (30)
H	Diseases of the eye and adnexa	0.98 (3)	0.01 (2)	0.98 (3)	0.01 (2)
I	Diseases of the circulatory system	4.56 (14)	0.24 (40)	4.56 (14)	0.24 (40)
J	Diseases of the respiratory system	3.91 (12)	0.21 (34)	3.91 (12)	0.21 (34)
K	Diseases of the digestive system	3.58 (11)	0.14 (23)	3.58 (11)	0.14 (23)
L	Diseases of the skin and subcutaneous tissue	0.33 (1)	0.03 (5)	0.33 (1)	0.03 (5)
M	Diseases of the musculoskeletal system and connective tissue	3.26 (10)	0.07 (11)	3.26 (10)	0.07 (11)
N	Diseases of the genitourinary system	2.28 (7)	0.14 (23)	2.28 (7)	0.14 (23)
Q	Congenital malformations, deformations and chromosomal abnormalities	0 (0)	0.01 (1)	0 (0)	0.01 (1)
R	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	4.23 (13)	0.16 (27)	4.23 (13)	0.16 (27)
STWVYX	Injury and external causes of morbidity and mortality	4.23 (13)	0.23 (38)	4.23 (13)	0.23 (38)

\* U82-U85 Resistance to antimicrobial and antineoplastic drugs (one case).

diseases, 10 of accidents, 4 of infections, 3 of abnormal laboratory findings, 3 of gastrointestinal disease, 2 of metabolic disease, 2 of neurological disease, 1 of skin disease, 1 of diseases of the genitourinary system, and thereby 3457 of other causes. When considering the levodopa add-on patients, these numbers increase, for details see supplementary Table A5.

#### 4. Discussion

It is well established that Parkinson's patients have a higher risk for death compared to the general population, but to our knowledge, the risk of death for patients using different treatment options has not been compared in detail. The main finding was that DA-users had a lower risk for death compared to MAO-B-users. This was clear also when accounting for relevant demographic variables (age, gender) and several illnesses (co-morbidity).

The MAO-B-users amounted to only 1.7%, and hence DA seems to be the clearly preferred initiating treatment for new Parkinson patients. This may reflect the prescriber's preferences when initiating anti-parkinson therapy, as also pointed out in Bide et al. [12]. A 2009 Cochrane report of two studies concluded that MAO-B inhibitors were less effective than DA, but they had less side effects than some DAs [19]. The decision to initiate treatment is based on the type and severity of symptoms and the patients all over health situation. One could speculate whether more fragile patients were given the drug class with assumed fewer side effects. From the given comorbidity factors, we could not conclude that one patient group was more severely ill than the other. Still, we did not have any detailed knowledge regarding the patients' health situation. It is possible that unknown patient characteristics regarding patients' health situation not accounted for in our analysis could explain the found differences. Considering the various diagnoses in NPR there were in general greater proportions of patients with specialist health care contacts among the MAO-B users compared to the DA users, supporting the possible explanation discussed above.

We found few studies comparing survival among MAO-B and DA monotherapy users. One exception is the Cochrane report [19] who also found a higher risk of death among MAO-B versus DA users, but not significant [odds ratio:1.30, CI:0.69;2.45] [19]. A study comparing MAO-B and DA versus levodopa initial treatment found no significant difference in death when initiating levodopa compared to MAO-B or DA treatment but does not report a comparison between MAO-B and DA treatment with respect to death [20]. Hence, their finding with respect to the latter comparison is unknown. A reason for few studies on this theme might be that most patients over time include additional drugs to their initial treatment, and hence differences in treatment regimens diminish over time [21]. This add-on drug practice makes it difficult to compare patients on each of the drugs (DA, MAO-B or levodopa) over time, and hence our study gives valuable information on the initial treatment of Parkinson's' patients.

The risk of death increased with age. Among the younger patients, women had a lower risk for death compared to men. Previous use of diabetes-, antihypertensive- and cardiac drugs were all associated with increased risk for death compared to no such previous use.

We have in this analysis compared two very different user groups: the small MAO-B-user group versus the large DA user group, where a greater fraction of the MAO-B-users initiated their treatment later in the observation period compared to the DA-users. Why MAO-B was relatively more frequent initiated in the later years is unknown to us. But we do notice that the MAO-B drug safinamide was approved in Europe in



2015, and this might explain some of the increased MAO-B drug use over time. This corresponds well to the finding that among new MAO-B users 35.2% initiated their treatment in 2015 or 2016 while the corresponding number for new DA users was only 19%. Although the median observed days was very different between the two user groups, we found the difference to be much smaller among those who died during the observation period. Our findings on Norwegian patients might differ from findings in other countries, and countries may differ with respect to both initial drug choice and initial combination drug practice.

Another finding was that overall, relatively few patients had specialist health care contacts during the study period. Hence, a general practitioner treated the majority, without the need of specialist health care contacts. Hence, Parkinson patients on monotherapy treatment are relatively healthy patients, who only to a small degree burden the specialist health care system.

Relatively few of the patients without hospitalization died, 13.7%, compared to those who spent at least one night in hospital of whom 36.7% died. The average percentage of days hospitalized during the observation period was much higher among those who died compared to those who did not die, as expected. Patients with hospitalizations had in general more underlying medical conditions and had an increased risk of death. Among patients with specialist health care contacts, both who survived and not, we found a large proportion having circulatory- and respiratory-system diseases, in accordance with previous findings [22,23].

Including patients who initiated add-on levodopa treatment revealed a greater proportion with specialist health care contacts and poorer survival odds during the study period. This seems reasonable as patients who initiate combination treatment with more antiparkinsonian medication likely experienced deterioration in their disease.

We have assumed that initiating MOA-B- and DA-treatment defines new Parkinson patients and that they continue to use their chosen treatment throughout the study period.

As a population-based analysis, there was no observational bias. However, we only compared choice of therapy and not the redemption frequency or patients' dose level. A study focusing on patients' dose level over time might provide further insight. However, this is a more complex task, and a subject for future research.

We have assumed that previous redemptions for diabetes-, -hypothyroid, antihypertensive-, and cardiac drugs indicated such diseases. We believe this to be reasonable, but we did not have the diagnosis as given by a general practitioner or specialist to confirm this assumption.

The MAO-B rasagiline was approved in 2006. Presumably many MAO-B-users early on used other MAO-B-drugs, such as selegiline, as it can take some time before doctors start prescribing new drugs. We don't know how this affects the MAO-B versus DA mortality comparison.

This analysis does not consider the medications efficacy, reported as for example the unified Parkinson's disease rating scale, nor side effects. Health registries data do not contain such information. However, we have focused on survival and hospitalizations for intercurrent diseases, which we can relate to the patient's quality of life and in a wider perspective to be interpreted as a partly indicator of medication effect.

## 5. Conclusion

DA-treatment seems to be the preferred drug choice when initiating treatment for new Parkinson patients. DA-users had a considerably lower risk for death compared to MAO-B-users. All over, only a small proportion of the patients had specialist health care contacts during the study, but among patients who had contact, both who survived and not, circulatory- and respiratory-system diseases were the most frequent cause of contact. It is still important to note that the MAO-B group was small, and we welcome comparative studies from other countries.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgment

We acknowledge NorPD and NPR for their helpful service in providing the data.

## Dedication

This paper is dedicated to the memory of Professor Bent Natvig, a true mentor, colleague and co-writer of two previous papers comparing the effect of Parkinson's drug choice with respect to effects and side effects.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.prdoa.2022.100136>.

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