ENTACAPONE DOES NOT INCREASE PROSTATE CANCER RISK OR MORTALITY IN PATIENTS WITH PARKINSON'S DISEASE

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The study has been registered in the ENCePP E-register of Studies.
For detailed information about the whole study, please visit: www.encepp.eu

BACKGROUND

The association between Parkinson's disease (PD) and prostate cancer (PCA), both common in elderly men, is disputable. In the STRIDE-PD study, prostate cancer developed in 9 patients (3.7%) receiving levodopa/carbidopa with entacapone (a catechol-O-methyltransferase inhibitor) versus 2 cases (0.9%) not receiving entacapone[1].

AIM

This pharmacoepidemiological study aimed to examine whether entacapone increases prostate cancer incidence or mortality in PD patients and if cumulative exposure affects these rates. This prompted the FDA to request a further investigation on entacapone use and potential PCA risk.

METHODS

Design: We performed a retrospective cohort study in Finland using population-wide health care registers with patient level linkage during 1998-2009. Treatment history was also validated for the years 1994-1997.

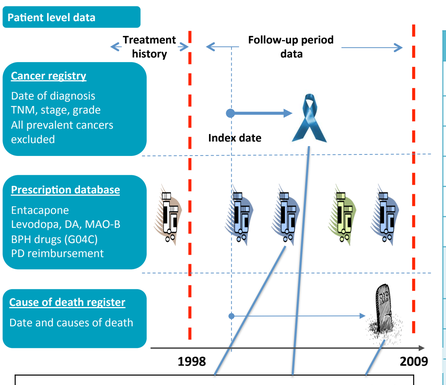
Data sources: Prostate cancer (ICD-O-3 C61) and other cancer cases, deaths and PD and benign prostatic hypertrophy (BPH) prescriptions obtained from the Finnish healthcare databases (Figure 1).

Population: Study cohort contained male patients who were entitled to special reimbursement for PD and who purchased (within 180 days before the start of follow-up) at least one prescription of levodopa/DDCI, dopamine agonist (DA), or monoamine oxidase B (MAO-B) inhibitor (Figure 2, Table 1). The follow-up started from the first date of new prescription of entacapone or another add-on therapy to levodopa/DDCI. Patients with any prior cancer were excluded.

Exposure: Drug exposure durations were estimated from the DDDs, with an additional exposure extension period of 30 days to avoid breaks between prescriptions. For comparisons, current exposure was defined by evaluating the membership of a patient to the following time-dependent exposure groups at any given time during the follow-up: current use of levodopa/DDCI with entacapone, current use of levodopa/DDCI without entacapone, and current use with no levodopa/DDCI exposure. Each patient could contribute follow-up time to these three groups during the study depending on current treatment status. Cumulative time-dependent exposure to each PD drug treatment was also calculated.

Statistical analyses: : The hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox's proportional hazards model with adjustments for relevant baseline and time-dependent variables. The robustness of the findings was evaluated in sensitivity analyses.

DATA SOURCES AND POPULATION



	Patients	PCA cases	PCA deaths
Current treatment			
G1 – with entacapone	4 404	78	11
G2 – without entacapone	10 613	205	41
G5 – other	10 331	76	37
Cumulative entacapone exposure			
No exposure	10 508	252	65
< 180 days	4 396	20	6
180 – 360 days	3 471	28	6
> 360 days	2 509	59	12

Abbreviations:
PCA: prostate cancer
G1: Levodopa/DDCI *with* entacapone +/- DA and/or MAO-B inhibitor
G2: Levodopa /DDCI *without* entacapone +/- DA and/or MAO-B inhibitor
G5: not G1 and not G2 at a given point during the follow-up

Figure 1. Data sources.

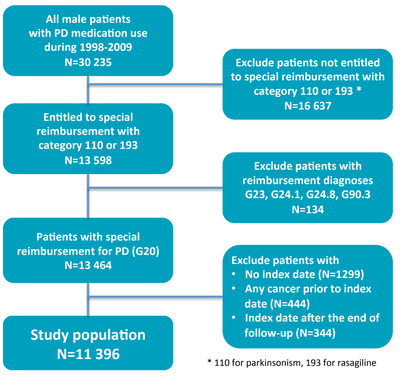


Figure 2. Study population – inclusion and exclusion criteria.

Table 1. Study population characteristics.

Variable	G1	G2	G5	Total
AGE - Mean (yrs)	71.6	70.6	72.6	70.1
YRS SINCE DIAGNOSIS				
0-1 yrs (%)	36.9	50.5	49.4	49.0
1-2 yrs (%)	16.2	11.3	8.5	11.3
2-5 yrs (%)	25.8	20.2	17.3	20.3
5-10 yrs (%)	13.3	12.5	15.6	13.0
> 10 yrs (%)	7.8	5.5	9.4	6.3
TREATMENT HISTORY				
Prior DA use (%)	18.5	25.3	11.6	22.5
Prior MAO-B inhibitor use (%)	19.6	42.6	37.8	39.5
Prior BPH drug use (%)	37.6	27.7	27.2	28.6
N	1 141	8 482	1 773	11 396

Abbreviations:
G1: Levodopa/DDCI *with* entacapone +/- DA and/or MAO-B inhibitor
G2: Levodopa /DDCI *without* entacapone +/- DA and/or MAO-B inhibitor
G5: not G1 and not G2 at a given point during the follow-up

RESULTS

Table 2. Background variables for PCA risk.

Variable		HR	95% CI	P-value
Age (yrs) vs. < 60 yrs	**60-64**	2.90	1.35-6.25	0.007
	65-69	3.83	1.87-7.83	<0.001
	70-74	5.30	2.65-10.59	<0.001
	75-79	5.70	2.85-11.44	<0.001
	80-84	5.49	2.68-11.28	<0.001
	85-99	5.72	2.63-12.44	<0.001
Time since PD diagnosis (yrs) vs. < 1 yr	**1-2**	0.90	0.64-1.27	0.551
	2-5	0.96	0.73-1.28	0.800
	5-10	0.75	0.52-1.07	0.117
	>10	0.72	0.44-1.17	0.187
DA before index date	**yes vs. no**	1.17	0.88-1.57	0.283
MAO-B before index date	**yes vs. no**	0.95	0.75-1.22	0.702
BPH drugs before index date	**yes vs. no**	0.56	0.40-0.76	<0.001
BPH drugs during follow-up vs. no	**<180 d before**	2.45	1.85-3.23	<0.001
	>180 d ago	1.22	0.85-1.78	0.263
Levodopa add-on*	**yes vs. no**	1.02	0.81-1.28	0.861
DA add-on*	**yes vs. no**	1.15	0.90-1.46	0.273
MAO-B add-on*	**yes vs. no**	0.93	0.58-1.49	0.776
Entacapone add-on*	**yes vs. no**	0.75	0.50-1.12	0.158
Cumulative exposure to				
Levodopa vs. < 180 d	**180-360 d**	0.73	0.45-1.19	0.208
	>360 d	0.84	0.50-1.42	0.521

*added within the previous six months

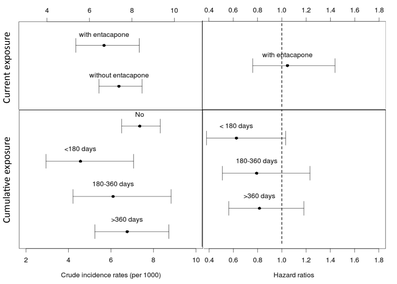


Figure 3. Analysis of PCA risk in different current and cumulative exposure groups.

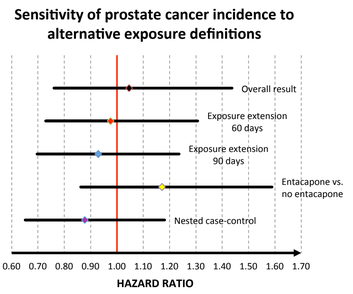


Figure 4. Sensitivity analyses.

CONCLUSIONS

- A total of 359 PCA cases occurred during a mean follow-up time of 4.6 years and 89 prostate cancer deaths occurred during a mean follow-up time of 4.7 years.
- The overall crude PCA rate was 6.91 per 1000 which is similar to the rate in the general population of the same age[2].
- Current exposure to treatment with levodopa/DDCI with entacapone was not associated with increased prostate cancer risk (HR 1.05 95% CI 0.76-1.44, p=0.78) (Figure 3) or an increased prostate cancer mortality (HR 0.93 95% CI 0.43-1.98, p=0.85) when compared to current treatment with levodopa /DDCI without entacapone.
- Cumulative exposure to entacapone during the follow-up was not associated with increased prostate cancer risk (Figure 3) or increased prostate cancer mortality.
- The results of the PCA incidence were found robust in various sensitivity analyses (Figure 4).
- In conclusion, we observed similar PCA rates in this PD cohort as in the general population of same age and found that prolonged entacapone use was not associated with increased PCA incidence or mortality.

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- http://www.encepp.eu/encepp/viewResource.htm?id=4463

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All data analysis and reporting was carried out according to the approved research protocol, amendments and the ENCePP Code Of Conduct.

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