RISK OF PARKINSON'S DISEASE (PD) IN PATIENTS TAKING BETA-ADRENERGIC DRUG TREATMENTS

Stacey J[1], Lovestone S[2], Harrison PJ[2], Denis M[2], Nevado-Holgado A[2], Newby D[2]
[1]TriNetX, Inc. Cambridge, MA, USA, [2]University of Oxford, Oxford, United Kingdom

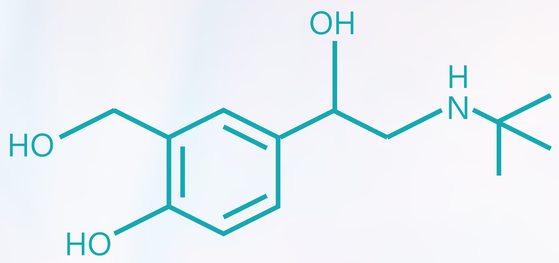
BACKGROUND

Parkinson's disease (PD) affects 0.1-0.2% of the general population, and up to 1% in individuals above 60 years of age, worldwide (1). PD is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and by the appearance of Lewy bodies—intracellular inclusions of aggregated α-synuclein (α-syn) which plays multiple roles in the pathogenesis of PD (2). A recent Norwegian study has shown that β2-adrenoceptors (β2AR) are linked to the transcription of α-syn and increased risk of PD, suggesting that they might represent novel targets for the development of anti-Parkinson's therapeutics (3).

OBJECTIVES

The purpose of this study was to replicate the retrospective observational Norwegian analysis which assessed the risk PD for two adrenergic drugs, salbutamol and propranolol, over 11 years in a global, real-world setting. This prior study found a greater risk of PD in relation to the β2AR antagonist propranolol, and a markedly lower risk of PD for the β2AR agonist salbutamol when compared to the general population [Fig 1]. The current study was expanded to explore risk of PD in broader β2AR antagonist and agonist exposure groups as well as over a longer index window of 20 years.

Salbutamol
(Reduced Risk)



Propranolol
(Increased Risk)

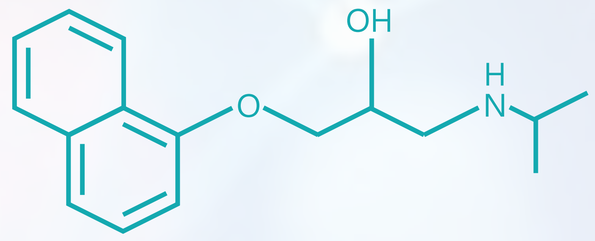


Figure 1. *Salbutamol use has shown a reduced risk of developing PD while the hypertension drug propranolol, which turns off β2AR, has shown an increased risk (4)*

METHODS

Data Source: Electronic medical records (EMR) of patients age ≥19 years receiving their first β2AR antagonist or agonist were evaluated using the TriNetX Analytics Network, a federated global health research network of ~39.6M patient lives as of October 2018.

Patient Cohorts: Four cohorts were compared to a derived control cohort. All cohorts had at least one year of medical history for evaluation, had no documentation of PD prior to the outcome windows, and never received the comparator drug(s) except for the control cohort that had no exposure to propranolol or salbutamol for the single-drug cohort comparisons and no exposure to β2AR antagonists or agonists for the drug class cohort comparisons.

1. Propranolol only.
2. Salbutamol only.
3. β2AR antagonists – any beta blocker as classified by RxNorm (which provides normalized names for clinical drugs and links its names to many of the drug vocabularies commonly used in pharmacy management and drug interaction software, including those of First Databank, Micromedex, Gold Standard Drug Database, and Multum).
4. β2AR agonists – all beta agonists as classified by the American Academy of Allergy, Asthma & Immunology (AAAAI).
5. Tylenol control – patients with acetaminophen documentation as a 'general population' comparator.

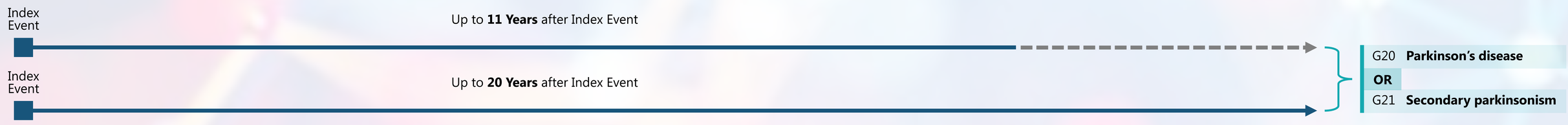


Figure 2. *Outcome windows and outcome parameters*

RESULTS

Cohort Comparisons

- Number of patients fulfilling each cohort eligibility criteria, gender, mean current age and mean index age provided in Table 1.
- Results for each cohort are grouped by the four analyses run—propranolol vs. control, salbutamol vs. control, all β2AR antagonist vs. control, and all β2AR agonists vs. control.
- Control cohorts were all larger in size to comparison cohorts.
- Propranolol only was the smallest comparator cohort; other beta blockers had higher patient counts in the data accessed.
- Gender, mean current age and mean index ages were comparable among cohorts analyzed together except β2AR antagonist vs. control cohorts with most significant differences in gender and both current and index ages.

Table 2. *Cohort results grouped by analysis*

Analysis	Cohorts	# of Patients	% Female	Mean Current Age +/- SD	Mean Index Age +/- SD
1	**Propranolol Only**	99,701	63%	53 +/- 18	47 +/-18
	Tylenol Control	2,557,899	58%	53 +/- 19	47 +/-19
2	**Salbutamol Only**	1,451,619	60%	55 +/- 19	49 +/- 19
	Tylenol Control	2,557,899	58%	53 +/- 19	47 +/- 19
3	**β2AR Antagonists**	1,276,009	50%	65 +/- 16	59 +/- 16
	Tylenol Control	1,808,763	61%	48 +/- 18	42 +/- 18
4	**β2AR Antagonists**	990,421	64%	49 +/- 18	43 +/- 19
	Tylenol Control	1,808,763	61%	48 +/- 18	42 +/- 18

3a & 3b: Propranolol vs. Control

a Measures of Association Excluding Patients with Outcome Prior to the Time Window

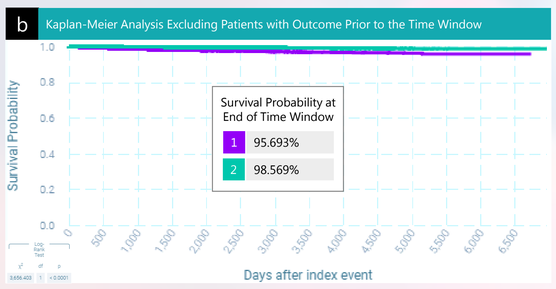
Cohort	Patients in Cohort	Patients with Outcome	Risk
1 Propranolol w/ age + 12 mo history + no salbutamol	93,211	1,641	1.761%
2 Tylenol Control Cohort	2,464,329	10,299	0.418%

Risk Difference	95 % CI	z	p	Risk Ratio	95 % CI	Odds Ratio	95 % CI
1.343%	(1.258%,1.427%)	59.026	< 0.0001	4.213	(4.4.436)	4.27	(4.052,4.5)

1,771 patients in Cohort 1 and 12,505 patients in Cohort 2 were excluded from results because they had they the outcome prior to the time window.
7,729 patients in Cohort 1 and 133,333 patients in Cohort 2 were excluded because they met the index event more than 20 years ago.

- Patients who took propranolol showed significant increased risk of PD over 20 years compared to control cohort (RR 4.213, 95% CI 4.0 to 4.436). Survival probability was significantly higher (p <0.0001) for control (98.569%) vs. propranolol (95.693%).
- These findings were similarly noted in the 11-year analysis—Risk 1.75% vs. 0.416%. (RR 4.205, 95% CI 3.99 to 4.429). Survival probability was significantly higher (p <0.0001) for control (98.961%) vs. propranolol (96.65%). [Not shown]

b Kaplan-Meier Analysis Excluding Patients with Outcome Prior to the Time Window



3c & 3d: Salbutamol vs. Control

c Measures of Association Excluding Patients with Outcome Prior to the Time Window

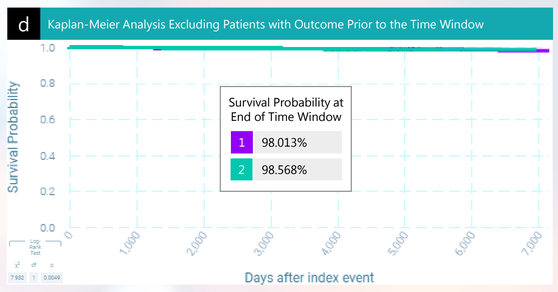
Cohort	Patients in Cohort	Patients with Outcome	Risk
1 Salbutamol w/ age + 12 mo history + no propranolol	1,359,626	6,153	0.453%
2 Tylenol Control Cohort	2,413,188	10,154	0.421%

Risk Difference	95 % CI	z	p	Risk Ratio	95 % CI	Odds Ratio	95 % CI
0.032%	(0.018%,0.046%)	4.518	< 0.0001	1.076	(1.042,1.11)	1.076	(1.042,1.111)

6,375 patients in Cohort 1 and 12,324 patients in Cohort 2 were excluded from results because they had they the outcome prior to the time window.
81,038 patients in Cohort 1 and 133,333 patients in Cohort 2 were excluded because they met the index event more than 20 years ago.

- Salbutamol patients compared to control cohort showed slight increased risk (risk difference 0.032%) of PD over 20 years compared to control cohort (RR 1.076, 95% CI 1.042 to 1.11). Survival probability was 98.568% for control vs. 98.013% salbutamol cohort (p <0.049).
- The 11-year analysis supported the 20-year results—Risk 0.448% vs. 0.416%. (RR 1.077, 95% CI 1.044 to 1.112). Survival probabilities were 98.961% for control vs. 98.966% for salbutamol (p <0.0018). [Not shown]

d Kaplan-Meier Analysis Excluding Patients with Outcome Prior to the Time Window



3e & 3f: β2AR antagonists vs. Control

e Measures of Association Excluding Patients with Outcome Prior to the Time Window

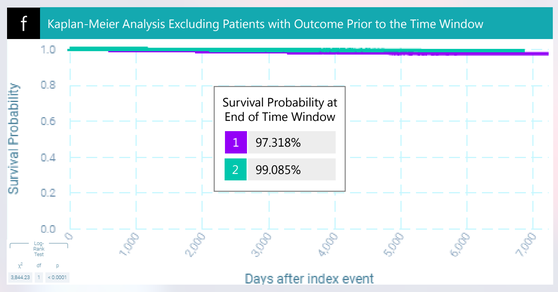
Cohort	Patients in Cohort	Patients with Outcome	Risk
1 b2antagonists w/ age + 12 mo history + no b2agonists	1,188,153	9,698	0.816%
2 Tylenol Control Cohort_b2 group comparator	1,714,540	4,818	0.281%

Risk Difference	95 % CI	z	p	Risk Ratio	95 % CI	Odds Ratio	95 % CI
0.535%	(0.517%,0.553%)	63.563	< 0.0001	2.905	(2.806,3.006)	2.92	(2.821,3.023)

9,603 patients in Cohort 1 and 6,410 patients in Cohort 2 were excluded from results because they had they the outcome prior to the time window.
79,699 patients in Cohort 1 and 93,036 patients in Cohort 2 were excluded because they met the index event more than 20 years ago.

- Patients on any β2AR antagonists had significant increased risk of PD over 20 years compared to control cohort (RR 2.905, 95% CI 2.803 to 3.006). Survival probability was significantly higher (p <0.0001) for control (99.085%) vs. β2AR antagonists (97.318%).
- Parallel evidence was observed from 11-year analysis results—Risk 0.806% vs. 0.278%. (RR 2.899, 95% CI 2.8 to 3.001). Survival probability was significantly higher (p <0.0001) for control (99.325%) vs. β2AR antagonists (98.109%). [Not shown]

f Kaplan-Meier Analysis Excluding Patients with Outcome Prior to the Time Window



3g & 3h: β2AR agonists vs. Control

g Measures of Association Excluding Patients with Outcome Prior to the Time Window

Cohort	Patients in Cohort	Patients with Outcome	Risk
1 b2agonists (+lth code) w/ age + 12 mo history + no b2antagonists	929,810	2,481	0.267%
2 Tylenol Control Cohort_b2 group comparator	1,714,540	4,818	0.281%

Risk Difference	95 % CI	z	p	Risk Ratio	95 % CI	Odds Ratio	95 % CI
-0.014%	(-0.027%,-0.001%)	-2.098	0.0359	0.95	(0.905,0.997)	0.949	(0.904,0.997)

2,701 patients in Cohort 1 and 6,410 patients in Cohort 2 were excluded from results because they had they the outcome prior to the time window.
59,214 patients in Cohort 1 and 93,036 patients in Cohort 2 were excluded because they met the index event more than 20 years ago.

- β2AR agonist patients compared to control cohort showed slight decreased risk (risk difference -0.014%) of PD over 20 years compared to control cohort (RR 0.95, 95% CI 0.905 to 0.997, p <0.0359). Survival probability was 99.085% for control vs. 99.157% β2AR agonist cohort (p <0.0001).
- Similar trends were also seen in 11-year analysis—Risk 0.264% vs. 0.278% (RR 0.949, 95% CI 0.904 to 0.996). Survival probability was higher (p <0.0001) for β2AR agonists (99.423%) vs. control (99.325%). [Not shown]

h Kaplan-Meier Analysis Excluding Patients with Outcome Prior to the Time Window

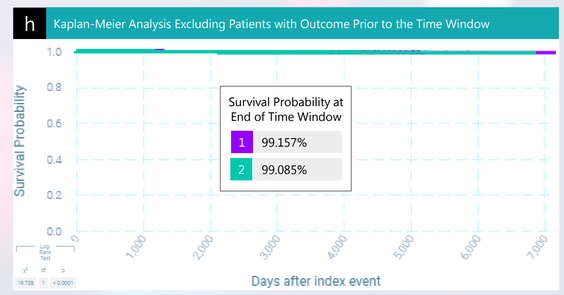


Figure 3. *Outcomes analyses*

CONCLUSIONS

- Our study was able to replicate the findings of Mittal et al, now with reproduced findings in a larger cohort with class effects and over a longer time frame.
- The results demonstrate that this is a class effect in relation to PD and not only specific to a compound such as propranolol or salbutamol.
- Current findings support the use of RWE/RWD/OHD analyses in drug development due to speed, efficiency, and reproducibility vs. data generated from costly and time-consuming randomized clinical trials (RCTs).

(1) Tysnes, OB & Storstein, A. "Epidemiology of Parkinson's disease." J Neural Transm (2017) 124: 901.
(2) Dehay, B et al. "Targeting α-synuclein for treatment of Parkinson's disease: mechanistic and therapeutic considerations." Lancet Neurol. 2015;14(8):855-866.
(3) Mittal, S et al. "β2-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease." Science (New York, N.Y.) vol. 357,6354 (2017): 891-898.
(4) Torrice, M. "Asthma Drugs May Reduce Parkinson's Risk." CEN RSS, 31 Aug. 2017, cen.acs.org/articles/95/i35/Asthma-drugs-reduce-Parkinsons-risk.html.

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