

Data Source Details

The data source for the study was the Sentinel distributed network which uses electronic health record and insurance claims. Data on demographics, diagnosis, and treatment are available and have been standardized and curated. Each of the participating research partners maintains a local version of its own data in a Common Data Model format in order to enable distributed queries. To ensure privacy and data protection, queries are distributed and results are returned through a secure portal. The current study leveraged electronic health data in the Sentinel distributed network locally transformed to a Common Data Model from the following 2 participating research partners: Anthem/Healthcore and Humana Healthcare Research Inc. (HHR)/ Humana HealthCare Research is a wholly owned subsidiary of Humana Inc. staffed with a research team to conduct patient-centered research engaging in publicly and privately funded research grants and contracts. More details are available from the following references

1. Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, et al. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. *Pharmacoepidemiol Drug Saf.* 2012;21 Suppl 1:9-11.
2. Platt R, Brown JS, Robb M, et al. The FDA Sentinel Initiative - An Evolving National Resource. *N Engl J Med.* 2018;379(22):2091-2093.
3. Behrman RE, Benner JS, Brown JS, McClellan M, Woodcock J, Platt R. Developing the Sentinel System--a national resource for evidence development. *N Engl J Med.* 2011;364(6):498-499.

Supplementary Table 1. Names of drugs used to identify Alzheimer's disease participants and antidopaminergic-antiparkinsonian prescribing cascade

<u>Alzheimer's Disease Drugs</u>	<u>Antipsychotics and Metoclopramide</u>	<u>Anti-Parkinsonian Agents</u>
Donepezil HCL	Typical antipsychotics	Dopamine precursors
Galantamine HBR	Promazine	Levodopa-Carbidopa
Memantine HCL/ Donepezil HCL	Chlorpromazine	Dopamine agonists
Memantine HCL	Haloperidol	Apomorphine
Rivastigmine	Loxapine	Bromocriptine
	Thioridazine	Pramipexole
	Molindone	Rotigotine
	Thiothixene	Ropinirole
	Fluphenazine	
	Mesoridazone	Mono-Amine Oxidase-B Inhibitors
	Trifluoperazine	Selegeline
	Pimozide	Rasagiline
	Perphenazine	Safinamide
	Flupenthixol	Catechol-o-methyl transferase inhibitors
	Prochlorperazine	Entacapone
	Sulpiride	Tolcapone
	Prochlorperazine	Antiviral
		Amantadine
	Atypical antipsychotics	Anticholinergics
	Clozapine	Trihexyphenidyl
	Olanzapine	Benzotropine
	Quetiapine	Ethopropazine
	Brexpiprazole	
	Aripiprazole	
	Ziprasidone	
	Risperidone	
	Asenapine	
	Iloperidone	
	Paliperidone	
	Lurasidone	
	Olanzapine/Fluoxetine	
	Metoclopramide	

Supplementary Table 2. List of Antipsychotics/Metoclopramide evaluated in the study		
Drugs	N (4534)	Percentage
Antipsychotics		
Aripiprazole	147	3.24
Asenapine maleate	5	0.11
Brexpiprazole	6	0.13
Chlorpromazine HCl	25	0.55
Clozapine	6	0.13
Fluphenazine HCl	6	0.13
Haloperidol	343	7.57
Haloperidol decanoate	2	0.04
Haloperidol lactate	86	1.9
Loxapine succinate	5	0.11
Lurasidone HCl	10	0.22
Olanzapine	330	7.28
Olanzapine/fluoxetine HCl	5	0.11
Paliperidone	6	0.13
Paliperidone palmitate	6	0.13
Perphenazine	12	0.26
Pimozide	6	0.13
Prochlorperazine	17	0.37
Prochlorperazine edisylate	6	0.13
Prochlorperazine maleate	177	3.9
Quetiapine fumarate	2,238	49.36
Risperidone	825	18.2
Risperidone microspheres	5	0.11
Thioridazine HCl	7	0.15
Thiothixene	1	0.02
Trifluoperazine HCl	3	0.07
Ziprasidone HCl	32	0.71
Ziprasidone mesylate	9	0.2
Metoclopramide HCl	307	6.77

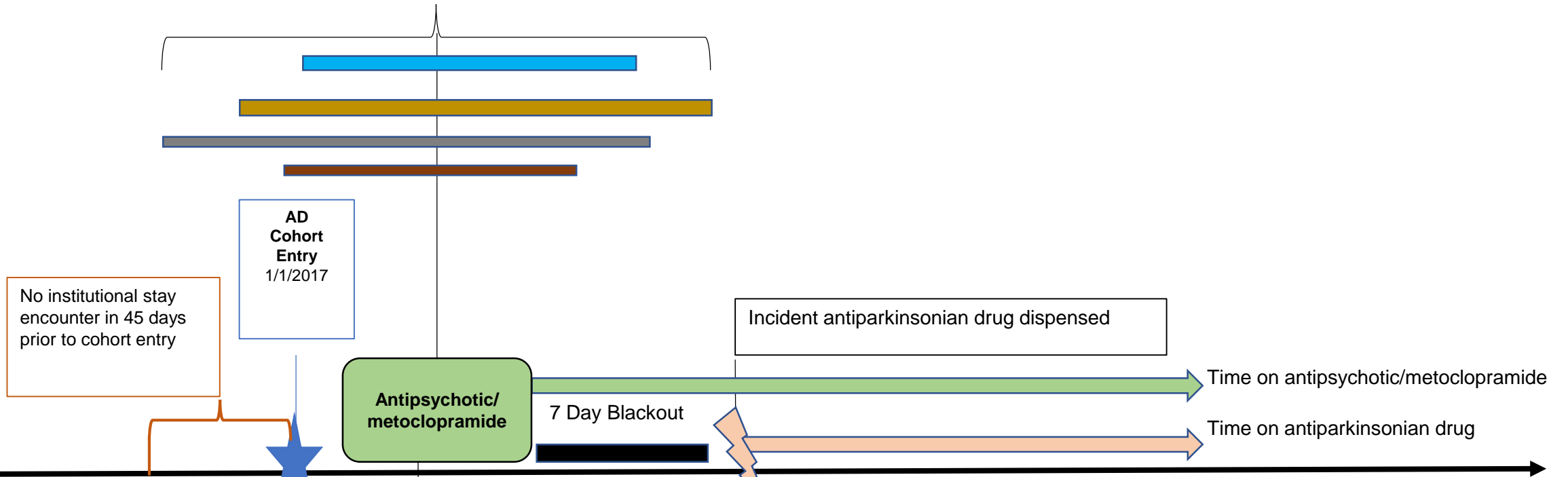
Supplementary Table 3. Disenrollment of Alzheimer’s disease participants.

Cohort	Cohort name	Denominator	Numerator	Censoring, data partner maximum	Censoring, disenrollment	Censoring, death	Censoring, Episode end antipsychotic/ metoclopramide	Censoring, Episode end antiparkinsonian
Alzheimer’s Disease		6253579	121538	74867	27715	18956	NA	NA
Cohort 1	Incident antipsychotic/metoclopramide use	121538	4534	303	428	394	3409	NA
	Incident antipsychotic/metoclopramide use with incident antiparkinsonian use	4534	36	3	6	2	0	25
Cohort 2	Polypharmacy	121538	3485	1601	1037	847	NA	NA
	Prescribing cascades among those with polypharmacy in Alzheimer’s Disease cohort	3485	20	2	4	1	0	15

NA= Not applicable

Supplementary Figure 1. Prescribing cascades among those with polypharmacy in Alzheimer's Disease cohort

Polypharmacy at dispensing of antipsychotic/metoclopramide**



No institutional stay encounter in 45 days prior to cohort entry

AD Cohort Entry
1/1/2017

Incident antiparkinsonian drug dispensed

Antipsychotic/
metoclopramide

7 Day Blackout

Time on antipsychotic/metoclopramide

Time on antiparkinsonian drug

Incident antipsychotic/metoclopramide dispensed

- 1. ADRD treatment for ≥ 1 day 365 days prior to cohort entry*
- 2. Continuous medical and pharmacy coverage in 365 days prior to cohort entry

- Censor when:
- Disenrolled from medical or pharmacy coverage
 - Death
 - Data partner end date

AD treatments include Donepezil, Galantamine, memantine and others
Antipsychotics include Quetiapine, Haloperidol, aripiprazole and others.
Antiparkinsonian drugs include Levodopa-carbidopa, selegiline, amantadine and others.