

Longitudinal Association Between Tricyclic Drug Exposure And Risk Of Alzheimer’s Disease And Related Dementia In Medicare Beneficiaries

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Real world evidence points to the potential repurposing of drugs shown to have anti inflammatory effects *in vitro*

INTRODUCTION

Alzheimer’s Disease and Related Dementia (ADRD) is a major public health challenge, with few disease-modifying therapies available.

Drug repurposing¹ targeting biological mechanisms implicated in ADRD, including inflammation² and proteotoxicity, is a promising approach.

In prior work³, we identified tricyclics as a drug class with protective effects in ADRD models. A subsequent cross-sectional pharmacoepidemiologic analysis of Medicare claims found tricyclic exposure associated with lower ADRD prevalence.

To strengthen causal inference and address temporality, we conducted a five year longitudinal study to evaluate the association between tricyclic exposure and incident ADRD

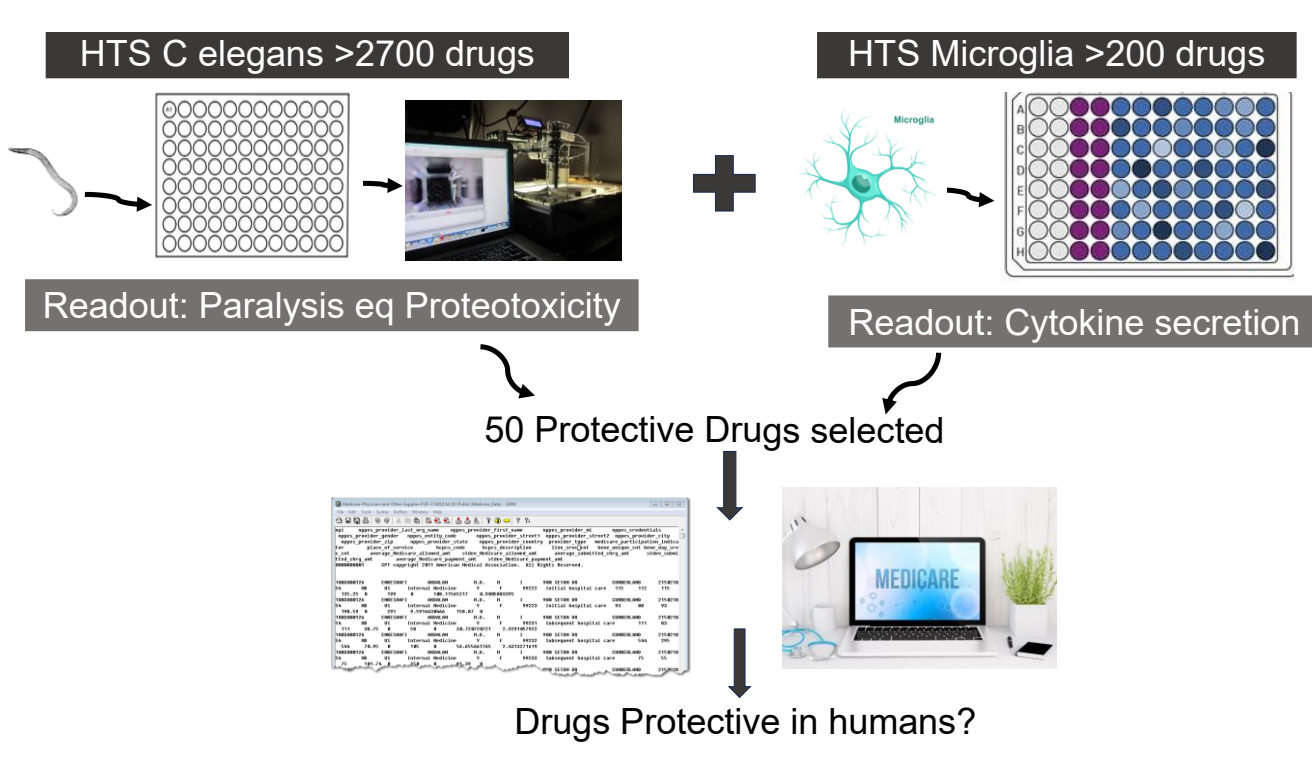
CONCLUSIONS

Cohort

Longitudinal

1

In vivo, in vitro and cross-sectional cohort Preliminary Studies



2

Epidemiological studies Longitudinal 5 year cohort study

Random sample of 1M Medicare fee for service Beneficiaries 65-75 years upon cohort entry

Primary outcome: ADRD, modified Bynum Algorithm

Exposure: Phenothiazines 2012-2016

Statistics: Covariates = behavioral, Cardiometabolic, psychiatric

Logistic regression to assess the Hazard Ratio (HR) of ADRD using Cox Proportional hazard models

Figure 1. Consort Diagram 2012 cohort

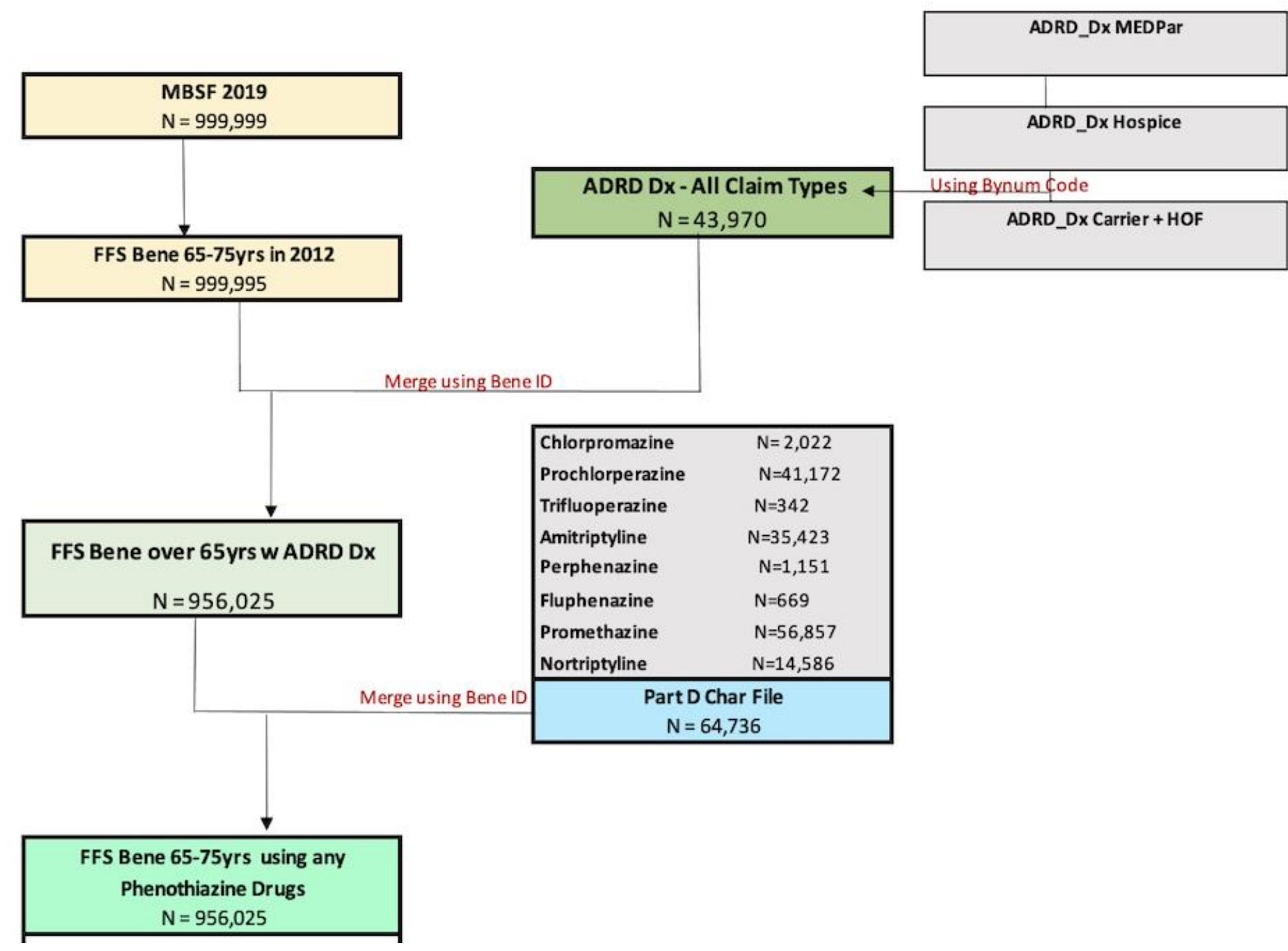


Table 1. Baseline characteristics of cohort population in 2012

Baseline covariate	Total N (%)	Any tricyclic of interest N (%)	No exposure to drugs of interest N (%)
Number of individuals	956,025	64,736	891,289
Age (yrs) mean (SD)	70.3 (2.8)	70.2 (2.8)	70.3 (2.8)
Race			
White, Non-Hispanic	822,755 (86%)	55,764 (86.1%)	766,991 (86%)
Black, Non-Hispanic	52,720 (5.5%)	3,962 (6.1%)	48,758 (5.4%)
Hispanic	40,749 (4.3%)	2,771 (4.2%)	37,978 (4.2%)
Other	40,265 (4.17%)	2,037 (3.1%)	33,195 (3.7%)
Female	548,825 (57.4%)	45,291 (70%)	503,535 (56.4%)
Have ADRD	0	0	0
Exposure to >=1 tricyclic	64,736 (6.8%)		
ADRD Risk factors			
Behavioral			
Smoking or tobacco use	82,955 (8.68%)	9,546 (14.7%)	73,398 (8.2%)
Other			
Traumatic Brain Injury	10,926 (1.14%)	1,520 (2.3%)	9,406 (1%)
Cardiometabolic			
Diabetes Mellitus	287,023 (30%)	24,669 (38.1%)	262,354 (29.4%)
Hypertension	663,751(69.4%)	51,205 (79%)	612,546 (68.7%)
Cerebrovascular disease (Stroke)	24,297 (2.5%)	2,815 (4.3%)	21,482 (2.4%)
Heart disease	218,466 (22.8%)	19,604 (30.3%)	198,862 (22.3%)
Psychiatric			
Depression	104,107 (10.9%)	15,401 (23.8%)	88,706 (9.9%)
Psychosis	8,093 (0.8%)	1,426 (2.2%)	6,667 (0.7%)

Table 2. Characteristics and exposure to tricyclic compounds during follow up

Drug name	FDA approval US	Indication for drug	Number of beneficiaries in cohort exposed to drugs, N (%)
CPZ Chlorpromazine	1957	Schizophrenia (positive symptoms), bipolar I acute manic type, acute agitation, nausea and vomiting, chronic hiccups, relief of apprehension before surgery, tetanus, porphyria	2,022 (0.21%)
TriHyd Trifluoperazine	1959	Schizophrenia, generalized anxiety disorder	342 (0.04%)
Nor Hyd Nortriptyline	1964	Depression, (off-label for: neuropathic pain, ADHD, smoking cessation, anxiety)	14,586 (1.5%)
Pro Hyd Promethazine	1951	Allergic conditions, nausea, motion sickness, sedation	56,857 (5.9%)
PFZ Perphenazine	1965	schizophrenia	1,151 (0.12%)
PCPZ Prochlorperazin	1956	Schizophrenia, nausea and vomiting	41,172 (4.3%)
Ami Hyd Amitriptyline	1961	Major depressive disorder	35,423 (3.7%)
FluP Fluphenazine	1960	Schizophrenia, bipolar I acute manic type	669 (0.07%)

Table 3. Association between intake of at least one tricyclic drug and incidence of dementia - Cox models. 2012–2016

Adjustment for age, sex, race, ADRD risk factors (behavioral, cardiometabolic, psychiatric)

Exposure to Drug/Class prior to ADRD Dx	N exposed beneficiaries	Adjusted model ^a HR (95% CI)	After exclusion beneficiaries without psychiatric conditions HR (95% CI)
Any Tricyclic Phenothiazine drug		1.03 (1.01, 1.06)	
chlorpromazine	2022	1.26 (1.10, 1.44)	1.38 (1.11, 1.7)
prochlorperazine	41172	0.77 (0.73, 0.80)	0.76 (0.7, 0.81)
trifluoperazine	342	1.12 (0.87, 1.45)	3.09 (1.54, 6.17)
amitriptyline	35423	1.08 (1.04, 1.12)	1.15 (1.15, 1.16)
perphenazine	1151	1.42 (1.24, 1.63)	2.54 (1.79, 3.59)
fluphenazine	669	1.53 (1.32, 1.77)	11.86 (6.74, 20.89)
promethazine	56857	1.15 (1.11, 1.18)	1.14 (1.09, 1.2)
nortriptyline	14586	0.92 (0.87, 0.98)	1.15 (1.04, 1.26)

In a large, nationally representative cohort of older adults, **exposure to prochlorperazine was associated with a reduced risk of incident ADRD over five years**. These findings reinforce and extend preclinical evidence supporting tricyclic compounds as modulators of neurodegenerative pathways. More broadly, this work demonstrates the **power of validating experimentally generated hypotheses in real-world human data to accelerate translation from bench to bedside**. Carefully designed prospective studies are now warranted to determine whether these associations reflect true neuroprotective effects and to define their potential role in ADRD prevention or treatment strategies.

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