Description of Antiparkinsonian Drug Use in a US Medicare Claims Database: A Feasibility Assessment

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BACKGROUND

- Most epidemiologic studies examining the relation between Parkinson's disease and cancer indicate that patients with Parkinson's disease have an increased risk of developing malignant melanoma and other skin cancers, whereas they face a decreased risk of several other cancers.[1-3] The increased risk has been reported to range from about 2 fold[2] to 6 fold.[1] To date, the risk of melanoma in relation to the medications used to treat Parkinson's disease has not been formally investigated in population-based studies.
- Rasagiline is a monoamine oxidase type-B (MAO-B) inhibitor indicated as monotherapy in early-stage idiopathic Parkinson's disease and as adjuvant therapy with levodopa in more advanced stages of the disease. The drug was approved for use in the United States (US) in May 2006.
- At the Food and Drug Administration's request, a protocol for a safety study to be implemented using US Medicare data was prepared with the following objectives:
  - To estimate and compare the incidence rate of melanoma in patients with Parkinson's disease who start new treatment with rasagiline and those who start new treatment with nonrasagiline antiparkinsonian drugs (APDs).
  - To examine the association between use of rasagiline and malignant melanoma among patients with Parkinson's disease.
  - To compare the incidence rate of melanoma in patients with Parkinson's disease not treated with rasagiline with the rate in patients without Parkinson's disease.
- A feasibility study was begun in 2013 with available Medicare data to explore several areas of uncertainty regarding the size of the study population needed for the full-scale safety study and the time at which sufficient data would be available from Medicare to conduct the full-scale study.

FEASIBILITY STUDY OBJECTIVES

- To assess the feasibility of conducting the planned full-scale safety study and specifically the following:
  - To estimate the study size, in person-years of follow-up, needed to reach desired precision of the effect estimate (upper 95% of the rate ratio of melanoma in rasagiline users vs. nonrasagiline APD users < 2.0)
  - To estimate the number of additional years of Medicare data needed for accrual of sufficient person-years of exposure follow-up
  - To estimate the rate of incident melanoma cases in persons with Parkinson's disease treated with nonrasagiline APDs
  - To inform the study size and precision of the effect estimate by calculating the estimated claims-based rate of incident melanoma in persons with Parkinson's disease treated with nonrasagiline APDs and the rate after medical-record case validation (still ongoing, not reported here)

METHODS

Study Design

- Retrospective descriptive cohort study

Data Source

- US Medicare claims data available at the time of our request (2006-2011)
- Medicare database research identifiable files: detailed patient-level records of Medicare eligibility, demographics, and claims for services from hospitals, physicians, pharmacies, and other providers.
- Medicare is a federally sponsored health insurance program in the US with enrollment of approximately 54 million people, including 45 million aged 65 years and older.[4] Medicare beneficiaries make up approximately 15% of the total US population and include more than 98% of the US population aged 65 years or older.[5]
- After approval of the study by the RTI institutional review board and the Centers for Medicare and Medicaid Services (CMS) Privacy Board, and after execution of required data-use agreements, RTI Health Solutions (RTI-HS) researchers accessed Medicare data files through the CMS Virtual Research Data Center (VRDC).

Source Population

- Adults aged 65 years and older enrolled in Medicare Parts A, B, and D through a fee-for-service plan (not managed care plan) during 2006 to 2011, with at least one claim with an ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) code 332.0 (paralysis agitans–parkinsonism or Parkinson's disease: idiopathic, primary, or not otherwise specified)

Study Population

Inclusion Criteria

- During 2006 to 2011, have a first prescription claim (no prior recorded claims for this drug in the available electronic data) for rasagiline or other nonrasagiline APD (cohort entry date) and the first prescription claim date occurred after at least 6 months of continuous enrollment in Part D
- At least two physician or outpatient visit claims on separate dates or at least one inpatient visit with an ICD-9-CM code of 332.0 (operational definition of Parkinson's disease) on or before the cohort entry date
- Have been continuously enrolled in Medicare Parts A, B, and D through fee-for-service plan (not managed care plan) for at least 6 months before the cohort entry date

Exclusion Criteria

- All individuals with any claim with an ICD-9-CM diagnosis code of 332.1 (secondary parkinsonism: neuroleptic-induced parkinsonism, parkinsonism due to drugs) occurring at any point in time

Study Cohorts

- Cohort A: new users of rasagiline
  - Cohort entry date was the date of the first rasagiline dispensing. This "first use" was defined as no dispensing in the prior available claims history and was considered the index exposure.
  - Cohort A could include prevalent users of other APDs at the cohort entry date, as well as patients who were previously included in cohort B.
- Cohort B: new users of nonrasagiline APDs who had never previously used rasagiline
  - Cohort entry date was the date of dispensing of the first nonrasagiline APD (index exposure) that fulfilled the above cohort definition.
  - Cohort B could include prevalent users of other APDs, with the exception of rasagiline, at the cohort entry date.

Follow-up Time

- Follow-up time began at cohort entry date and ended on the earliest of the following:
  - Disenrollment from Medicare Part A, B, or D, or switch to a managed care plan
  - Date of death in Medicare records
  - End of study period (December 31, 2011)
- Additional events/dates for end of follow-up for cohort B were:
  - Date of first use of rasagiline
  - Date of the first occurrence of melanoma

Study Size

- Study size was estimated in the full-scale study protocol, dated October 16, 2012, and was based on low (146 per 100,000 person-years) or intermediate (292 per 100,000 person-years) assumed estimates for the incidence of melanoma in the nonrasagiline Parkinson's disease population (Table 1).
  - With these incidence estimates, a probability of 0.8, and a ratio of 4 nonrasagiline Parkinson's disease patients to 1 rasagiline Parkinson's disease patient, the following numbers of person-years of follow-up after the start of rasagiline will be needed: low incidence, 13,966; intermediate incidence, 6,973.
  - These estimates correspond to a total of approximately 100 observed cases of melanoma to obtain an 80% probability that the rate ratio will have an upper 95% confidence limit less than 2.0, assuming a rate ratio of 1.

Analysis

- Analyses were descriptive and included the following:
  - Description of characteristics of study cohorts
  - Tabulation of number of new users of rasagiline annually
  - Calculation of annual rate of loss to follow-up among eligible patients
  - Estimation of number of person-years of follow-up among rasagiline users and users of other APDs, for the overall study period and the number of years of follow-up beginning 3 years after cohort entry
  - Estimation of the impact of requiring a 12-month versus 6-month minimum baseline enrollment period on study size in both cohorts
  - Estimation of the impact on study size of excluding users of selegiline, a drug in the same class as rasagiline
  - Calculation of annual losses to follow-up among rasagiline initiators
  - Description of rasagiline utilization parameters
  - Description of APD use other than the index exposure at the cohort entry date

RESULTS

Characteristics of Study Cohorts

- Individuals in cohort A (rasagiline initiators) were, on average, 2 years younger than individuals in cohort B (nonrasagiline APD initiators) (Table 2).
- Compared with cohort B, cohort A had a higher proportion of males and a lower proportion of individuals with Medicare low-income subsidy status.
- Overall, 91% of individuals in cohort A and 57% in cohort B had used one or more APD other than the qualifying drug before cohort entry.

Estimated Follow-up Time and Study Size

- Annual losses to follow-up in cohort A averaged about 10% per year. Most losses were because of death. Only about 2% to 3% of patients annually switched to a managed care plan, and disenrollment in Medicare Parts A, B, or D was rare (≤ 1% of patients/year).
- In 2006, the year rasagiline was approved in the US, there were 1,714 new users. From 2007 through 2011, between 2,000 and 3,000 patients initiated rasagiline each year (Table 3).
- Overall, about 5% of individuals in cohort B initiated rasagiline during follow-up.
- Exclusion of selegiline users, a drug in the same class as rasagiline, at cohort entry resulted in the loss of about 10% of cohort A and 5% of cohort B (Table 3).
- With the currently available data through 2011, and using a 6-month baseline enrollment period, there were 30,672 total person-years of rasagiline follow-up, and 25,755 person-years if selegiline users were excluded to avoid a possible class effect (Table 3).
- Assuming the low estimate of melanoma incidence rate (146 per 100,000 person-years), as shown in Table 1, the study would require approximately 14,000 person-years of rasagiline follow-up to identify 100 melanoma cases, which would give an 80% probability of achieving the targeted precision. To ascertain 100 melanoma cases validated via chart review (with estimated 50% chart retrieval and 70% validation rate), it would be necessary have an estimated 40,000 (14,000/0.5/0.7) person-years of rasagiline follow-up.

Rasagiline Utilization Patterns

- On average, rasagiline initiators filled about 10 prescriptions for rasagiline during the follow-up period, with 24% having more than 500 total days of exposure (Table 4).
- At the cohort entry date, 88% of rasagiline initiators did not have concurrent use of another APD.

Table 1. Study Size Calculations for Probabilities of 0.8 and 0.9 to Detect a Rate Ratio With an Upper 95% Confidence Limit Less Than 2.0 From Full-Scale Study Protocol

Estimated Melanoma Incidence per 100,000	Probability	Ratio of Nonrasagiline to Rasagiline	Cohort Size in Person-Years		Total Number of Cases[a]
			Rasagiline	Nonrasagiline	
146	0.8	1:1	22,346	22,346	65
		2:1	16,760	33,520	73
		4:1	13,966	55,864	102
		10:1	12,291	122,910	197
	0.9	1:1	29,915	29,915	87
		2:1	22,437	44,874	98
		4:1	18,697	74,788	136
		10:1	16,454	164,540	264
292	0.8	1:1	11,157	11,157	65
		2:1	8,368	16,736	73
		4:1	6,973	27,892	102
		10:1	6,137	61,370	197
	0.9	1:1	14,936	14,936	87
		2:1	11,203	22,406	98
		4:1	9,336	37,344	136
		10:1	8,215	82,150	264

[a] Number of cases assuming the null hypothesis that the rate is the same in both groups.

Table 2. Characteristics of Study Cohorts at Entry Date

Variable	Cohort A N = 14,170		Cohort B N = 120,262	
	n	%	n	%
Age in years				
Mean (SD)	76 (6.5)		78 (7.2)	
Distribution in years				
65-69	2,837	20	16,482	14
70-74	3,505	25	21,678	18
75-79	3,535	25	28,127	23
80-84	2,781	20	28,274	24
85+	1,512	11	25,701	21
Sex				
Female	6,456	46	63,910	53
Male	7,714	54	56,352	47
Race				
White	12,943	91	105,882	88
Black	314	2	6,375	5
Asian	321	2	2,487	2
Hispanic	334	2	3,501	3
Other	247	2	1,864	2
Unknown	11	0	153	0
Geographic region of residence				
Midwest	3,031	21	32,892	27
Northeast	2,756	19	21,303	18
South	5,339	38	46,849	39
West	3,044	21	19,218	16
Low-income subsidy status				
Yes	3,518	25	53,461	44
No	10,652	75	66,801	56
Year of cohort entry				
2006[a]	1,714	12	14,989	12
2007	2,449	17	27,940	23
2008	2,075	15	23,420	19
2009	2,482	18	20,772	17
2010	2,734	19	17,564	15
2011	2,716	19	15,577	13
Prior use of APDs before cohort entry	12,959	91	68,889	57
History of selegiline[b] use on or before cohort entry date	1,473	10	6,388	5

[a] Rasagiline was approved in May 2006.

[b] Selegiline is an APD in the same class as rasagiline and was evaluated as a possible exclusion variable.

Table 3. Estimated Follow-up Time in Study Cohorts Using 2006-2011 Medicare Data

Variable	Cohort A		Cohort B	
	n	Person-Years	n	Person-Years
Requiring minimum 6-months baseline enrollment				
Index year				
2006	1,714	6,177	14,989	43,191
2007	2,449	8,139	27,940	76,276
2008	2,075	5,731	23,420	55,379
2009	2,482	5,406	20,772	38,867
2010	2,734	3,843	17,564	21,804
2011	2,716	1,375	15,577	7,224
Entire cohort	14,170	30,672	120,262	242,742
Excluding selegiline users[a]	12,697	25,755	113,874	224,210
Post 3-year follow-up entire cohort[b]	4,032	4,809	32,048	34,720
Post 3-year follow-up excluding selegiline users[a]	3,245	3,756	29,006	31,038
Requiring minimum 12-months baseline enrollment				
Entire cohort	13,015	27,907	107,151	216,383
Excluding selegiline users[a]	11,637	23,398	101,616	200,303
Post 3-year follow-up, entire cohort[b]	3,606	4,252	28,449	30,660
Post 3-year follow-up excluding selegiline users[a]	2,897	3,324	25,813	27,466

[a] Follow-up time truncated at first use of selegiline, a drug in the same class as rasagiline.

[b] Number of patients followed for more than 3 years after cohort entry date. Post 3-year person-years is the number of years of follow-up excluding the first 3 years for each person with more than 3 years of follow-up.

Table 4. Rasagiline Utilization Patterns (N = 14,170)

Variable	n	%
Number of prescriptions		
Mean (SD)	9.7	(11.8)
Distribution		
1	3,060	22
2	1,616	11
3-5	2,873	20
6-10	2,314	16
> 10	4,307	30
Total days of exposure		
Mean (SD)	345 (404)	
Distribution		
< 60	3,332	24
60-174	3,712	26
175-500	3,688	26
> 500	3,438	24
Initial daily dose, mg		
< 0.5	186	1
0.5	5,326	38
> 0.5-< 1.0	159	1
1.0	8,433	60
> 1.0	66	< 1
Concurrent use of other APDs at cohort entry date[a]		
None	12,515	88
1 levodopa or other dopamine agonist	1,136	8
≥ 1 levodopa, ≥ 1 dopamine agonist, or ≥ 2 dopamine agonists	49	< 1
1 other APD (not levodopa or dopamine agonist)	458	3
2 other APDs (not levodopa or dopamine agonist)	12	< 1

[a] Concurrent use with rasagiline defined as at least one dispensing for another APD in the 60 days before and including the cohort entry date.

CONCLUSIONS

- With the observed uptake of rasagiline in US seniors and preliminary data from the melanoma validation component of the pilot study, it may be necessary to add at least 2 additional years of Medicare data for accrual of sufficient follow-up time (estimated 40,000 person-years) to reach the desired precision of the effect estimate for evaluating melanoma as an outcome and conducting comparative exposure analyses. The additional years would increase the person-years of follow-up for the existing cohort and add about 5,000 new rasagiline initiators.
- Upon completion of the feasibility analyses to determine the melanoma incidence rate in the nonrasagiline APD cohort based on the claims algorithm and medical record–verified cases, it will be possible to make accurate study projections to fulfill the pilot study objectives.
- Medicare data through 2014 (3 additional years) will be available by December 2015, so the full safety study could be initiated in 2016.
- The observed usage patterns of rasagiline appear consistent with the product labeling.
- The observed differences in characteristics of rasagiline initiators and other APD initiators (age and sex distribution, socioeconomic status indicator) are important possible confounding factors for the safety study, as the incidence of melanoma in the US is higher in males than females and among persons with higher than lower socioeconomic status.

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CONFLICT OF INTEREST STATEMENT

The study was funded by Teva Pharmaceutical Industries. Sigal Kaplan is an employee of Teva Pharmaceutical Industries and ElizaBeth Grubb is a former employee. The other co-authors are employees of RTI Health Solutions and have an independent right to publish.

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