Supplementary Online Content

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eAppendix. Receipt of Multiple, Concurrent Fracture-Associated Drugs and Hip Fracture Risk

Cohort Creation:

Because of the two-year Parts A and B coverage requirement, the minimum age was 67 years at the start of Part D drug receipt observation.

Patients with cancer (except non-melanoma of the skin) were conservatively excluded due to risk of pathologic fracture that may be unrelated to drug exposure and imperfectly identified as a cancer-related fracture in claims. Patients with advanced renal disease were also excluded due to risk of fracture related to renal failure and the possibility of receiving drugs during dialysis that would not appear in our claims data. We excluded hospice patients because some medications are included in the hospice per diem payments and thus may not be apparent in our claims data.

We excluded beneficiaries with vertebral fractures at any time during the look-back or observation because the temporal relationship between occurrence and diagnosis of vertebral fractures can vary tremendously. Vertebral fractures are often found incidentally on images obtained for reasons unrelated to fracture. All patients with a past fragility fracture were conservatively excluded from this study because we aimed to study *first* fragility fractures rather than a beneficiary's second or third fragility fracture. Prior fracture is an important fracture risk factor and undoubtedly an effect modifier; this small, high-risk, population must be studied separately by methods appropriate for smaller populations with an event as the key cohort inclusions criterion.[1] Additionally, fragility fracture survivors have a distinctly high fracture risk and their prescriptions may be managed distinctly as a result; their vulnerability to additive adverse drug effects may be different as well. We will study them separately.

Patients censored due to disenrollment in fee-for-service A, B and D plans were permitted to reenter the study as long as they met the inclusion criteria.

Drug Exposure:

For fracture associated drugs, the LexiComp Basic database was used to obtain the active ingredient and product information for each National Drug Code (NDC) apparent in the

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Part D Event file. Exposure was assumed to begin on the date of prescription dispensing. We used the "days supply" variable to set exposure duration. Overlapping supplies were carried forward (e.g. a fill occurring 80 days after a 90-day fill resulted in a 10-day supply carried forward). For drugs not refilled at the end of the days-supply, discontinuation was assigned after a time elapse of 120% of most recent days-supply, assuming imperfect adherence.

Other drug exposures that were classified as non-fracture associated drug (Non-FAD) exposures represented 552 distinct systemic drug ingredients according to the First Databank (FDB, South San Francisco, CA) Hierarchical Ingredient Code Parent HIC4 Sequence Number (HIC_ROOT); FDB groups ingredients with the same base drug molecule. A 4-level, non-FAD exposure indicator variable was created which flagged 0 or 1 non-FAD exposures on a single day, and aggregated any 2 concurrent non-FAD drug exposures on a single day, and separately any 3 or more concurrent non-FAD drug exposures on a single day. Thus other drug exposures were always included in models as a categorical/numeric indicator for 0, 1, 2 and 3+ concurrent non-FAD exposures. See Technical Appendix Table 1 below for the Ultimate Parent Enhanced Therapeutic Classification Names that contributed to the top 20 most common non-FADs. For example, Cardiovascular Therapy Agents included angiotensin converting enzyme-inhibitors, statins, and angiotensin II receptor blockers, and Analgesic, Anti-inflammatory or Antipyretic drugs included non-narcotic analgesics and NSAID analgesics (COX Non-Specific).

Outcomes:

Hip fractures were selected as the outcome for this study of fracture associated drugs (FADs) because hip fractures are generally treated in the inpatient setting. Thus, the date of fracture occurrence can be reliably ascertained in claims, as can the sequence of prescription receipt and fracture. This issue of sequence of drug receipt and fracture is particularly challenging when assessing other fragility fractures (humerus, wrist, vertebra) as small differences or errors in recorded dates can affect the apparent sequence between medication receipt and fracture occurrence and result in erroneous causal inference. This is especially important for opioids which are often prescribed to treat fracture pain.

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Analytic Approach:

The study design assured model assumptions were satisfied with regard to non-informative censoring; individuals were censored with the occurrence of death or disenrollment from fee-for-service Medicare Part A, B or D. The probability of a fracture occurring is not related to disenrollment, but may be related to unmeasured factors associated with death.

Risk Adjustment and Stratified, Hierarchical Models. Our empirical analysis addresses two key issues in the identification of fracture risks associated with multiple drug use. First, concerns about unmeasured confounding are addressed by risk-adjustment and stratification by sex. This is further explored in sex-specific age stratified models. Additionally, we perform a sensitivity analysis with a model including only non-drug variables (no drug exposure indicators) to explore the estimates associated with known risk factors when prescription exposure is not considered. Second, we ran hierarchical models using increasingly granular definitions of drug exposures. Our first models include total drug exposure: as a continuous variable and then, separately as a categorical variable representing 0, 1, 2 or 3 or more total concurrent drugs. We then grouped drugs into FAD and non-FAD categories representing 0, 1, 2 or 3-or-more concurrent drugs to determine if combinations of FAD or non-FAD exposures confer greater risk than none, or single exposures. We repeated this categorical approach using FAD and non-FAD designations in age-stratified models. Finally, we assessed approximately 200 specific single and combination exposures in a sex-specific models, applying the Benjamini-Hochberg false-discovery-rate (FDR) control procedure.[2,3] With the very large number of possible drug combinations, we are concerned about falsely rejecting the null for specific interaction effects and therefore control for multiple testing.

Our study has been designed to control for both time varying drug exposures and time varying covariates. We use the counting process survival analysis approach[7,8] to capture exposures with high sensitivity (at a day level) allowing each beneficiary to contribute time to diverse categories of exposure person days (control) in observed follow-up times. Additionally, we accounted for acquisition of health conditions over time that may impact medications received and risk of fracture. Models were stratified on sex, an anticipated effect modifier.

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Cox Models. In the FAD count exposure analysis, the exposure predictors are binary indicators of the number of FADs taken at time *t*, where *t* ranges over the days the beneficiary meets eligibility criteria. Because patients change status with respect to these variables over follow-up and the time to fracture may be censored, we use the counting process form of the Cox model to estimate the risk of each number of FADs. The model has the form

$$h(t|\boldsymbol{X_i}(t)) = h_0(t)\exp(\beta_1 X_{1i}(t) + \beta_2 X_{2i}(t) + \beta_3 X_{(3+)i}(t) + \boldsymbol{\beta_{cov}^T}\,\boldsymbol{X_{cov,i}}(t))$$

where $X_{ki}(t) = 1$ if patient *i* received *k* FAD at time t and 0 otherwise for $k = 1, 2, \geq 3$ and the regression coefficients β_k represent the effect of a patient receiving k FAD versus 0 FAD at a given time. In addition, $X_{cov}(t)$ is a vector of covariates comprising:

COVStatic = covariates that do not change over observation time, i.e. sex, race, original eligibility

COVAnnual = covariates that are updated annually= age, LIS, Medicaid eligibility

COVAbsorptive = covariates that once in are always in for an individual, i.e. comorbidities, LTC

In the drug and drug-pair specific analysis, for each drug exposure (RX) the time-dependent exposure will equal either a single FAD (single exposure (SE), n=21 FADs), a double exposure of two distinct FADs (double exposure (DE), n=210 combined exposures), or a general three-or-more distinct FAD exposure at time t. The model has the form:

$$\begin{aligned}
&h(t|\boldsymbol{X_i}(t)) \\
&= h_0(t)\exp(\beta_1 RXSEFAD_{1i}(t) + \cdots + \beta_{21} RXSEFAD_{21i}(t) + \beta_{22} RXDEFAD_{1i}(t) + \cdots \\
&+ \beta_{231} RXDEFAD_{210i}(t) + \beta_{232} FAD_{(3+)i}(t) \\
&+ \beta_{RXPro} RX_{RXPro,i}(t) + \beta_{1NonFAD} RXNonFAD_{1i}(t) + \beta_{2NonFAD} RXNonFAD_{2i}(t) + \beta_{3+NonFAD} RXNonFAD_{3+i}(t) \\
&+ \boldsymbol{\beta_{cov}^T}\,\boldsymbol{X_{cov,i}}(t))
\end{aligned}$$

where $RXSEFAD_{ki}(t) = 1$ if drug $k = 1, \ldots, 21$ is the only single FAD taken by patient *i* at time *t*, $RXDEFAD_{ki}(t) = 1$ if drug pair $k = 1, \ldots, 210$ corresponds to the only two FADs patient *i* is taking at time *t*, $RXNonFAD_{ki}(t) = 1$, 2, 3+ if drug $k = 1,2,3+$ corresponds to Non-FADs taken by patient *i* at time *t*, and $RX_{RXPro,i}(t) = 1$ if drug(s) taken by patient *i* is an osteoprotective drug.

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Competing Risk Analysis. In sensitivity analyses, Cox proportional hazard models were fit in the presence of the potential competing risk of death using the Fine-Gray method which models the cumulative incidence of an event of interest (fracture) given a competing event (death). The resulting subdistribution hazard ratio (SHR) describes the probability of events occurring over time associated with the relative effect of a covariate.[9,10] Sensitivity analyses were additionally run using the cause-specific hazard models which estimate the effect of covariates on the rate of events over time.[9].

Results

Risk adjustment, drug exposure and crude rates. Hierarchical conditions category (HCC) score was calculated to facilitate comparison of our cohort to the general, Medicare population, (national median is 1.0); higher scores indicate more morbidities.[11,12] Hierarchical conditions category scores (mean, SD) were 0.97 (0.91) for women and 1.01 (0.99) for men.
Among women, 27% of person-days were exposed to zero non-FADs, 17% to one non-FAD, 18% to two non-FADs and 38% to three-or-more non-FADs. Exposure among men was similar. See Table 2 in main text.

Crude fracture rates associated with non-FADs were modestly higher than those of women. Receipt of none, or any one, two, or three or more non-FADs was associated with crude fracture rates of 4.44/1000 PY, 6.16/1000 PY, 6.80/1000 PY and 8.38/1000 PY among women, and 2.00/1000 PY, 2.73/1000 PY, 3.01/1000 PY and 3.71/1000 PY for men, respectively (Appendix Figure 2 and Technical Appendix Tables 2a and 2b, respectively for women and men). Person years of exposure to increasing FADs were similar across age strata, and crude rates increased with age and drug use, as expected.

Hierarchical Cox Models. The risk estimates for chronic conditions (but not other risk factors such as age/race) were slightly higher in models that did not include any drug exposure variable (Appendix Table 6, Model A). With increasing granularity of drug definition, these estimates were further abrogated. This is particularly notable when the categorical total drug exposure

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variable (Appendix Table 6, Models C1) is separated into FAD versus non-FAD exposures Appendix Table 6 Model C2).

Among results for exclusive single and double FAD exposures (Appendix Tables 7 and Figure 2A and Appendix Table 8 and Figure 2B). For women only one FAD (muscle relaxers) and 44 combinations in women did not achieve False Discovery Rate significant fracture risk. Among men, 5 single FAD exposures (muscle relaxers, tricyclic antidepressants, central acting antihypertensives, 1st generation antihistamines and barbiturates) and 53 double FAD exposures did not achieve False Discovery Rate significance.

Competing Risk Analysis. Cox model results for FAD and non-FAD exposure were slightly higher than results from subdistribution hazard ratios and nearly identical to cause-specific hazard ratio models (Technical Appendix Table 3). Models for single and combination FAD exposures were also run using the subdistribution and cause-specific hazard ratio; results were similar to those obtained from Cox models (data provided upon request).

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Technical Appendix Table 1. Ultimate Parent First Databank Enhanced Therapeutic Classification Names for the most commonly received non-FAD groups in a 20% Study Cohort, 2006-2014.
Cardiovascular Therapy Agents
Analgesic, Anti-inflammatory or Antipyretic
Endocrine
Anti-Infective Agents
Vaccines
Respiratory Therapy Agents
Gastrointestinal Therapy Agents
Electrolyte Balance-Nutritional Products
Genitourinary Therapy

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Technical Appendix Table 2a. Person Years Exposure and Crude Fracture Rate Associated with Fracture Associated Drugs (FADs) and Non-FADs Across Age Strata in Women

		Fracture Associated Drug (FAD) Exposure					Other Drug (Non-FAD) Exposure			
		FX	PY	Crude Fracture Rate (FX/1000 PY)	% Total PY Exposure		FX	PY	Crude Fracture Rate (FX/1000 PY)	% Total PY Exposure
Total		47,387	7,126,267	6.65			47,387	7,126,267	6.65	
n=1,615,613	**0 Drugs**	12,299	3,680,607	3.34	51.65	**0 Drugs**	8,419	1,896,251	4.44	26.61
	1 Drug	11,823	1,827,305	6.47	25.64	**1 Drug**	7,553	1,227,066	6.16	17.22
	2 Drugs	9,471	912,855	10.38	12.81	**2 Drugs**	8,870	1,305,244	6.80	18.32
	3+ Drugs	13,794	705,500	19.55	9.90	**3+ Drugs**	22,545	2,697,706	8.36	37.86
67-69		6,422	2,719,708	2.36			6,422	2,719,708	2.36	
n=326,256	**0 Drugs**	1427	1,443,036	0.99	53.06	**0 Drugs**	1030	694846	1.48	25.55
	1 Drug	1391	675,794	2.06	24.85	**1 Drug**	1028	517876.8	1.99	19.04
	2 Drugs	1192	331,825	3.59	12.20	**2 Drugs**	1074	509339.8	2.11	18.73
	3+ Drugs	2412	269053.4	8.96	9.89	**3+ Drugs**	3290	997644.9	3.30	36.68
70-74		7,183	1,725,284	4.16			7,183	1,725,284	4.16	
n=436,790	**0 Drugs**	1831	889718.7	2.06	51.57	**0 Drugs**	1250	479871.3	2.60	27.81
	1 Drug	1674	450499	3.72	26.11	**1 Drug**	1063	290328	3.66	16.83
	2 Drugs	1390	220097.3	6.32	12.76	**2 Drugs**	1276	309557.7	4.12	17.94
	3+ Drugs	2288	164969.1	13.87	9.56	**3+ Drugs**	3594	645527.1	5.57	37.42
75-79		9,937	1,299,459	7.65			9,937	1,299,459	7.65	
n=322,991	**0 Drugs**	2536	650903.6	3.90	50.09	**0 Drugs**	1716	343245.5	5.00	26.41
	1 Drug	2494	348411	7.16	26.81	**1 Drug**	1528	206402.5	7.40	15.88
	2 Drugs	2005	172601.6	11.62	13.28	**2 Drugs**	1824	236420.9	7.72	18.19
	3+ Drugs	2902	127543.2	22.75	9.82	**3+ Drugs**	4869	513390.4	9.48	39.51
80-84		11,282	830,290	13.59			11,282	830,290	13.59	
n=243,570	**0 Drugs**	2944	410550.3	7.17	49.45	**0 Drugs**	1918	216936.8	8.84	26.13
	1 Drug	2953	219526.9	13.45	26.44	**1 Drug**	1781	127518.9	13.97	15.36
	2 Drugs	2310	114487.1	20.18	13.79	**2 Drugs**	2197	150837.7	14.57	18.17
	3+ Drugs	3075	85725.3	35.87	10.32	**3+ Drugs**	5386	334996.2	16.08	40.35
85+		12,563	551,526	22.78			12,563	551,526	22.78	
n=287,663	**0 Drugs**	3561	286397.4	12.43	51.93	**0 Drugs**	2505	161351.3	15.53	29.26
	1 Drug	3311	133074.3	24.88	24.13	**1 Drug**	2153	84940.01	25.35	15.40
	2 Drugs	2574	73844.7	34.86	13.39	**2 Drugs**	2499	99087.56	25.22	17.97
	3+ Drugs	3117	58209.47	53.55	10.55	**3+ Drugs**	5406	206147.1	26.22	37.38

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Technical Appendix Table 2b. Person Years Exposure and Crude Fracture Rate Associated with Fracture Associated Drugs (FADs) and Non-FADs Across Age Strata in Men

	Fracture Associated Drug (FAD) Exposure					Other Drug (Non-FAD) Exposure				
		FX	PY	Crude Fracture Rate (FX/1000 PY)	% Total PY Exposure		FX	PY	Crude Fracture Rate (FX/1000 PY)	% Total PY Exposure
Total		12,317	4,160,502	2.96			12,317	4,160,502	2.96	
n=1,030,642	**0 Drugs**	3,616	2,502,076	1.45	60.14	**0 Drugs**	2,376	1,187,243	2.00	28.54
	1 Drug	3,150	999,979	3.15	24.04	**1 Drug**	1,676	613,447	2.73	14.74
	2 Drugs	2,435	409,441	5.95	9.84	**2 Drugs**	2,087	692,737	3.01	16.65
	3+ Drugs	3,116	249,006	12.51	5.98	**3+ Drugs**	6,178	1,667,075	3.71	40.07
67-69		2,531	1,878,320	1.35			2,531	1,878,320	1.35	
n=249,638	**0 Drugs**	706	1139329	1.31	60.66	**0 Drugs**	485	491861.7	0.99	26.19
	1 Drug	577	444999.6	3.17	23.69	**1 Drug**	354	298599	1.19	15.90
	2 Drugs	458	180312.6	6.64	9.60	**2 Drugs**	422	328196.7	1.29	17.47
	3+ Drugs	790	113679.1	18.93	6.05	**3+ Drugs**	1270	759662.8	1.67	40.44
70-74		2,300	1,090,187	2.11			2,300	1,090,187	2.11	
n=326,887	**0 Drugs**	715	658340.3	0.85	60.39	**0 Drugs**	463	329396.8	1.41	30.21
	1 Drug	561	265664.5	1.63	24.37	**1 Drug**	299	154448	1.94	14.17
	2 Drugs	438	105151.6	3.27	9.65	**2 Drugs**	367	176504.4	2.08	16.19
	3+ Drugs	586	61030.19	7.63	5.60	**3+ Drugs**	1171	429837.4	2.72	39.43
75-79		2,639	674,997	3.91			2,639	674,997	3.91	
n=217,042	**0 Drugs**	784	398421.6	1.15	59.03	**0 Drugs**	479	201267.3	2.38	29.82
	1 Drug	679	167432.7	2.08	24.80	**1 Drug**	347	91274.39	3.80	13.52
	2 Drugs	536	68866.2	4.13	10.20	**2 Drugs**	427	108058.4	3.95	16.01
	3+ Drugs	640	40276.53	9.41	5.97	**3+ Drugs**	1386	274,397	5.05	40.65
80-84		2,465	345,945	7.13			2,465	345,945	7.13	
n=133,943	**0 Drugs**	707	203721.5	1.97	58.89	**0 Drugs**	464	107294.4	4.32	31.01
	1 Drug	683	83304.37	4.17	24.08	**1 Drug**	326	46158.46	7.06	13.34
	2 Drugs	501	36745.19	7.33	10.62	**2 Drugs**	420	53938.43	7.79	15.59
	3+ Drugs	574	22173.67	14.76	6.41	**3+ Drugs**	1255	138553.5	9.06	40.05
85+		2,382	171,053	13.93			2,382	171,053	13.93	
n=109,148	**0 Drugs**	704	102263.9	3.12	59.78	**0 Drugs**	485	57422.4	8.45	33.57
	1 Drug	650	38577.73	7.44	22.55	**1 Drug**	350	22967.26	15.24	13.43
	2 Drugs	502	18365.61	12.63	10.74	**2 Drugs**	451	26039.19	17.32	15.22
	3+ Drugs	526	11845.73	44.40	6.93	**3+ Drugs**	1096	64624.15	16.96	37.78

FAD is fracture associated drug group. Non-FADs are all other prescription drug groups. PY is Person Year. 3+ FAD is a classification of person days with 3 or more concurrent FADs. Frequencies of exposure categories are derived from person-day level data. For FADs, status of receipt of 21 single drugs (1 FAD) and 210 concurrent drug pairs (2 FAD) is classified for each person, for each day of observation. The same approach was taken to identify non-FAD exposures; status of receipt of any 1 non-FAD expsoure (1 Non-FAD), 2 concurrent non-FAD exposures (2 Non-FAD), 3+ Non-FAD is a classification of person days with 3 or more concurrent Non-FADs.

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Technical Appendix Table 3. Cox Regression Models (Figure 1A) and, for comparison, Competing Risk Models with Sub Distribution or Cause Specific Hazard Ratio Estimates Demonstrating Hip-Fracture Risk Associated with Exposure to prescription FADs and Non-FADs

	Cox Model Fracture			Competing Risk (SHR)			Competing Risk (CSH)		
	Hazard Ratio (HR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	Sub Distribution Hazard Ratio (SHR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	Cause-Specific Hazard Ratio (CHR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval
Women (Fracture = 47,318; Death n=157,807)									
0 FAD	1.00			1.00			1.00		
1 FAD	2.04	1.99	2.11	2.00	1.94	2.06	2.04	1.98	2.11
2 FAD	2.86	2.77	2.95	2.76	2.66	2.85	2.86	2.76	2.96
3+ FAD	4.50	4.36	4.65	4.17	4.02	4.32	4.50	4.34	4.67
0 Non-FAD	1.00			1.00			1.00		
1 Non-FAD	0.93	0.90	0.96	0.94	0.91	0.97	0.93	0.90	0.96
2 Non-FAD	0.84	0.81	0.87	0.85	0.83	0.88	0.84	0.81	0.87
3+ Non-FAD	0.74	0.72	0.77	0.76	0.74	0.78	0.74	0.72	0.77
Men (Fracture = 12,299; Death = 98,927)									
0 FAD	1.00			1.00			1.00		
1 FAD	2.23	2.11	2.36	2.17	2.05	2.30	2.23	2.10	2.36
2 FAD	3.40	3.20	3.61	3.22	3.02	3.43	3.39	3.18	3.62
3+ FAD	5.18	4.87	5.52	4.60	4.30	4.92	5.17	4.83	5.54
0 Non-FAD	1.00			1.00			1.00		
1 Non-FAD	0.90	0.84	0.96	0.91	0.85	0.98	0.90	0.84	0.96
2 Non-FAD	0.84	0.79	0.89	0.86	0.81	0.92	0.84	0.79	0.89
3+ Non-FAD	0.71	0.67	0.75	0.73	0.69	0.78	0.71	0.67	0.75

Total person years of observation = 7,126,266 for women, 4,160,502 for men. For FADs, status of receipt of 21 single drugs (1 FAD) and 210 concurrent drug pairs (2 FAD) is classified for each person, for each day of observation. 3+ FAD is a classification of person days with 3 or more concurrent FADs. The same approach was taken to identify 552 non-FAD exposures; status of receipt of any 1 non-FAD expsoure (1 Non-FAD), 2 concurrent non-FAD exposures (2 Non-FAD), 3+ Non-FAD is a classification of person days with 3 or more concurrent Non-FADs. All models were stratified on sex and adjusted for time varying patient factors; Medicaid eligibility and Medicare Part D low income subsidy are two poverty indicators. Long-term care indicator is defined as 50% or more annual prescription fills dispensed by a long-ter m care pharmacy. The three categories of drugs protective of fracture are: 1. osteoporosis treatments: oral and injected bisphosphonates, calcitonin, denosumab, parathyroid hormone, 2. Estrogens- systemic estrogens, selective estrogen receptor modulators, and 3. beta-blockers. The "Tobacco/Chronic Obstructive Lung Disease" co-morbidity includes patients with Chronic Obstructive Lung Disease diagnosis and/or tobacco use diagnosis.

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eAppendix References

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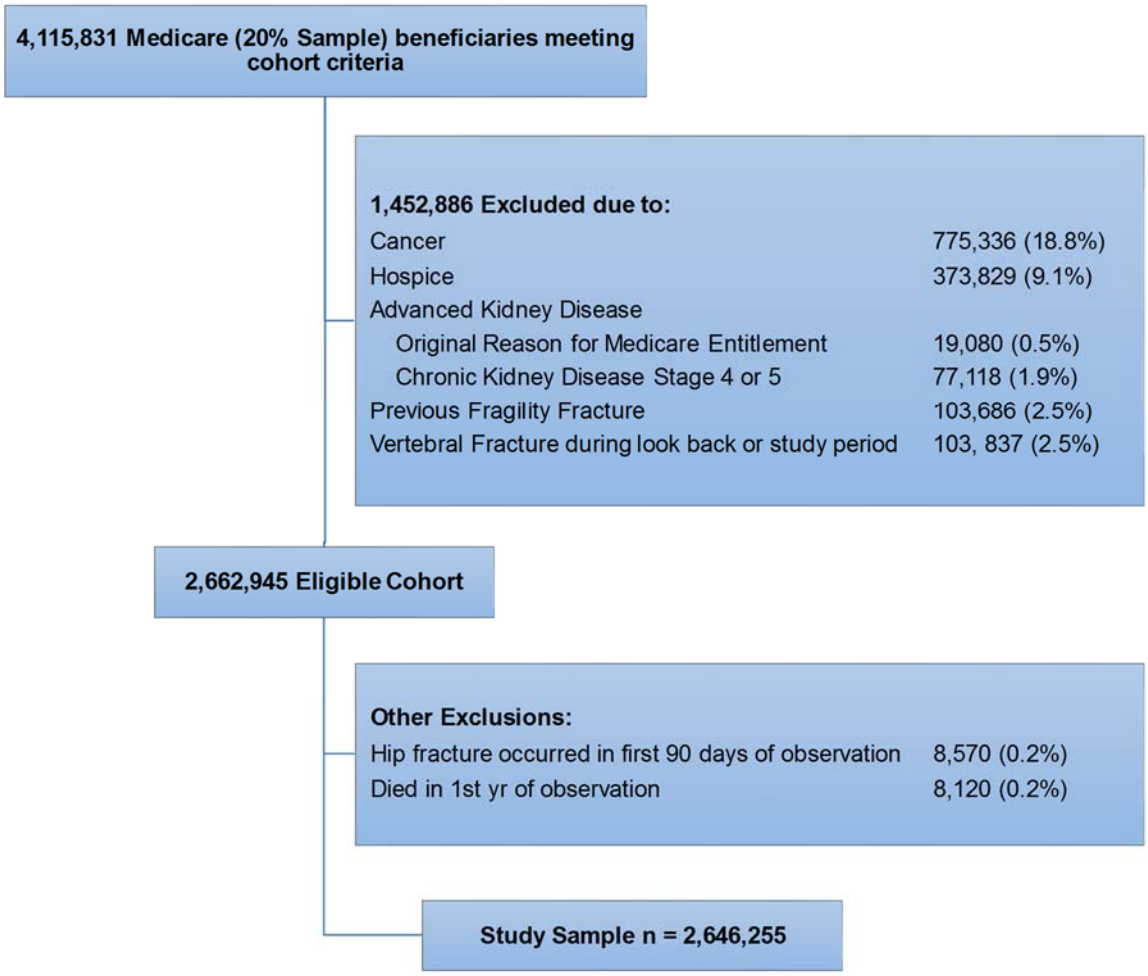
eFigure 1. Cohort Creation Diagram

Cohort inclusion criteria: U.S. ZIP Code, 24 months or more of fee-for-service Medicare Parts A and B enrollment prior to the start of Part D drug receipt observation period, continuous enrollment in fee for service Medicare Parts A, B, and D for at least 12 months between 2006-2014, alive at least 12 months after start of Part D drug use observation.



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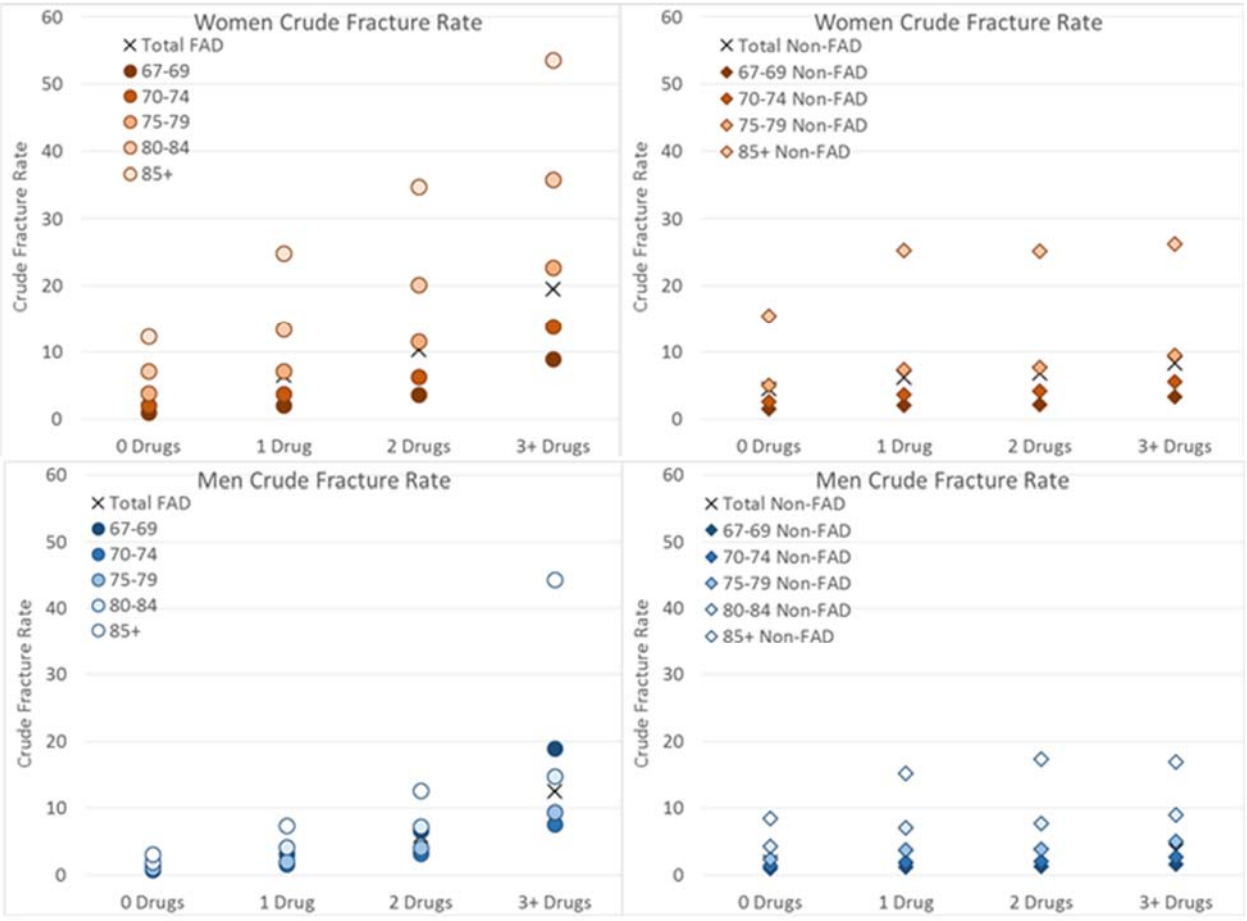
eFigure 2. Total and Age-Group Specific Crude Fracture Rates Among Women and Men Exposed to FADs and Non-FADs



Total is crude rate for women or men exposed to FAD or non-FAD, regardless of age group.

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eTable 1. Select Literature Summary, Mechanisms Through Which Drugs Confer Fracture Risk

Potential Mechanism of Increased Fracture Risk	Drug Class
Direct skeletal cell effects (on either osteoclasts (bone resorption) or osteoblasts and osteocytes (bone formation)) :	Anticonvulsants [1-10]
· via 25-hydroxylase enzyme inhibition and decreased vitamin D	**Antihistamines (H1 Blockers)[11,12]**
· Folic acid depletion and hyperhomocysteinemia	**Antipsychotics (1st and 2nd generation) [13-17]**
· Decrease serum calcium (increase excretion, decrease absorption, unknown mechanism)	Glucocorticoids[18-23]
· Hypogonadism (aromatase enzyme inhibition, hyperprolactinemia, suppression of hypothalamic, pituitary-gonadal axis)	**Histamine 2 Receptor Antagonists [11,12,24]**
· hypoglycemia	**Loop diuretics[25-28]**
	Nitrates[26,29,30]
	Proton pump inhibitors[24,31-36]
	Opioids[37,38]
	Selective serotonin reuptake inhibitors[39-48]
	Thiazide Diuretics[49-51]
	Thiazolidinediones[52,53]
	Tricyclic antidepressants [54]
Increase fall risk	**Antihistamines (H1 Blockers)[55]**
· Sedation/Dizziness/Anticholinergic	AntiParkinson'sAgents[56]
· Orthostatic hypotension	**Antipsychotics (1st and 2nd generation) [57-61]**
	Barbiturates[62]
	Benzodiazepines[58,61,63,64]
	Centrally-acting antihypertensives[65]
	Histamine 2 Receptor Antagonists [24]
	Loop diuretics[66]
	Muscle Relaxers[67-69]
	Non-Benzodiazepine Sedative Hypnotics[57,58,61]
	Opioids[37,38,70]
	Selective serotonin reuptake inhibitors[57,58,71]
	Thiazide Diuretics[49-51]
	Tricyclic antidepressants [57,58,61,71]
Increase fall risk · Decrease muscle mass	Glucocortcoids[19]

Bold font indicates drug groups that have been associated with both risk of falls and bone weakening.

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eTable 2. *International Classification of Diseases, Ninth Revision* (ICD-9) Diagnosis Codes Used to Identify Fractures and Morbidities

Hip Fracture	82000 82001 82002 82003 82009 82010 82011 82012 82013 82019 82020 82021 82022 82030 82031 82032 8208 8209 82100 82101 82110 82111
Distal Radius/Wrist Fragility Fracture	81340 81341 81342 81343 81344 81345 81346 81347 81350 81351 81352 81353 81354 81400 81410
Humerus Fragility Fracture	81200 81201 81202 81203 81209 81210 81211 81212 81213 81219
Vertebral Fragility Fracture	805.0x 805.2x 805.4x 805.6x 805.8x
Pathologic Fracture	73310 73311 73312 73313 73314 73315 73316 73319
Chronic Kidney Disease Stages 4/5 or Dialysis Status	5854 5855 5856 5880 40301 40311 40391 40402 40403 40412 40413 40492 40493 99656 99668 99673 V4511 V4512 V560 V561 V562 V5631 V5632 V568 5854 5855 5856 5880 40301 40311 40391 40402 40403 40412 40413 40492 40493 99656 99668 99673 V4511 V4512 V560 V561 V562 V5631 V5632 V568
Cancer (except non-melanoma of skin)	1400-1729 1740-20935 20970-20979 2350-2399 V1000-V1091 1960-1192
Tobacco /Chronic Obstructive Pumonary Disease	415.0 416.8 416.9 491.0 492.0 494.0 496.0 305.1 V15.82 989.84
Depression	296.2 296.21 296.22 296.3 296.23 296.25 296.26 296.30 296.31 296.32 296.33 296.35 296.36 300.4 301.10 301.11 301.12 301.13 309.1 311
Serious Mental Illness	295.00 295.01 295.02 295.03 295.04 295.05 295.10 295.11 295.12 295.13 295.14 295.15 295.20 295.21 295.22 295.23 295.24 295.25 295.30 295.31 295.32 295.33,295.34 295.35 295.40 295.41 295.42 295.43 295.44 295.45 295.50 295.51 295.52 295.53 295.54 295.55 295.60 295.61 295.62 295.63 295.64 295.65 295.70 295.71 295.72 295.73 295.74 295.75 295.80 295.81 295.82 295.83 295.84 295.85 295.90 295.91 295.92 295.93 295.94 295.95 296.00 296.01 296.02 296.03 296.04 296.05 296.06 296.10 296.11 296.12 296.13 296.14 296.15 296.16 296.24 296.34 296.40 296.41 296.42 296.43 296.44 296.45 296.46 296.50 296.51 296.52 296.53 296.54 296.55 296.56 296.60 296.61 296.62 296.63 296.64 296.65 296.66 296.7 296.80 296.81 296.82 296.89 296.90 296.99 297.0 297.1 297.2 297.3 297.8 297.9 2980 2981 2982 2983 2984 2988 2989
Alcohol Abuse	V113.x V791.x 291.0-291.9 303.0-303.9** Please see note below on data redaction
Obesity Overweight	27801 27803 V8535 V8536 V8537 V8538 V8539 V854 V8541 V8542 V8543 V8544 V8545 27800 V853 V8530 V8531 V8532 V8533 V8534 27802 V852 V8521 V8522 V8523 V8524 V8525
Osteoporosis/osteopenia	73300-73309
Dementia	046 046.11 046.19 046.2 046.3 046.71 046.72 046.79 046.8 046.9 290 290.1 290.11 290.12 290.13 290.2 290.21 290.3 290.4 290.41 290.42 290.43 290.8 290.9 294 294.1 294.11 294.2 294.21 294.8 294.9 330 330.1 330.2 330.3 330.8 330.9 331 331.7 331.11 331.19 331.2 331.6 331.81 331.82 331.89 331.9
Diabetes	'24900','24901','24910','24911','24920','24921','24930','24931','24940','24941','24950','24951','24960','24961','24970','24971','24980','24981','24990','24991','25000','25001','25002','25003','25010','25011','25012','25013','25020','25021','25022','25023','25030','25031','25032','25033','25040','25041','25042','25043','25050','25051','25052','25053','25060','25061','25062','25063','25070','25071','25072','25073','25080','25081','25082','25083','25090','25091','25092','25093','36201','36203','36204','36205','36206','36207','36641','V5867',
Liver Disease	'5550','5551','5552','5559','5560','5561','5562','5563','5564','5565','5566','5568','5569',
Pancreatic Diseaase	'0402','0723','2514','2515','2518','2519','5770','5771','5772','5778','5779','5790','5791','5792','5793','5794','5798','5799',
Inflammatory Bowel Disease	'5550','5551','5552','5559','5560','5561','5562','5563','5564','5565','5566','5568','5569',
Rheumatologic Disease	'0993','1361','4460','4461','44620','44621','44629','4463','4464','4465','4466','4467','6960','7100','7101','7102','7103','7104','7105','7108','7109','71110','71111','71112','71113','71114','71115','71116','71117','71118','71119','71120','71121','71122','71123','71124','71125','71126','71127','71128','71129','7140','7141','7142','71430','71431','71432','71433','7144','71481','71489','7149','7200','7201','7202','72081','72089','7209','725',
Spinal Cord disease or injury	'0522','05314','05474','32302','32342','32352','32363','32372','32382','3340','3341','3342','3343','3344','3348','3349','3350','33510','33511','33519','33520','33521','33522','33523','33524','33529','3358','3359','3360','3361','3362','3363','3368','3369','34120','34121','34122','3430','3432','34400','34401','34402','34403','34404','34409','3441','34460','34461','34481','7400','7401','7402','74100','74101','74102','74103','74190','74191','74192','74193','7420','7421','7422','7423','7424','74251','74253','74259','7428','7429','78072','80600','80601','80602','80603','80604','80605','80606','80607','80608','80609','80610','80611','80612','80613','80614','80615','80616','80617','80618','80619','80620','80621','80622','80623','80624','80625','80626','80627','80628','80629','80630','80631','80632','80633','80634','80635','80636','80637','80638','80639','8064','8065','80660','80661','80662','80669','80670','80671','80672','80679','8068','8069','9072','95200','95201','95202','95203','95204','95205','95206','95207','95208','95209','95210','95211','95212','95213','95214','95215','95216','95217','95218','95219','9522','9523','9524','9528','9529',
Serious Neurologic Disease	'33700','33701','33709','3371','33720','33721','33722','33729','3373','3379','340','3410','3411','3418','3419','3560','3561','3562','3563','3564','3568','3569','3570','3571','3572','3573','3574','3575','3576','3577','35781','35782','35789','3579','35800','35801','3581','3582','35830','35831','35839','3588','3589','3590','3591','35921','35922','35923','35924','35929','3593','3594','3595','3596','35971','35979','35981','35989','3599',
Parkinson's and Huntington's Diseases	3320','3321','3330','3334', '3320','3321','3330','3334',
Seizure Disorders and Convulsions	'34500','34501','34510','34511','3452','3453','34540','34541','34550','34551','34560','34561','34570','34571','34580','34581','34590','34591','78031','78032','78033','78039',
Congestive heart failure	'39891','40201','40211','40291','40401','40411','40491','4150','4160','4161','4168','4169','4170','4171','4178','4179','4250','4251','42511','42518','4252','4253','4254','4255','4257','4258','4259','4280','4281','42820','42821','42822','42823','42830','42831','42832','42833','42840','42841','42842','42843','4289','4290','4291',
Coronary Artery Disease	'41000','41001','41002','41010','41011','41012','41020','41021','41022','41030','41031','41032','41040','41041','41042','41050','41051','41052','41060','41061','41062','41070','41071','41072','41080','41081','41082','41090','41091','41092','4110','4111','41181','41189','412','4130','4131','4139','4295','4296',
Cerebrovascular Disease	'09487','34200','34201','34202','34210','34211','34212','34280','34281','34282','34290','34291','34292','3431','3434','3442','34430','34431','34432','34440','34441','34442','3445','34481','34489','3449','430','431','4320','4321','4329','43301','43311','43321','43331','43381','43391','43401','43411','43491','436','43820','43821','43822','43830','43831','43832','43840','43841','43842','43850','43851','43852','43853','99702',

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eTable 2 continued

Peripheral Vascular Disease	'0400','41511','41512','41513','41519','4162','4400','4401','44020','44021','44022','44023','44024','44029','44030','44031','44032','4404','44100','44101','44102','44103','4411','4412','4413','4414','4415','4416','4417','4419','4420','4421','4422','4423','44281','44282','44283','44284','44289','4429','4431','44321','44322','44323','44324','44329','44381','44382','44389','4439','4440','44401','44409','4441','44421','44422','44481','44489','4449','44501','44502','44581','44589','4470','4471','4472','4473','4474','4475','4476','44770','44771','44772','44773','4478','4479','4480','449','45111','45119','45181','45183','4530','4532','4533','45340','45341','45342','45350','45351','45352','45372','45374','45375','45376','45377','4538','45382','45384','45385','45386','45387','4540','4542','45911','45913','45931','45933','5570','5571','5579','59381','7854',
Traumatic Brain Injury	'80000','80001','80002','80003','80004','80005','80006','80009','80010','80011','80012','80013','80014','80015','80016','80019','80020','80021','80022','80023','80024','80025','80026','80029','80030','80031','80032','80033','80034','80035','80036','80039','80040','80041','80042','80043','80044','80045','80046','80049','80050','80051','80052','80053','80054','80055','80056','80059','80060','80061','80062','80063','80064','80065','80066','80069','80070','80071','80072','80073','80074','80075','80076','80079','80080','80081','80082','80083','80084','80085','80086','80089','80090','80091','80092','80093','80094','80095','80096','80099','80100','80101','80102','80103','80104','80105','80106','80109','80110','80111','80112','80113','80114','80115','80116','80119','80120','80121','80122','80123','80124','80125','80126','80129','80130','80131','80132','80133','80134','80135','80136','80139','80140','80141','80142','80143','80144','80145','80146','80149','80150','80151','80152','80153','80154','80155','80156','80159','80160','80161','80162','80163','80164','80165','80166','80169','80170','80171','80172','80173','80174','80175','80176','80179','80180','80181','80182','80183','80184','80185','80186','80189','80190','80191','80192','80193','80194','80195','80196','80199','80220','80221','80222','80223','80224','80225','80226','80227','80228','80229','80230','80231','80232','80233','80234','80235','80236','80237','80238','80239','8024','8025','8026','8027','8028','8029','80300','80301','80302','80303','80304','80305','80306','80309','80310','80311','80312','80313','80314','80315','80316','80319','80320','80321','80322','80323','80324','80325','80326','80329','80330','80331','80332','80333','80334','80335','80336','80339','80340','80341','80342','80343','80344','80345','80346','80349','80350','80351','80352','80353','80354','80355','80356','80359','80360','80361','80362','80363','80364','80365','80366','80369','80370','80371','80372','80373','80374','80375','80376','80379','80380','80381','80382','80383','80384','80385','80386','80389','80390','80391','80392','80393','80394','80395','80396','80399','80400','80401','80402','80403','80404','80405','80406','80409','80410','80411','80412','80413','80414','80415','80416','80419','80420','80421','80422','80423','80424','80425','80426','80429','80430','80431','80432','80433','80434','80435','80436','80439','80440','80441','80442','80443','80444','80445','80446','80449','80450','80451','80452','80453','80454','80455','80456','80459','80460','80461','80462','80463','80464','80465','80466','80469','80470','80471','80472','80473','80474','80475','80476','80479','80480','80481','80482','80483','80484','80485','80486','80489','80490','80491','80492','80493','80494','80495','80496','80499','8502','8503','8504','85100','85101','85102','85103','85104','85105','85106','85109','85110','85111','85112','85113','85114','85115','85116','85119','85120','85121','85122','85123','85124','85125','85126','85129','85130','85131','85132','85133','85134','85135','85136','85139','85140','85141','85142','85143','85144','85145','85146','85149','85150','85151','85152','85153','85154','85155','85156','85159','85160','85161','85162','85163','85164','85165','85166','85169','85170','85171','85172','85173','85174','85175','85176','85179','85180','85181','85182','85183','85184','85185','85186','85189','85190','85191','85192','85193','85194','85195','85196','85199','85200','85201','85202','85203','85204','85205','85206','85209','85210','85211','85212','85213','85214','85215','85216','85219','85220','85221','85222','85223','85224','85225','85226','85229','85230','85231','85232','85233','85234','85235','85236','85239','85240','85241','85242','85243','85244','85245','85246','85249','85250','85251','85252','85253','85254','85255','85256','85259','85300','85301','85302','85303','85304','85305','85306','85309','85310','85311','85312','85313','85314','85315','85316','85319','85400','85401','85402','85403','85404','85405','85406','85409','85410','85411','85412','85413','85414','85415','85416','85419','9050','9070',
Amputee	'3536','9059','99760','99761','99762','99769','V4970','V4971','V4972','V4973','V4974','V4975','V4976','V4977','V521',

Some diagnoses of alcohol abuse will be missing due to redaction of data data associated with addiction care for the years (2013-2014). See https://www.resdac.org/resconnect/articles/203

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eTable 3. Specific Drugs Included in Fracture-Associated and Fracture-Protective Drug Groups

Fracture Associated
Inhaled Steroids
beclomethasone
budesonide
dexamethasone
flunisolide
fluticasone
mometasone
triamcinolone
ciclesonide
Oral Steroids
betamethasone
budesonide
cortisone
dexamethasone
fludrocortisone
hydrocortisone
methylprednisolone
prednisolone
prednisone
triamcinolone
Proton Pump Inhibitors
dexlansoprazole
esomeprazole
lansoprazole
omeprazole
pantoprazole
rabeprazole
H2 Antagonists/ Histamine 2 Receptor Antagonists
cimetidine
famotidine
nizatidine
ranitidine
ranitidine bismuth citrate
SSRI/SNRI Selective Serotonin and Selective Noradrenergic Reuptake Inhibitors
citalopram
desvenlafaxine
escitalopram
FLUoxetine
fluvoxaMINE
PARoxetine
sertraline
venlafaxine
vortioxetine
levomilnacipran
milnacipran
DULoxetine
Tricyclic Antidepressants
amitriptyline
amoxapine
clomipramine
desipramine
imipramine
nortriptyline
protriptyline
trimipramine
doxepin
Thiazolidinediones
pioglitazone
rosiglitazone

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eTable 3 continued

Anticonvulsants
felbamate
tiagabine
topiramate
vigabatrin
valproate
carbamazepine
eslicarbazepine
ethosuximide
ethotoin
ezogabine
fosphenytoin
gabapentin
lacosamide
lamotrigine
levetiracetam
mephenytoin
methsuximide
oxcarbazepine
perampanel
phensuximide
phenytoin
pregabalin
rufinamide
zonisamide
Benzodiazepines
alprazolam
chlordiazepoxide
clobazam
clonazepam
clorazepate
diazepam
estazolam
flurazepam
halazepam
lorazepam
midazolam
oxazepam
prazepam
quazepam
temazepam
triazolam
Barbiturates
butabarbital
butalbital
mephobarbital
pentobarbital
phenobarbital
secobarbital
primidone

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eTable 3 continued

Opioids
alfentanil
butorphanol
codeine
dezocine
dihydrocodeine
fentanyl
hydrocodone
hydromorphone
levorphanol
meperidine
methadone
morphine
morphine liposomal
nalbuphine
opium
oxycodone
oxymorphone
paregoric
pentazocine
propoxyphene
remifentanil
sufentanil
tapentadol
tramadol
naloxone
buprenorphine
Muscle relaxers
meprobamate
methocarbamol
carisoprodol
1st Generation Antihistamines/ H1 Receptor Antagonists
azatadine
bromodiphenhydramine
brompheniramine
carbinoxamine
chlorcyclizine
chlorpheniramine
clemastine
cyclizine
cyproheptadine
dexbrompheniramine
dexchlorpheniramine
dimenhydrinate
diphenhydramine
doxylamine
hydroxyzine
meclizine
pheniramine
promethazine
pyrilamine
triprolidine
triethylperazine

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eTable 3 continued

Anti- Parkinson's Disease
amantadine
apomorphine
bromocriptine
cabergoline
carbidopa
entacapone
levodopa
pergolide
pramipexole
rasagiline
ropinirole
rotigotine
selegiline
tolcapone
dihydroergocryptine
benztropine
biperiden
orphenadrine
procyclidine
trihexyphenidyl
profenamine
Centrally-Acting Antihypertensives
clonidine
guanabenz
guanfacine
methyldopa
tizanidine
1st-Generation Antipsychotics (FGAP)
chlorpromazine
droperidol
fluphenazine
haloperidol
loxapine
mesoridazine
methotrimeprazine
molindone
perphenazine
pimozide
prochlorperazine
thioridazine
thiothixene
trifluoperazine
triflupromazine
2nd-Generation Antipsychotics (SGAP)
aripiprazole
asenapine
clozapine
iloperidone
lurasidone
olanzapine
paliperidone
quetiapine
risperidone
ziprasidone
brexpiprazole
cariprazine
pimavanserin

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eTable 3 continued

Nitrates* (do not include sublingual tablets, oral and transdermal only)
erythrityl tetranitrate
pentaerythritol
nitroglycerin
isosorbide dinitrate
isosorbide mononitrate
Loop Diuretics
bumetanide
furosemide
torsemide
ethacrynic acid
Thiazide and Thiazide-like Diuretics
bendroflumethiazide
chlorothiazide
chlorthalidone
hydrochlorothiazide
indapamide
methyclothiazide
metolazone
polythiazide
benzthiazide
Sedative Hypnotics
acetylcarbromal
busPIRone
chloral hydrate
chlormezanone
doxepin
doxylamine
ethchlorvynol
hydrOXYzine
melatonin
meprobamate
paraldehyde
pyrilamine
ramelteon
sodium oxybate
tasimelteon
dichloralphenazone
suvorexant
eszopiclone
zaleplon
zolpidem
zopiclone

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eTable 3 continued

Fracture Protective Drugs
Systemic Estrogens
conjugated estrogens
esterified estrogens
estradiol
estradiol
estradiol
estradiol
estropipate
estrone
ethinyl estradiol
ethinyl estradiol
synthetic conjugated estrogens, A
synthetic conjugated estrogens, B
estriol
Bisphosphonates
alendronate
etidronate
ibandronate
risedronate
tiludronate
zoledronate
zoledronate
zoledronate
zoledronate
ibandronate
etidronate
pamidronate
Calcitonin
calcitonin
calcitonin
calcitonin, human
Monoclonal Antibiody (RANK L)
denosumab
Parathyroid Hormone (PTH)
teriparatide
Selective Estrogen Receptor Modulators
raloxifene
lasofoxifene
ospemifene
bazedoxifene
tamoxifen
Beta Blockers
acebutolol
atenolol
betaxolol
bisoprolol
carteolol
carvedilol
labetalol
metoprolol
nadolol
nebivolol
penbutolol
pindolol
propranolol
timolol
All fracture associated drugs were identified use National Drug Code variable in Medicare Part D Drug Event file and the Multum LexiComp Basic database (Lexicomp). Denver: Cerner Multum. Zoledronic Acid receipt by infusion was also ascertained from Carrier file using Healthcare Common Procedure Coding System codes: j3487, j3488, j3489, Q2051, J1740, J1436, J2430

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eTable 4. Descriptive Distribution of Drug Use Over Study Period by Sex

Cohort total = 2,646,255 beneficiaries 1,615,613 women, 1,030,642 men, total observation years = 11,286,768; 63.14% women, 36.86% men

Table 4a: Women						
	Cohort Drug Receipt			**Individual Level Drug Receipt in Person Years**		
	Percent with Any Exposure	**Total Time Exposed in Person Years**	**% of Observed Time Exposed**	**Mean**	**Standard Deviation**	**Median**
Fracture Associated Drugs (alone or incombination with other FAD use)						
Thiazide Diuretics	40.49	1,447,094	20.32	2.21	2.15	1.28
Proton Pump Inhibitors	36.83	941,159	13.22	1.58	1.84	0.89
SSRI/SNRI	27.76	763,953	10.73	1.70	1.93	1.00
Loop Diuretics	22.37	522,112	7.33	1.44	1.78	0.69
Opioids	54.99	463,419	6.51	0.52	1.13	0.08
Anticonvulsants	18.32	334,594	4.70	1.13	1.60	0.39
Sedative Hypnotics	16.94	247,517	3.48	0.90	1.42	0.25
H2 Receptor Antagonists	11.20	174,796	2.46	0.97	1.40	0.30
Nitrates	10.73	170,486	2.39	0.98	1.65	0.19
Inhaled Glucocorticoids	9.58	154,467	2.17	1.00	1.39	0.39
Oral Glucocorticoids	33.92	146,070	2.05	0.27	0.74	0.04
Tricyclic Antidepressants	6.79	145,666	2.05	1.33	1.84	0.39
Benzodiazepine	17.58	129,405	1.82	0.46	0.63	0.20
2nd Generation Antispychotics	6.04	128,523	1.81	1.32	1.69	0.59
Antiparkinson Agents	5.32	115,705	1.63	1.35	1.80	0.49
Central Acting Antihypertensives	6.89	115,664	1.62	1.04	1.62	0.26
Thiazolidinediones	4.13	109,814	1.54	1.65	1.70	1.01
1st Generation Antihistamines	17.60	56,849	0.80	0.20	0.54	0.05
Muscle Relaxers	3.74	22,009	0.31	0.36	0.83	0.10
1st Generation Antipsychotics	3.12	20,411	0.29	0.41	1.09	0.03
Barbiturates	1.41	18,367	0.26	0.81	1.46	0.13
Top 20 Most Common Combinations						
PPI & Thiazide Diuretics	13.66	273,718	3.84	1.24	1.54	0.60
PPI & SSRI/SNRI	11.58	221,779	3.11	1.19	1.50	0.58
SSRI/SNRI & Thiazide Diuretics	9.57	198,221	2.78	1.28	1.58	0.64
PPI & Opioids	16.57	147,759	2.08	0.55	1.04	0.11
PPI & Loop Diuretics	8.97	145,621	2.05	1.00	1.36	0.40
Thiazide Diuretics & Opioids	17.57	128,398	1.80	0.45	0.93	0.09
SSRI/SNRI & Opioids	12.99	125,785	1.77	0.60	1.11	0.11
Opioids & Loop Diuretics	6.62	112,616	1.58	1.05	1.42	0.42
PPI & Anticonvulsants	7.21	102,539	1.44	0.88	1.26	0.30
Anticonvulsants & SSRI/SNRI	6.10	96,376	1.35	0.98	1.37	0.36
Opioids & Loop Diuretics	10.24	91,040	1.28	0.55	1.00	0.12
Anticonvulsants & Thiazide Diuretics	6.27	86,716	1.22	0.86	1.26	0.30
Anticonvulsants & Opioids	9.10	85,358	1.20	0.58	1.05	0.13
SSRI/SNRI & Sedative Hypnotics	5.40	74,537	1.05	0.85	1.27	0.30
PPI & Sedative Hypnotics	5.90	72,010	1.01	0.76	1.16	0.24
Thiazide Diuretics & Loop Diuretics	7.02	69,002	0.97	0.61	0.99	0.22
Sedative Hypnotics & Thiazide Diuretics	5.31	66,484	0.93	0.78	1.21	0.23
Anticonvulsants & Loop Diuretics	4.52	62,889	0.88	0.86	1.26	0.30
SSRI/SNRI & SGAP	3.33	61,350	0.86	1.14	1.50	0.50
Nitrates & Loop Diuretics	3.79	54,180	0.76	0.89	1.38	0.22
0 FAD	100					
1 FAD	84.96					
2 FAD	61.90					
3+ FAD	39.62					
Non-Fracture Associated Drugs						
0 Non-FAD	66.46					
1 Non-FAD	51.52					
2 Non-FAD	59.51					
3+ Non-FAD	69.16					
Drugs protective of fracture						
Beta Blockers	50.24	1,575,275	22.11	1.94	2.03	1.11
Osteoporosis medications	25.92	559,704	7.85	1.34	1.56	0.69
Estrogen	18.00	369,450	5.18	1.27	1.62	0.58

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eTable 4 continued

Table 4b: Men						
	Cohort Drug Receipt			Individual Level Drug Receipt in Person Years		
	Percent with Any Exposure	Total Time Exposed in Person Years	% of Observed Time Exposed	Mean	Standard Deviation	Median
Fracture Associated Drugs (not exclusive to other concurrent FAD use)						
Thiazide Diuretics	31.02	617,566	14.85	1.93	1.98	1.13
Proton Pump Inhibitors	29.86	433,643	10.43	1.41	1.71	0.73
Loop Diuretics	18.59	246,196	5.92	1.28	1.62	0.59
SSRI/SNRI	15.73	227,489	5.47	1.40	1.71	0.75
Opioids	50.11	184,621	4.44	0.36	0.92	0.05
Anticonvulsants	14.08	152,255	3.66	1.05	1.52	0.36
Nitrates	13.55	110,253	2.65	0.79	1.44	0.16
Sedative Hypnotics	12.69	106,411	2.56	0.81	1.30	0.21
Thiazolidinediones	5.11	87,790	2.11	1.67	1.69	1.06
H2 Receptor Antagonists	8.19	82,587	1.99	0.98	1.42	0.30
Inhaled Glucocorticoids	8.25	81,502	1.96	0.96	1.33	0.39
Oral Glucocorticoids	29.30	72,475	1.74	0.24	0.66	0.04
Antiparkinson Agents	4.96	67,235	1.62	1.32	1.72	0.55
2nd Generation Antispychotics	4.43	53,465	1.29	1.17	1.58	0.49
Benzodiazepine	11.22	49,972	1.20	0.43	0.63	0.18
Central Acting Antihypertensives	4.38	42,186	1.02	0.93	1.48	0.22
Tricyclic Antidepressants	3.64	39,298	0.95	1.05	1.57	0.30
1st Generation Antihistamines	10.52	18,498	0.45	0.17	0.48	0.04
Barbiturates	1.11	11,530	0.28	1.01	1.52	0.30
Muscle Relaxers	2.83	9,003	0.22	0.31	0.74	0.10
1st Generation Antipsychotics	2.00	8,677	0.21	0.42	1.09	0.04
Top 20 Most Common Combinations (not exclusive to other concurrent FAD use)						
PPI & Thiazide Diuretics	8.36	95,544	2.30	1.11	1.42	0.52
PPI & SSRI/SNRI	5.67	58,322	1.40	1.00	1.33	0.42
PPI & Loop Diuretics	6.15	53,634	1.29	0.85	1.20	0.30
PPI & Opioids	11.44	47,514	1.14	0.40	0.87	0.07
SSRI/SNRI & Thiazide Diuretics	4.02	43,313	1.04	1.05	1.37	0.47
Thiazide Diuretics & Opioids	11.64	39,073	0.94	0.33	0.77	0.05
PPI & Anticonvulsants	4.58	36,900	0.89	0.78	1.15	0.30
SSRI/SNRI & Loop Diuretics	3.62	32,960	0.79	0.88	1.24	0.33
SSRI/SNRI & Opioids	6.36	30,711	0.74	0.47	0.94	0.09
Anticonvulsants & Opioids	6.28	30,446	0.73	0.47	0.92	0.10
Anticonvulsants & Thiazide Diuretics	3.69	30,350	0.73	0.80	1.19	0.30
Opioids & Loop Diuretics	7.30	29,580	0.71	0.39	0.81	0.08
Anticonvulsants & SSRI/SNRI	3.22	29,400	0.71	0.89	1.29	0.30
Thiazide Diuretics & Loop Diuretics	4.75	27,869	0.67	0.57	0.92	0.21
Nitrates & Loop Diuretics	3.64	27,451	0.66	0.73	1.20	0.18
PPI & Nitrates	4.13	27,228	0.66	0.64	1.13	0.15
PPI & Sedative Hypnotics	3.83	27,098	0.65	0.69	1.08	0.21
Anticonvulsants & Loop Diuretics	3.10	25,203	0.61	0.79	1.18	0.28
TZD & Thiazide Diuretics	1.75	23,445	0.56	1.30	1.44	0.84
SSRI/SNRI & SGAP	2.12	22,036	0.53	1.01	1.40	0.41
0 FAD	100					
1 FAD	80.35					
2 FAD	51.77					
3+ FAD	28.54					
Non-Fracture Associated Drugs						
0 Non-FAD	64.79					
1 Non-FAD	43.29					
2 Non-FAD	52.03					
3+ Non-FAD	68.62					
Drugs protective of fracture						
Beta Blockers	42.45	912,897	21.94	2.09	2.09	1.18
Osteoporosis medications	3.13	39,563	0.95	1.23	1.49	0.59
Estrogen	0.10	743	0.02	0.71	1.07	0.28

Tables present distribution of use of the 21 fracture associated drugs (FADs) of interest, Non-FADs, and three categories of drugs protective of fracture including: 1. Osteoporosis treatments: bisphosphonates, calcitonin, denosumab and parathyroid hormone 2. Estrogens: systemic estrogens and selective estrogen receptor modulators, and 3. Beta-blockers. SSRI/SNRI =combined drug group of selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors. Sedative Hypnotics include non-benzodiazepine drugs only. For FADs, status of receipt of 21 single drugs (1 FAD) and 210 concurrent drug pairs (2 FAD) is classified for each person, for each day of observation. 3+ FAD is a classification of person days with 3 or more concurrent FADs. The same approach was taken to identify 552 non-FAD exposures; status of receipt of any 1 non-FAD expsoure (1 Non-FAD), 2 concurrent non-FAD exposures (2 Non-FAD), 3+ Non-FAD is a classification of person days with 3 or more concurrent Non-FADs. Double exposures with population-relevant risk are italicized.

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eTable 5. Number and Category of Fracture-Associated Drug Group Exposures Included in Drug-Specific Models

	Women	Men
Single Fracture Associated Drug Groups Possible	21	21
Single Fracture Associated Drug Groups Excluded	0	0
Single Fracture Associated Drug Groups Included in Models	**21**	**21**
Double Fracture Associated Drug Groups Possible	210	210
Double Fracture Associated Drug Groups Excluded (due to <100 PY exposure time)	27	45
Double Fracture Associated Drug Groups Included in Models	**183**	**165**
Total Specific Fracture Associated Drug Group Exposures Estimated in Model	**204**	**186**
Aggregated other exposure (double exposures pairs with < 100PY observation)	1	1
Indicator for Any Three-or-more Fracture Associated Drug Group Exposure Days	1	1
Total Fracture Associated Drug Group Exposure Indicators Included in Models	206	188
For statistical stability, within each sex-specific cohort, all exposure pairs for which we had less than 100 total person years of observation, were aggregated into an "FAD pairs with < 100 PY" indicator variable.		

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eTable 6. Cox Regression Model Results, Associations Between Number of Current Fracture-Associated Drugs and Other Drugs with Hip Fracture

From 20% random sample of Medicare beneficiaries meeting inclusion criteria, stratified by sex. Hip fracture counts: women, 47 386; men, 12 317. Person-years of observation: women, 7 126 266; men: 4 160 502.

Women

Parameter		Model A= Sensitivity analysis excluding any drug exposure variable				Model B= Continuous exposure variable for total drug use.				Model C1=Categorized exposure indicator variables for total drug use (1,2,3+ drugs versus none).			
Parameter		Ratio (HR)	Confidence	Confidence	p-value	(HR)	Confidence	Confidence	p-value	(HR)	Confidence	Confidence	p-value
Age (reference 67-69)													
Age 70-74		1.30	1.24	1.35	<.0000001	1.29	1.24	1.35	<.0000001	1.30	1.25	1.36	<.0000001
Age 75-79		2.17	2.09	2.25	<.0000001	2.16	2.08	2.25	<.0000001	2.17	2.09	2.25	<.0000001
Age 80-84		3.34	3.22	3.46	<.0000001	3.33	3.21	3.46	<.0000001	3.33	3.20	3.45	<.0000001
Age 85+		5.32	5.12	5.52	<.0000001	5.35	5.16	5.56	<.0000001	5.29	5.09	5.49	<.0000001
Race/Ethnicity (reference white)													
Black		0.48	0.46	0.50	<.0000001	0.50	0.48	0.53	<.0000001	0.49	0.47	0.51	<.0000001
Hispanic		0.75	0.71	0.78	<.0000001	0.79	0.75	0.83	<.0000001	0.77	0.73	0.80	<.0000001
Asian		0.67	0.63	0.72	<.0000001	0.72	0.67	0.77	<.0000001	0.70	0.65	0.74	<.0000001
Other		1.01	0.93	1.10	0.8291614	1.05	0.96	1.15	0.2534495	1.03	0.95	1.13	0.4756557
Low Income Subsidy		1.08	1.04	1.12	0.0000680	1.04	1.00	1.08	0.0542511	1.06	1.02	1.11	0.0017187
Original Medicare eligibility (%)													
Disability		1.42	0.79	2.57	0.2444908	1.45	0.80	2.62	0.2171435	1.42	0.79	2.57	0.2411746
Aged		1.11	0.61	2.01	0.7285464	1.19	0.66	2.15	0.5693099	1.13	0.63	2.05	0.6820753
Long term care		1.41	1.38	1.45	<.0000001	1.40	1.37	1.44	<.0000001	1.41	1.38	1.44	<.0000001
Dual eligible		0.95	0.91	0.99	0.0091583	0.93	0.89	0.97	0.0003144	0.95	0.91	0.99	0.0071514
Chronic Conditions													
Osteoporosis/Osteopenia		3.31	3.24	3.39	<.0000001	3.30	3.23	3.38	<.0000001	3.29	3.22	3.37	<.0000001
Dementia		3.58	3.49	3.67	<.0000001	3.59	3.50	3.68	<.0000001	3.56	3.47	3.65	<.0000001
Obesity		1.06	1.02	1.11	0.0016393	1.00	0.97	1.04	0.8705696	1.05	1.01	1.09	0.0190190
Depression		1.50	1.46	1.54	<.0000001	1.38	1.34	1.41	<.0000001	1.45	1.41	1.49	<.0000001
Serious Mental Illness		1.32	1.27	1.38	<.0000001	1.30	1.24	1.35	<.0000001	1.32	1.26	1.37	<.0000001
Alcohol Abuse		1.88	1.61	2.19	<.0000001	1.97	1.69	2.30	<.0000001	1.91	1.64	2.22	<.0000001
Tobacco/Chronic Lung Disease		2.23	2.17	2.29	<.0000001	2.15	2.10	2.21	<.0000001	2.20	2.14	2.25	<.0000001
Diabetes		0.96	0.94	0.97	0.0000045	0.88	0.86	0.90	<.0000001	0.92	0.90	0.94	<.0000001
Liver Disease		1.05	0.98	1.12	0.2003985	1.04	0.97	1.12	0.2365604	1.05	0.98	1.12	0.1971215
Pancreatic Disease		0.89	0.85	0.93	0.0000003	0.88	0.84	0.92	<.0000001	0.89	0.85	0.93	0.0000001
Inflammatory Bowel Disease		0.82	0.77	0.88	<.0000001	0.81	0.76	0.86	<.0000001	0.82	0.77	0.87	<.0000001
Rheumatologic Disease		1.06	1.03	1.08	0.0000262	1.02	0.99	1.04	0.1816280	1.04	1.01	1.07	0.0026841
Spinal Cord Disease or Injury		1.14	1.09	1.20	<.0000001	1.13	1.08	1.19	0.0000003	1.14	1.09	1.20	<.0000001
Serious Neurologic Disease		1.06	1.03	1.08	0.0000285	1.01	0.98	1.04	0.4878350	1.04	1.01	1.07	0.0022126
Parkinson's/Huntington's Disease		1.02	0.98	1.07	0.3318953	0.99	0.95	1.04	0.7726600	1.01	0.97	1.06	0.5927205
Seizure Disorder		0.89	0.86	0.92	<.0000001	0.88	0.85	0.92	<.0000001	0.89	0.86	0.92	<.0000001
Congestive Heart Failure		1.04	1.01	1.06	0.0019404	0.96	0.94	0.98	0.0002307	1.00	0.98	1.02	0.9734547
Coronary Artery Disease		0.96	0.94	0.99	0.0015668	0.93	0.91	0.96	<.0000001	0.95	0.93	0.97	0.0000132
Cerebrovascular Disease		0.90	0.88	0.93	<.0000001	0.89	0.87	0.91	<.0000001	0.89	0.87	0.92	<.0000001
Peripheral Vascular Disease		0.94	0.92	0.96	<.0000001	0.91	0.90	0.93	<.0000001	0.92	0.90	0.94	<.0000001
Traumatic Brain Injury		1.21	1.16	1.26	<.0000001	1.22	1.17	1.27	<.0000001	1.21	1.16	1.26	<.0000001
Amputee		1.04	0.92	1.17	0.5447029	1.03	0.91	1.15	0.6759613	1.04	0.93	1.17	0.5138780
Estrogen		0.92	0.87	0.96	0.0002199	0.86	0.82	0.90	<.0000001	0.88	0.84	0.93	0.0000002
Osteoporosis medications		1.20	1.17	1.24	<.0000001	1.14	1.11	1.17	<.0000001	1.16	1.13	1.20	<.0000001
Beta Blockers		1.55	1.52	1.58	<.0000001	1.42	1.39	1.45	<.0000001	1.46	1.43	1.49	<.0000001
Continuous Count of Total Drug Use (FAD & non-FAD)		-	-	-	-	1.10	1.09	1.10	<.0000001				
Total Drug Use	0 Drug									1.00			
	1 Drug									1.08	1.04	1.13	0.0004536
	2 Drugs									1.17	1.12	1.22	<.0000001
	3+ Drugs									1.56	1.51	1.61	<.0000001
FAD	0 Drug												
	1 Drug												
	2 Drugs												
	3+ Drugs												
NON-FAD	0 Drug												
	1 Drug												
	2 Drugs												
	3+ Drugs												

Parameter		Model C2 (Figure 1A)= Exposure indicator variables for concurrent use of fracture associated drugs (FAD 1,2,3+ versus none) as well as all other drug use (Non-FAD 1,2,3+ versus none).				Model C3 (Figure 1B)= Age Stratified analysis of exposure indicator variables for concurrent use of fracture associated drugs (FAD 1,2,3+ versus none) as well as all other drug use (Non-FAD 1,2,3+ versus none). Age 67-69 (hip fracture n=6,421)			
Parameter		(HR)	Interval	Confidence Interval	p-value	(HR)	Confidence	Confidence	p-value
Age (reference 67-69)									
Age 70-74		1.24	1.19	1.29	<.0000001				
Age 75-79		2.09	2.01	2.18	<.0000001				
Age 80-84		3.25	3.12	3.37	<.0000001				
Age 85+		5.11	4.92	5.31	<.0000001				
Race/Ethnicity (reference white)									
Black		0.51	0.49	0.53	<.0000001	0.49	0.44	0.55	<.0000001
Hispanic		0.80	0.77	0.84	<.0000001	0.77	0.69	0.86	0.000004
Asian		0.77	0.72	0.82	<.0000001	0.74	0.62	0.89	0.001500
Other		1.07	0.98	1.17	0.1237977	1.10	0.90	1.35	0.345813
Low Income Subsidy		1.02	0.98	1.06	0.2956492	1.04	0.93	1.17	0.496723
Original Medicare eligibility (%)									
Disability		1.27	0.71	2.30	0.4236478	1.77	0.44	7.08	0.420632
Aged		1.08	0.60	1.95	0.8085012	1.63	0.41	6.52	0.491851
Long term care		1.34	1.30	1.37	<.0000001	1.86	1.71	2.03	<.0000001
Dual eligible		0.89	0.85	0.92	<.0000001	1.07	0.94	1.20	0.308453
Chronic Conditions									
Osteoporosis/Osteopenia		3.30	3.23	3.38	<.0000001	4.06	3.80	4.33	<.0000001
Dementia		3.50	3.41	3.59	<.0000001	2.46	2.23	2.71	<.0000001
Obesity		1.00	0.96	1.04	0.9774711	1.08	1.00	1.17	0.046427
Depression		1.24	1.20	1.27	<.0000001	1.48	1.38	1.58	<.0000001
Serious Mental Illness		1.22	1.17	1.27	<.0000001	0.93	0.84	1.04	0.228675
Alcohol Abuse		1.94	1.67	2.26	<.0000001	3.06	2.42	3.85	<.0000001
Tobacco/Chronic Lung Disease		2.19	2.14	2.25	<.0000001	2.59	2.43	2.76	<.0000001
Diabetes		0.93	0.91	0.95	<.0000001	0.99	0.94	1.05	0.824373
Liver Disease		1.03	0.96	1.10	0.4057815	1.03	0.89	1.19	0.716669
Pancreatic Disease		0.87	0.83	0.91	<.0000001	0.89	0.80	1.00	0.042732
Inflammatory Bowel Disease		0.80	0.75	0.85	<.0000001	0.74	0.64	0.87	0.000187
Rheumatologic Disease		0.98	0.96	1.00	0.1048958	1.06	1.00	1.13	0.066325
Spinal Cord Disease or Injury		1.11	1.06	1.17	0.0000134	1.13	1.00	1.27	0.044723
Serious Neurologic Disease		0.97	0.95	1.00	0.0179386	1.04	0.98	1.11	0.197622
Parkinson's/Huntington's Disease		0.89	0.85	0.93	0.0000003	1.11	0.98	1.25	0.105596
Seizure Disorder		0.84	0.81	0.87	<.0000001	0.91	0.83	1.00	0.038213
Congestive Heart Failure		0.97	0.95	0.99	0.0076765	0.99	0.93	1.06	0.799222
Coronary Artery Disease		0.95	0.93	0.97	0.0000019	0.81	0.76	0.87	<.0000001
Cerebrovascular Disease		0.91	0.89	0.94	<.0000001	1.19	1.11	1.27	0.000002
Peripheral Vascular Disease		0.91	0.89	0.93	<.0000001	1.10	1.04	1.17	0.001143
Traumatic Brain Injury		1.18	1.13	1.23	<.0000001	1.23	1.08	1.40	0.001629
Amputee		1.02	0.91	1.15	0.7147438	1.40	1.10	1.78	0.005819
Estrogen		0.83	0.79	0.87	<.0000001	0.77	0.69	0.86	0.000002
Osteoporosis medications		1.13	1.10	1.16	<.0000001	1.39	1.29	1.50	<.0000001
Beta Blockers		1.34	1.31	1.37	<.0000001	1.31	1.24	1.39	<.0000001
Continuous Count of Total Drug Use (FAD & non-FAD)									
Total Drug Use	0 Drug								
	1 Drug								
	2 Drugs								
	3+ Drugs								
FAD	0 Drug	1.00							
	1 Drug	2.04	1.99	2.11	<.0000001	2.15	1.98	2.33	<.0000001
	2 Drugs	2.86	2.77	2.95	<.0000001	3.28	3.00	3.58	<.0000001
	3+ Drugs	4.50	4.36	4.65	<.0000001	5.68	5.21	6.19	<.0000001
NON-FAD	0 Drug	1.00							
	1 Drug	0.93	0.90	0.96	0.0000191	0.88	0.80	0.96	0.005234
	2 Drugs	0.84	0.81	0.87	<.0000001	0.73	0.67	0.80	<.0000001
	3+ Drugs	0.74	0.72	0.77	<.0000001	0.66	0.61	0.72	<.0000001

Parameter		Model C3 (Figure 1B), Age 70-74 (hip fracture n=7,183)				Age 75-79 (hip fracture n=9,937)			
Parameter		Ratio (HR)	Confidence	Confidence	p-value	Ratio (HR)	Confidence	Confidence	p-value
Age (reference 67-69)									
Age 70-74									
Age 75-79									
Age 80-84									
Age 85+									
Race/Ethnicity (reference white)									
Black		0.46	0.41	0.51	<.0000001	0.47	0.42	0.52	<.0000001
Hispanic		0.67	0.60	0.75	<.0000001	0.81	0.74	0.89	0.000010
Asian		0.70	0.60	0.82	0.000013	0.74	0.65	0.85	0.000019
Other		1.09	0.89	1.34	0.400359	1.05	0.86	1.27	0.648979
Low Income Subsidy		1.13	1.02	1.26	0.022109	1.08	0.99	1.18	0.070101
Original Medicare eligibility (%)									
Disability		1.82	0.58	5.64	0.302553	1.07	0.35	3.32	0.905407
Aged		1.66	0.53	5.15	0.383524	0.97	0.31	3.03	0.961985
Long term care		1.75	1.62	1.88	<.0000001	1.60	1.52	1.69	<.0000001
Dual eligible		0.97	0.87	1.08	0.588197	0.86	0.79	0.94	0.001359
Chronic Conditions									
Osteoporosis/Osteopenia		3.97	3.74	4.22	<.0000001	3.54	3.37	3.72	<.0000001
Dementia		3.15	2.91	3.41	<.0000001	3.95	3.73	4.18	<.0000001
Obesity		1.05	0.97	1.14	0.270863	0.91	0.84	0.99	0.029551
Depression		1.31	1.22	1.40	<.0000001	1.17	1.10	1.24	0.000000
Serious Mental Illness		1.01	0.90	1.13	0.871746	1.06	0.97	1.17	0.215288
Alcohol Abuse		1.59	1.14	2.22	0.006958	1.52	1.06	2.20	0.024287
Tobacco/Chronic Lung Disease		2.31	2.17	2.45	<.0000001	2.14	2.03	2.26	<.0000001
Diabetes		0.94	0.89	0.99	0.022182	0.94	0.90	0.98	0.004289
Liver Disease		1.25	1.08	1.44	0.002139	0.94	0.81	1.10	0.463581
Pancreatic Disease		0.92	0.82	1.02	0.107798	0.87	0.79	0.96	0.003725
Inflammatory Bowel Disease		0.81	0.70	0.94	0.004228	0.89	0.78	1.01	0.066161
Rheumatologic Disease		1.06	1.00	1.12	0.072162	0.95	0.91	1.01	0.083395
Spinal Cord Disease or Injury		1.18	1.05	1.32	0.006272	1.07	0.97	1.19	0.197687
Serious Neurologic Disease		0.97	0.91	1.03	0.293126	0.94	0.89	1.00	0.036934
Parkinson's/Huntington's Disease		1.03	0.93	1.15	0.560801	0.95	0.87	1.04	0.267755
Seizure Disorder		0.89	0.82	0.98	0.015022	0.81	0.74	0.87	<.0000001
Congestive Heart Failure		1.03	0.98	1.10	0.264155	0.96	0.91	1.01	0.079761
Coronary Artery Disease		0.91	0.86	0.97	0.002749	0.93	0.89	0.98	0.005149
Cerebrovascular Disease		1.00	0.94	1.07	0.951918	0.93	0.88	0.98	0.006702
Peripheral Vascular Disease		0.98	0.93	1.04	0.484029	0.93	0.89	0.98	0.002111
Traumatic Brain Injury		1.29	1.15	1.45	0.000022	1.23	1.12	1.35	0.000013
Amputee		1.41	1.09	1.82	0.008362	0.84	0.64	1.11	0.215144
Estrogen		0.76	0.68	0.85	0.000001	0.93	0.85	1.03	0.144166
Osteoporosis medications		1.27	1.19	1.37	<.0000001	1.10	1.04	1.17	0.001439
Beta Blockers		1.30	1.23	1.37	<.0000001	1.32	1.26	1.38	<.0000001
Continuous Count of Total Drug Use (FAD & non-FAD)									
Total Drug Use	0 Drug								
	1 Drug								
	2 Drugs								
	3+ Drugs								
FAD	0 Drug								
	1 Drug	1.85	1.72	2.00	<.0000001	1.93	1.81	2.06	<.0000001
	2 Drugs	2.74	2.52	2.97	<.0000001	2.79	2.61	2.99	<.0000001
	3+ Drugs	4.44	4.09	4.82	<.0000001	4.40	4.10	4.73	<.0000001
NON-FAD	0 Drug								
	1 Drug	0.92	0.84	1.00	0.061216	0.93	0.86	1.00	0.041794
	2 Drugs	0.86	0.79	0.94	0.000528	0.83	0.77	0.89	0.000001
	3+ Drugs	0.77	0.71	0.83	<.0000001	0.74	0.69	0.79	<.0000001

Parameter		Model C3 (Figure 1B), Age 80-84 (hip fracture n=n=11,282)				Age 85+ (hip fracture n=2,563)			
Parameter		Ratio (HR)	Confidence	Confidence	p-value	Ratio (HR)	Confidence	Confidence	p-value
Age (reference 67-69)									
Age 70-74									
Age 75-79									
Age 80-84									
Age 85+									
Race/Ethnicity (reference white)									
Black		0.47	0.42	0.51	<.0000001	0.61	0.56	0.66	<.0000001
Hispanic		0.83	0.76	0.92	0.000151	0.92	0.83	1.01	0.077876
Asian		0.76	0.66	0.86	0.000035	0.88	0.77	1.00	0.047553
Other		0.99	0.81	1.21	0.904379	1.07	0.90	1.28	0.435667
Low Income Subsidy		1.03	0.96	1.12	0.424994	0.91	0.85	0.98	0.009339
Original Medicare eligibility (%)									
Disability		0.53	0.08	3.78	0.528830	2.35	0.59	9.42	0.226990
Aged		0.54	0.08	3.80	0.531608	2.55	0.64	10.26	0.186421
Long term care		1.30	1.24	1.36	<.0000001	1.05	1.01	1.09	0.014441
Dual eligible		0.84	0.77	0.91	0.000041	0.87	0.81	0.93	0.000123
Chronic Conditions									
Osteoporosis/Osteopenia		3.13	2.99	3.28	<.0000001	2.84	2.72	2.97	<.0000001
Dementia		3.73	3.55	3.92	<.0000001	3.80	3.64	3.96	<.0000001
Obesity		0.86	0.78	0.94	0.001207	0.72	0.63	0.83	0.000002
Depression		1.19	1.13	1.26	<.0000001	1.09	1.03	1.15	0.001787
Serious Mental Illness		1.27	1.17	1.39	0.000000	1.29	1.18	1.41	<.0000001
Alcohol Abuse		1.08	0.70	1.66	0.727326	0.84	0.42	1.68	0.618927
Tobacco/Chronic Lung Disease		1.85	1.75	1.95	<.0000001	1.94	1.83	2.05	<.0000001
Diabetes		0.92	0.89	0.96	0.000128	0.87	0.84	0.91	<.0000001
Liver Disease		0.93	0.79	1.10	0.418279	0.84	0.70	1.02	0.070647
Pancreatic Disease		0.83	0.76	0.91	0.000063	0.84	0.77	0.92	0.000265
Inflammatory Bowel Disease		0.78	0.68	0.89	0.000198	0.75	0.64	0.88	0.000262
Rheumatologic Disease		0.96	0.91	1.01	0.083694	0.92	0.87	0.98	0.004427
Spinal Cord Disease or Injury		0.99	0.90	1.10	0.905101	1.13	1.02	1.24	0.021885
Serious Neurologic Disease		0.96	0.91	1.01	0.112406	0.90	0.85	0.95	0.000169
Parkinson's/Huntington's Disease		0.82	0.75	0.89	0.000004	0.74	0.67	0.81	<.0000001
Seizure Disorder		0.76	0.70	0.82	<.0000001	0.71	0.66	0.77	<.0000001
Congestive Heart Failure		1.00	0.96	1.05	0.907463	0.93	0.89	0.96	0.000146
Coronary Artery Disease		1.00	0.96	1.05	0.880317	0.99	0.95	1.04	0.736151
Cerebrovascular Disease		0.86	0.82	0.91	<.0000001	0.81	0.77	0.84	<.0000001
Peripheral Vascular Disease		0.87	0.83	0.90	<.0000001	0.82	0.79	0.85	<.0000001
Traumatic Brain Injury		1.20	1.11	1.31	0.000010	1.11	1.03	1.20	0.007612
Amputee		0.80	0.61	1.06	0.115415	0.77	0.59	1.00	0.047735
Estrogen		0.85	0.77	0.94	0.002169	0.91	0.81	1.01	0.085415
Osteoporosis medications		1.03	0.97	1.09	0.341592	1.02	0.96	1.09	0.465379
Beta Blockers		1.35	1.29	1.40	<.0000001	1.42	1.36	1.48	<.0000001
Continuous Count of Total Drug Use (FAD & non-FAD)									
Total Drug Use	0 Drug								
	1 Drug								
	2 Drugs								
	3+ Drugs								
FAD	0 Drug								
	1 Drug	1.98	1.87	2.11	<.0000001	2.41	2.28	2.55	<.0000001
	2 Drugs	2.72	2.55	2.90	<.0000001	3.28	3.08	3.49	<.0000001
	3+ Drugs	4.16	3.89	4.45	<.0000001	4.78	4.49	5.09	<.0000001
NON-FAD	0 Drug								
	1 Drug	0.98	0.92	1.05	0.634905	0.95	0.90	1.02	0.135165
	2 Drugs	0.90	0.84	0.96	0.001704	0.86	0.81	0.92	0.000002
	3+ Drugs	0.77	0.73	0.82	<.0000001	0.77	0.72	0.81	<.0000001

Men

Parameter		Model A= Sensitivity analysis excluding any drug exposure variable				Model B= Continuous exposure variable for total drug use.				Model C1=Categorized exposure indicator variables for total drug use (1,2,3+ drugs versus none).			
Parameter		Hazard Ratio (HR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	p-value	Hazard Ratio (HR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	p-value	Hazard Ratio (HR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	p-value
Age (reference 67-69)													
Age 70-74		1.24	1.17	1.33	<.0000001	1.24	1.17	1.33	<.0000001	1.25	1.18	1.34	<.0000001
Age 75-79		1.89	1.78	2.02	<.0000001	1.90	1.79	2.02	<.0000001	1.91	1.79	2.03	<.0000001
Age 80-84		3.09	2.91	3.29	<.0000001	3.11	2.92	3.31	<.0000001	3.12	2.93	3.32	<.0000001
Age 85+		5.63	5.29	5.99	<.0000001	5.69	5.34	6.06	<.0000001	5.66	5.32	6.03	<.0000001
Race/Ethnicity (reference white)													
Black		0.52	0.48	0.57	<.0000001	0.55	0.50	0.60	<.0000001	0.54	0.49	0.58	<.0000001
Hispanic		0.65	0.60	0.70	<.0000001	0.68	0.63	0.74	<.0000001	0.67	0.61	0.72	<.0000001
Asian		0.45	0.40	0.52	<.0000001	0.46	0.41	0.53	<.0000001	0.46	0.40	0.52	<.0000001
Other		0.88	0.74	1.04	0.1292927	0.89	0.76	1.06	0.1878222	0.89	0.75	1.05	0.1726889
Low Income Subsidy		1.23	1.13	1.34	0.0000010	1.22	1.12	1.32	0.0000040	1.24	1.14	1.35	0.0000004
Original Medicare eligibility (%)													
Disability		1.19	0.38	3.68	0.7687277	1.17	0.38	3.64	0.7833651	1.19	0.38	3.69	0.7639888
Aged		0.90	0.29	2.79	0.8549026	0.92	0.30	2.86	0.8861022	0.92	0.30	2.84	0.8780788
Long term care		1.55	1.48	1.63	<.0000001	1.53	1.46	1.61	<.0000001	1.54	1.46	1.62	<.0000001
Dual eligible		0.93	0.86	1.02	0.1227305	0.90	0.82	0.98	0.0154687	0.92	0.85	1.01	0.0664971
Chronic Conditions													
Osteoporosis/Osteopenia		4.53	4.21	4.89	<.0000001	4.51	4.18	4.86	<.0000001	4.51	4.18	4.85	<.0000001
Dementia		4.03	3.82	4.24	<.0000001	3.99	3.79	4.20	<.0000001	3.98	3.78	4.19	<.0000001
Obesity		1.02	0.94	1.10	0.6749073	0.96	0.89	1.04	0.3335763	1.00	0.93	1.08	0.9211443
Depression		1.53	1.44	1.62	<.0000001	1.43	1.35	1.51	<.0000001	1.49	1.41	1.58	<.0000001
Serious Mental Illness		1.43	1.32	1.54	<.0000001	1.41	1.30	1.52	<.0000001	1.42	1.31	1.54	<.0000001
Alcohol Abuse		1.67	1.46	1.91	<.0000001	1.76	1.53	2.01	<.0000001	1.71	1.50	1.96	<.0000001
Tobacco/Chronic Lung Disease		2.60	2.49	2.71	<.0000001	2.52	2.41	2.63	<.0000001	2.55	2.45	2.67	<.0000001
Diabetes		0.90	0.87	0.94	0.0000001	0.83	0.80	0.86	<.0000001	0.86	0.83	0.90	<.0000001
Liver Disease		1.11	1.00	1.24	0.0569526	1.10	0.99	1.23	0.0748928	1.11	1.00	1.24	0.0508873
Pancreatic Disease		0.91	0.83	1.00	0.0379488	0.90	0.83	0.99	0.0244078	0.91	0.83	0.99	0.0328794
Inflammatory Bowel Disease		1.00	0.89	1.14	0.9626643	0.99	0.87	1.12	0.8228687	1.00	0.88	1.13	0.9495637
Rheumatologic Disease		1.07	1.01	1.13	0.0193104	1.04	0.98	1.10	0.1772737	1.06	1.00	1.12	0.0553019
Spinal Cord Disease or Injury		1.11	1.02	1.21	0.0145727	1.10	1.01	1.20	0.0270094	1.11	1.02	1.21	0.0127472
Serious Neurologic Disease		1.13	1.08	1.18	0.0000005	1.08	1.03	1.13	0.0014721	1.11	1.06	1.17	0.0000105
Parkinson's/Huntington's Disease		1.42	1.33	1.51	<.0000001	1.38	1.29	1.46	<.0000001	1.40	1.31	1.49	<.0000001
Seizure Disorder		0.99	0.93	1.06	0.8343915	0.98	0.92	1.05	0.5768890	0.99	0.93	1.05	0.6936826
Congestive Heart Failure		1.17	1.12	1.22	<.0000001	1.09	1.04	1.14	0.0000668	1.13	1.09	1.18	<.0000001
Coronary Artery Disease		0.90	0.86	0.94	0.0000004	0.88	0.84	0.91	<.0000001	0.89	0.85	0.92	<.0000001
Cerebrovascular Disease		1.03	0.98	1.07	0.2883028	1.01	0.97	1.06	0.6587586	1.02	0.97	1.06	0.5004384
Peripheral Vascular Disease		1.06	1.01	1.10	0.0091996	1.02	0.98	1.06	0.3292395	1.03	0.99	1.07	0.1562596
Traumatic Brain Injury		1.31	1.21	1.41	<.0000001	1.33	1.23	1.44	<.0000001	1.32	1.22	1.43	<.0000001
Amputee		1.38	1.21	1.57	0.0000024	1.37	1.20	1.57	0.0000031	1.38	1.21	1.57	0.0000020
Estrogen		0.68	0.28	1.64	0.3926226	0.62	0.26	1.49	0.2814806	0.65	0.27	1.56	0.3361772
Osteoporosis medications		0.99	0.87	1.12	0.8115713	0.90	0.79	1.02	0.0960561	0.94	0.83	1.07	0.3588648
Beta Blockers		1.52	1.46	1.59	<.0000001	1.36	1.30	1.41	<.0000001	1.41	1.35	1.47	<.0000001
Continuous Count of Total Drug Use (FAD & non-FAD)		-	-	-	-	1.10	1.09	1.11	<.0000001				
Total Drug Use	0 Drug									1.00			
	1 Drug									1.07	0.99	1.17	0.0956744
	2 Drugs									1.13	1.05	1.22	0.0018700
	3+ Drugs									1.55	1.46	1.65	<.0000001
FAD	0 Drug												
	1 Drug												
	2 Drugs												
	3+ Drugs												
NON-FAD	0 Drug												
	1 Drug												
	2 Drugs												
	3+ Drugs												

Parameter		Model C2 (Figure 1A)= Exposure indicator variables for concurrent use of fracture associated drugs (FAD 1,2,3+ versus none) as well as all other drug use (Non-FAD 1,2,3+ versus none).				Model C3 (Figure 1C)= Age Stratified analysis of exposure indicator variables for concurrent use of fracture associated drugs (FAD 1,2,3+ versus none) as well as all other drug use (Non-FAD 1,2,3+ versus none). Age 67-69 (hip fracture n=2,531)			
Parameter		Hazard Ratio (HR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	p-value	Hazard Ratio (HR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	p-value
Age (reference 67-69)									
Age 70-74		1.19	1.12	1.27	0.0000001				
Age 75-79		1.83	1.72	1.95	<.0000001				
Age 80-84		2.98	2.80	3.18	<.0000001				
Age 85+		5.33	5.00	5.68	<.0000001				
Race/Ethnicity (reference white)									
Black		0.55	0.51	0.60	<.0000001	0.57	0.48	0.68	<.0000001
Hispanic		0.70	0.64	0.76	<.0000001	0.75	0.63	0.89	0.001000
Asian		0.50	0.44	0.57	<.0000001	0.49	0.35	0.69	0.000038
Other		0.91	0.77	1.08	0.2836978	0.89	0.66	1.22	0.480472
Low Income Subsidy		1.19	1.09	1.29	0.0000627	1.11	0.91	1.35	0.327521
Original Medicare eligibility (%)									
Disability		1.06	0.34	3.28	0.9228518	0.00	0.00	0.00	0.918105
Aged		0.88	0.29	2.74	0.8298957	0.00	0.00	0.00	0.915780
Long term care		1.45	1.37	1.52	<.0000001	1.91	1.67	2.17	<.0000001
Dual eligible		0.85	0.78	0.93	0.0002646	1.20	0.98	1.47	0.076721
Chronic Conditions									
Osteoporosis/Osteopenia		4.45	4.13	4.79	<.0000001	5.21	4.38	6.19	<.0000001
Dementia		3.79	3.60	3.99	<.0000001	2.65	2.30	3.04	<.0000001
Obesity		0.96	0.88	1.03	0.2404810	0.97	0.85	1.11	0.662054
Depression		1.27	1.20	1.34	<.0000001	1.44	1.28	1.63	<.0000001
Serious Mental Illness		1.31	1.21	1.42	<.0000001	0.99	0.85	1.16	0.906020
Alcohol Abuse		1.70	1.48	1.94	<.0000001	1.64	1.33	2.02	0.000004
Tobacco/Chronic Lung Disease		2.54	2.44	2.66	<.0000001	3.00	2.73	3.30	<.0000001
Diabetes		0.87	0.84	0.90	<.0000001	0.93	0.85	1.02	0.112535
Liver Disease		1.07	0.96	1.19	0.2202379	1.01	0.83	1.22	0.925833
Pancreatic Disease		0.88	0.80	0.96	0.0038325	0.97	0.81	1.16	0.721830
Inflammatory Bowel Disease		0.98	0.87	1.11	0.7982742	1.09	0.85	1.40	0.492856
Rheumatologic Disease		1.00	0.95	1.06	0.9445934	1.14	1.00	1.28	0.045005
Spinal Cord Disease or Injury		1.10	1.01	1.19	0.0355464	1.22	1.04	1.43	0.016632
Serious Neurologic Disease		1.03	0.98	1.08	0.2921994	1.06	0.96	1.18	0.233899
Parkinson's/Huntington's Disease		1.20	1.12	1.27	<.0000001	1.45	1.26	1.69	0.000001
Seizure Disorder		0.90	0.84	0.96	0.0009620	0.95	0.84	1.09	0.479772
Congestive Heart Failure		1.10	1.05	1.14	0.0000201	1.03	0.94	1.14	0.506936
Coronary Artery Disease		0.90	0.86	0.94	0.0000007	0.78	0.71	0.86	0.000001
Cerebrovascular Disease		1.03	0.99	1.08	0.1697974	1.32	1.19	1.47	0.000000
Peripheral Vascular Disease		1.02	0.98	1.06	0.4227959	1.05	0.96	1.15	0.293747
Traumatic Brain Injury		1.30	1.20	1.40	<.0000001	1.35	1.13	1.60	0.000744
Amputee		1.37	1.20	1.56	0.0000033	1.91	1.54	2.37	<.0000001
Estrogen		0.52	0.22	1.25	0.1442681	0.89	0.22	3.56	0.864695
Osteoporosis medications		0.86	0.75	0.97	0.0180487	0.66	0.48	0.91	0.011169
Beta Blockers		1.26	1.21	1.32	<.0000001	1.20	1.09	1.31	0.000120
Continuous Count of Total Drug Use (FAD & non-FAD)									
Total Drug Use	0 Drug								
	1 Drug								
	2 Drugs								
	3+ Drugs								
FAD	0 Drug	1.00							
	1 Drug	2.23	2.11	2.36	<.0000001	2.26	2.00	2.55	<.0000001
	2 Drugs	3.40	3.20	3.61	<.0000001	3.55	3.10	4.06	<.0000001
	3+ Drugs	5.18	4.87	5.52	<.0000001	6.09	5.32	6.97	<.0000001
NON-FAD	0 Drug	1.00							
	1 Drug	0.90	0.84	0.96	0.0011528	0.82	0.71	0.95	0.006783
	2 Drugs	0.84	0.79	0.89	<.0000001	0.75	0.65	0.86	0.000056
	3+ Drugs	0.71	0.67	0.75	<.0000001	0.58	0.51	0.66	<.0000001

Parameter		Model C3 (Figure 1C), Age 70-74 (hip fracture n=2,300)				Age 75-79 (hip fracture n=2,639)			
Parameter		Hazard Ratio (HR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	p-value	Hazard Ratio (HR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	p-value
Age (reference 67-69)									
Age 70-74									
Age 75-79									
Age 80-84									
Age 85+									
Race/Ethnicity (reference white)									
Black		0.61	0.51	0.74	0.000000	0.43	0.35	0.53	<.0000001
Hispanic		0.65	0.54	0.79	0.000010	0.61	0.50	0.73	0.000000
Asian		0.55	0.41	0.74	0.000073	0.44	0.33	0.58	<.0000001
Other		0.98	0.70	1.38	0.918198	0.72	0.48	1.08	0.114190
Low Income Subsidy		1.23	1.01	1.51	0.043557	1.25	1.04	1.50	0.019812
Original Medicare eligibility (%)									
Disability		0.00	0.00	0.00	0.928170	0.85	0.12	6.05	0.871904
Aged		0.00	0.00	0.00	0.927191	0.86	0.12	6.13	0.880002
Long term care		1.90	1.66	2.18	<.0000001	1.59	1.42	1.78	<.0000001
Dual eligible		0.96	0.78	1.18	0.682322	0.78	0.65	0.95	0.014331
Chronic Conditions									
Osteoporosis/Osteopenia		4.08	3.37	4.95	<.0000001	4.74	4.03	5.56	<.0000001
Dementia		3.11	2.71	3.56	<.0000001	4.47	4.00	4.99	<.0000001
Obesity		0.93	0.79	1.09	0.366819	0.82	0.69	0.97	0.024035
Depression		1.34	1.17	1.53	0.000025	1.27	1.12	1.44	0.000164
Serious Mental Illness		1.17	0.98	1.40	0.084260	1.17	0.98	1.40	0.093130
Alcohol Abuse		1.29	0.97	1.72	0.082544	1.52	1.11	2.06	0.008206
Tobacco/Chronic Lung Disease		2.87	2.60	3.17	<.0000001	2.47	2.25	2.70	<.0000001
Diabetes		0.85	0.78	0.93	0.000497	0.90	0.83	0.98	0.015899
Liver Disease		1.16	0.94	1.45	0.173561	0.97	0.76	1.23	0.790006
Pancreatic Disease		0.82	0.67	1.02	0.071216	0.84	0.69	1.02	0.075144
Inflammatory Bowel Disease		1.11	0.86	1.44	0.423851	1.08	0.84	1.40	0.552178
Rheumatologic Disease		0.99	0.87	1.13	0.872952	0.93	0.82	1.05	0.221220
Spinal Cord Disease or Injury		1.09	0.90	1.32	0.382023	0.88	0.73	1.07	0.203580
Serious Neurologic Disease		1.14	1.03	1.27	0.014088	1.06	0.96	1.17	0.289245
Parkinson's/Huntington's Disease		1.43	1.23	1.65	0.000002	1.24	1.09	1.41	0.001058
Seizure Disorder		0.81	0.70	0.94	0.006074	0.95	0.84	1.09	0.492711
Congestive Heart Failure		1.08	0.98	1.19	0.128634	1.18	1.08	1.29	0.000282
Coronary Artery Disease		0.90	0.81	0.99	0.026457	0.90	0.82	0.99	0.021268
Cerebrovascular Disease		1.23	1.11	1.37	0.000119	1.03	0.93	1.13	0.610479
Peripheral Vascular Disease		1.01	0.92	1.11	0.819072	1.06	0.97	1.15	0.205913
Traumatic Brain Injury		1.68	1.42	2.00	<.0000001	1.15	0.96	1.37	0.122027
Amputee		1.43	1.08	1.89	0.013722	1.02	0.74	1.42	0.895252
Estrogen		0.75	0.11	5.32	0.770501	0.00	0.00	0.00	0.920327
Osteoporosis medications		1.25	0.94	1.65	0.124524	0.90	0.69	1.17	0.416641
Beta Blockers		1.23	1.11	1.35	0.000031	1.35	1.23	1.47	<.0000001
Continuous Count of Total Drug Use (FAD & non-FAD)									
Total Drug Use	0 Drug								
	1 Drug								
	2 Drugs								
	3+ Drugs								
FAD	0 Drug								
	1 Drug	2.03	1.79	2.30	<.0000001	2.00	1.78	2.25	<.0000001
	2 Drugs	3.25	2.82	3.73	<.0000001	3.16	2.77	3.59	<.0000001
	3+ Drugs	4.85	4.18	5.61	<.0000001	4.57	3.99	5.24	<.0000001
NON-FAD	0 Drug								
	1 Drug	0.89	0.76	1.04	0.126793	0.98	0.85	1.14	0.797947
	2 Drugs	0.81	0.70	0.95	0.007596	0.89	0.77	1.03	0.103180
	3+ Drugs	0.71	0.62	0.81	0.000000	0.80	0.70	0.91	0.000487

Parameter		Model C3 (Figure 1C), Age 80-84 (hip fracture n=2,465)				Age 85+ (hip fracture n=2,382)			
Parameter		Hazard Ratio (HR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	p-value	Hazard Ratio (HR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	p-value
Age (reference 67-69)									
Age 70-74									
Age 75-79									
Age 80-84									
Age 85+									
Race/Ethnicity (reference white)									
Black		0.62	0.51	0.76	0.000002	0.43	0.33	0.55	<.0000001
Hispanic		0.87	0.73	1.05	0.143907	0.71	0.58	0.88	0.001755
Asian		0.56	0.43	0.74	0.000037	0.52	0.39	0.69	0.000004
Other		0.96	0.62	1.49	0.849820	1.10	0.71	1.69	0.678910
Low Income Subsidy		1.18	0.99	1.42	0.072028	1.26	1.06	1.49	0.008008
Original Medicare eligibility (%)									
Disability		17.07	4.25	68.52	0.000063	0.00	0.00	0.00	0.949397
Aged		15.60	3.86	63.00	0.000115	0.00	0.00	0.00	0.950931
Long term care		1.23	1.11	1.37	0.000104	1.07	0.97	1.17	0.200700
Dual eligible		0.72	0.60	0.88	0.000904	0.68	0.57	0.81	0.000024
Chronic Conditions									
Osteoporosis/Osteopenia		4.47	3.82	5.24	<.0000001	4.38	3.75	5.11	<.0000001
Dementia		4.74	4.27	5.25	<.0000001	4.12	3.74	4.54	<.0000001
Obesity		1.05	0.86	1.29	0.621565	0.89	0.66	1.20	0.447464
Depression		1.17	1.03	1.33	0.020062	1.06	0.92	1.22	0.392228
Serious Mental Illness		1.66	1.39	1.98	<.0000001	1.28	1.04	1.59	0.020416
Alcohol Abuse		1.45	0.97	2.16	0.069517	0.66	0.27	1.59	0.353600
Tobacco/Chronic Lung Disease		2.23	2.02	2.45	<.0000001	2.09	1.88	2.32	<.0000001
Diabetes		0.82	0.76	0.90	0.000008	0.85	0.78	0.93	0.000327
Liver Disease		0.99	0.74	1.32	0.924961	0.96	0.67	1.38	0.818423
Pancreatic Disease		0.83	0.68	1.02	0.080619	0.95	0.78	1.17	0.650708
Inflammatory Bowel Disease		0.90	0.66	1.22	0.487844	0.67	0.47	0.96	0.027782
Rheumatologic Disease		0.94	0.82	1.07	0.343030	1.12	0.98	1.28	0.101937
Spinal Cord Disease or Injury		1.00	0.82	1.22	0.990004	1.19	0.97	1.47	0.103250
Serious Neurologic Disease		0.89	0.80	0.99	0.037071	0.92	0.82	1.03	0.156311
Parkinson's/Huntington's Disease		1.11	0.97	1.27	0.122113	0.91	0.78	1.06	0.209984
Seizure Disorder		0.80	0.69	0.93	0.003134	0.71	0.60	0.84	0.000092
Congestive Heart Failure		1.16	1.06	1.27	0.000940	0.98	0.90	1.08	0.706801
Coronary Artery Disease		0.93	0.85	1.01	0.092862	1.02	0.93	1.12	0.708320
Cerebrovascular Disease		0.93	0.84	1.02	0.125750	0.76	0.69	0.85	0.000000
Peripheral Vascular Disease		0.97	0.89	1.06	0.439279	0.95	0.87	1.04	0.237426
Traumatic Brain Injury		1.24	1.04	1.48	0.017558	1.17	0.98	1.39	0.081451
Amputee		1.03	0.71	1.48	0.883465	0.74	0.47	1.18	0.208920
Estrogen		0.00	0.00	0.00	0.912962	0.66	0.16	2.65	0.556981
Osteoporosis medications		0.71	0.52	0.96	0.024852	0.80	0.61	1.06	0.115273
Beta Blockers		1.30	1.19	1.42	<.0000001	1.29	1.17	1.41	0.000000
Continuous Count of Total Drug Use (FAD & non-FAD)									
Total Drug Use	0 Drug								
	1 Drug								
	2 Drugs								
	3+ Drugs								
FAD	0 Drug								
	1 Drug	2.41	2.14	2.72	<.0000001	2.69	2.37	3.05	<.0000001
	2 Drugs	3.44	3.01	3.94	<.0000001	4.13	3.60	4.75	<.0000001
	3+ Drugs	5.16	4.48	5.94	<.0000001	6.02	5.20	6.96	<.0000001
NON-FAD	0 Drug								
	1 Drug	0.94	0.81	1.09	0.411367	0.94	0.81	1.09	0.424149
	2 Drugs	0.90	0.78	1.04	0.154285	0.93	0.81	1.08	0.346405
	3+ Drugs	0.79	0.70	0.91	0.000515	0.75	0.66	0.85	0.000011

Estimates are from Cox regression models. Total person years of observation = 7,126,266 for women, 4,160,502 for men. Total Drug Use = fracture associated drugs (FADs) + non-FADS. For FADs, status of receipt of 21 single drug (1 FAD) and 210 concurrent drug pairs (2 FAD) is classified for each person, for each day of observation. 3+ FAD is a classification of person days with 3 or more concurrent FADs. The same approach was taken to identify 552 non-FAD exposures: 1 non-FAD expsoure (1 Non-FAD), 2 concurrent non-FAD exposures (2 Non-FAD), 3+ Non-FAD is a classification of person days with 3 or more concurrent Non-FADs. Model A= Sensitivity analysis excluding any drug exposure variable. Model B= Continuous exposure variable for total drug use. Model C1=Categorized exposure indicator variables for total drug use (1,2,3+ drugs versus none). Model C2=Exposure indicator variables for concurrent use of fracture associated drugs (FAD 1,2,3+ versus none) as well as all other drug use (Non-FAD 1,2,3+ versus none). Model C3= Model C2 stratified on age category (5 year increments except for the first and the last). All models were stratified on sex and adjusted for time varying patient factors; Medicaid eligibility and Medicare Part D low income subsidy are two poverty indicators. Long-term care indicator is defined as 50% or more annual prescription fills dispensed by a long-term care pharmacy. The three categories of drugs protective of fracture are: 1. osteoporosis treatments: oral and injected bisphosphonates, calcitonin, denosumab, parathyroid hormone, 2. Estrogens- systemic estrogens, selective estrogen receptor modulators, and 3. beta-blockers. The "Tobacco/Chronic Obstructive Lung Disease" co-morbidity includes patients with Chronic Obstructive Lung Disease diagnosis and/or tobacco use diagnosis.

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eTable 7. Cox Proportional Hazard Model Output: Hip Fracture Risk Associated With Fracture-Associated Drugs Among Women

In 20% Medicare sample, person-years of exposure and crude fracture rate per exposure group, adjusted for sociodemographic factors, comorbidities, non-fracture-associated drug use (person-years, 7 126 266).

			Cox Regression Model (Hip Fracture n = 47,386)				
Parameter	Person Years	Fracture Rate (# Fracture per 1000 PY)	Hazard Ratio (HR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	p-value	False Discovery Rate p-value
Age (reference 67-69)							
Age 70-74	-	-	**1.24**	**1.19**	**1.29**	**2.70E-24**	**1.30E-23**
Age 75-79	-	-	**2.10**	**2.02**	**2.18**	**1.00E-300**	**4.00E-299**
Age 80-84	-	-	**3.24**	**3.12**	**3.37**	**0.00E+00**	**0.00E+00**
Age 85+	-	-	**5.09**	**4.90**	**5.28**	**0.00E+00**	**0.00E+00**
Race/Ethnicity (reference white)							
Black	-	-	**0.51**	**0.49**	**0.54**	**3.00E-192**	**7.00E-191**
Hispanic	-	-	**0.81**	**0.77**	**0.84**	**7.50E-21**	**3.00E-20**
Asian	-	-	**0.78**	**0.73**	**0.83**	**1.20E-13**	**3.10E-13**
Other	-	-	1.07	0.98	1.17	1.20E-01	1.40E-01
Low Income Subsidy	-	-	1.02	0.98	1.06	3.40E-01	3.80E-01
Original Medicare eligibility (%)							
Disability	-	-	1.28	0.71	2.30	4.20E-01	4.60E-01
Aged	-	-	1.09	0.60	1.97	7.70E-01	8.00E-01
Long term care	-	-	**1.33**	**1.29**	**1.36**	**7.00E-114**	**1.00E-112**
Dual eligible	-	-	**0.89**	**0.85**	**0.92**	**3.90E-09**	**8.00E-09**
Chronic Conditions							
Osteoporosis/Osteopenia	-	-	**3.28**	**3.21**	**3.36**	**0.00E+00**	**0.00E+00**
Dementia	-	-	**3.46**	**3.38**	**3.55**	**0.00E+00**	**0.00E+00**
Obesity	-	-	1.00	0.96	1.04	8.60E-01	8.80E-01
Depression	-	-	**1.22**	**1.19**	**1.26**	**7.40E-49**	**5.50E-48**
Serious Mental Illness	-	-	**1.22**	**1.16**	**1.27**	**9.90E-19**	**3.50E-18**
Alcohol Abuse	-	-	**1.90**	**1.63**	**2.21**	**1.70E-16**	**5.30E-16**
Tobacco/Chronic Lung Disease	-	-	**2.17**	**2.12**	**2.23**	**0.00E+00**	**0.00E+00**
Diabetes	-	-	**0.93**	**0.91**	**0.95**	**9.90E-14**	**2.60E-13**
Liver Disease	-	-	1.03	0.96	1.11	3.80E-01	4.20E-01
Pancreatic Disease	-	-	**0.87**	**0.83**	**0.91**	**3.10E-10**	**6.60E-10**
Inflammatory Bowel Disease	-	-	**0.80**	**0.75**	**0.86**	**1.40E-11**	**3.30E-11**
Rheumatologic Disease	-	-	**0.97**	**0.94**	**0.99**	**7.50E-03**	**1.00E-02**
Spinal Cord Disease or Injury	-	-	**1.11**	**1.06**	**1.16**	**3.10E-05**	**5.20E-05**
Serious Neurologic Disease	-	-	**0.96**	**0.94**	**0.99**	**4.50E-03**	**6.20E-03**
Parkinson's/Huntington's Disease	-	-	**0.86**	**0.82**	**0.90**	**4.20E-11**	**9.30E-11**
Seizure Disorder	-	-	**0.84**	**0.81**	**0.87**	**5.60E-20**	**2.10E-19**
Congestive Heart Failure	-	-	**0.96**	**0.94**	**0.98**	**1.20E-04**	**1.80E-04**
Coronary Artery Disease	-	-	**0.95**	**0.93**	**0.98**	**5.60E-05**	**9.00E-05**
Cerebrovascular Disease	-	-	**0.92**	**0.89**	**0.94**	**1.80E-12**	**4.40E-12**
Peripheral Vascular Disease	-	-	**0.91**	**0.89**	**0.93**	**6.20E-19**	**2.20E-18**
Traumatic Brain Injury	-	-	**1.18**	**1.13**	**1.23**	**3.60E-14**	**9.60E-14**
Amputee	-	-	1.02	0.90	1.14	7.90E-01	8.20E-01
Estrogen	-	-	**0.83**	**0.79**	**0.87**	**8.70E-15**	**2.40E-14**
Osteoporosis medications	-	-	**1.14**	**1.10**	**1.17**	**3.30E-18**	**1.10E-17**
Beta Blockers	-	-	**1.35**	**1.32**	**1.38**	**3.00E-177**	**6.00E-176**
Single FAD Exposures							
Thiazide Diuretics	**733,478**	**4.35**	**1.74**	**1.67**	**1.82**	**5.00E-147**	**9.00E-146**
Proton Pump Inhibitors (PPI)	**252,621**	**5.30**	**1.71**	**1.62**	**1.82**	**1.20E-73**	**1.10E-72**
SSRI/SNRI	**185,004**	**8.98**	**2.32**	**2.20**	**2.44**	**9.00E-207**	**2.00E-205**
Loop Diuretics	**146,816**	**10.97**	**2.45**	**2.32**	**2.59**	**3.00E-222**	**8.00E-221**
Opioids	**81,726**	**11.45**	**3.26**	**3.04**	**3.49**	**2.00E-253**	**6.00E-252**
Anticonvulsants	**60,055**	**7.51**	**2.24**	**2.04**	**2.47**	**2.60E-61**	**2.10E-60**
Sedative Hypnotics	**53,415**	**4.79**	**1.59**	**1.41**	**1.81**	**2.10E-13**	**5.30E-13**
Inhaled Glucocorticoids	**40,444**	**5.29**	**1.79**	**1.57**	**2.06**	**4.10E-17**	**1.30E-16**
H2 Receptor Antagonists (H2RA)	**37,878**	**5.97**	**1.59**	**1.39**	**1.81**	**7.50E-12**	**1.80E-11**
Oral Glucocorticoids	**37,674**	**7.59**	**2.29**	**2.03**	**2.58**	**9.40E-43**	**6.40E-42**
Nitrates	**32,143**	**7.44**	**1.62**	**1.43**	**1.85**	**2.20E-13**	**5.50E-13**
Tricyclic Antidepressants (TCA)	**30,279**	**4.56**	**1.60**	**1.35**	**1.89**	**4.30E-08**	**8.30E-08**
Thiazolidinediones (TZD)	**29,469**	**6.11**	**2.62**	**2.26**	**3.04**	**4.10E-37**	**2.70E-36**
Benzodiazepine	**25,085**	**7.10**	**2.38**	**2.05**	**2.77**	**3.10E-30**	**1.90E-29**
Central Acting Antihypertensives (CAAH)	**20,473**	**5.47**	**1.67**	**1.39**	**2.01**	**7.60E-08**	**1.50E-07**
2nd Generation Antipsychotics (SGAP)	**19,480**	**20.89**	**2.50**	**2.26**	**2.76**	**5.00E-71**	**4.60E-70**
Anti Parkinson's Agents	**19,373**	**12.18**	**3.29**	**2.89**	**3.76**	**2.50E-70**	**2.20E-69**
1st Generation Antihistamines (H1 Blockers)	**12,368**	**7.60**	**1.99**	**1.62**	**2.44**	**3.50E-11**	**7.90E-11**
Barbiturates	**3,308**	**10.58**	**2.74**	**1.97**	**3.82**	**2.60E-09**	**5.40E-09**
1st Generation Antipsychotics (FGAP)	**3,230**	**8.36**	**1.54**	**1.05**	**2.24**	**2.60E-02**	**3.30E-02**
Muscle Relaxers	2,986	<11	1.10	0.55	2.19	8.00E-01	8.20E-01

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eTable 7 continued

Concurrent Exposure to 2 FADs							
PPI & Thiazide Diuretics	116,220	4.68	1.93	1.76	2.10	1.20E-48	8.70E-48
SSRI/SNRI & Thiazide Diuretics	70,540	7.57	2.59	2.37	2.83	1.90E-98	2.30E-97
PPI & SSRI/SNRI	49,199	10.51	2.59	2.36	2.83	2.60E-95	3.10E-94
PPI & Loop Diuretics	34,016	12.85	2.67	2.42	2.94	2.80E-86	3.10E-85
Thiazide Diuretics & Opioids	32,651	12.07	4.45	4.02	4.92	6.00E-181	1.00E-179
Anticonvulsants & Thiazide Diuretics	22,172	5.59	2.11	1.77	2.52	2.00E-16	6.20E-16
PPI & Opioids	*20,891*	*14.31*	*4.00*	*3.56*	*4.49*	*8.00E-121*	*1.00E-119*
Thiazide Diuretics & Loop Diuretics	20,555	11.48	3.42	3.00	3.90	2.30E-76	2.30E-75
SSRI/SNRI & Loop Diuretics	*19,946*	*20.46*	*3.05*	*2.75*	*3.37*	*2.00E-103*	*3.00E-102*
Sedative Hypnotics & Thiazide Diuretics	18,496	6.33	2.44	2.03	2.92	1.40E-21	5.80E-21
TZD & Thiazide Diuretics	17,475	5.32	2.81	2.29	3.45	6.30E-23	2.90E-22
H2RA & Thiazide Diuretics	17,259	5.33	2.00	1.63	2.46	3.70E-11	8.30E-11
CAAH & Thiazide Diuretics	17,147	5.89	2.35	1.93	2.86	1.70E-17	5.60E-17
SSRI/SNRI & Opioids	*14,980*	*17.29*	*3.91*	*3.46*	*4.43*	*3.00E-102*	*4.00E-101*
Inhaled Glucocorticoids & Thiazide Diuretics	14,174	5.43	2.18	1.74	2.73	1.00E-11	2.40E-11
PPI & Anticonvulsants	13,998	8.14	2.39	1.99	2.88	3.20E-20	1.20E-19
SSRI/SNRI & Sedative Hypnotics	13,415	10.21	3.15	2.66	3.73	2.50E-40	1.70E-39
Opioids & Loop Diuretics	*13,206*	*20.14*	*4.48*	*3.96*	*5.07*	*9.00E-126*	*1.00E-124*
Anticonvulsants & SSRI/SNRI	12,976	9.71	2.41	2.02	2.88	1.60E-22	7.20E-22
TCA & Thiazide Diuretics	12,787	6.02	2.46	1.96	3.08	4.60E-15	1.30E-14
Nitrates & Loop Diuretics	*12,579*	*17.57*	*3.25*	*2.84*	*3.72*	*1.90E-65*	*1.60E-64*
Thiazide Diuretics & Nitrates	12,383	8.96	2.51	2.08	3.02	1.00E-21	4.30E-21
SSRI/SNRI & SGAP	12,179	25.54	2.96	2.64	3.32	1.00E-76	1.00E-75
PPI & Sedative Hypnotics	11,389	8.43	2.71	2.22	3.32	3.00E-22	1.30E-21
Oral Glucocorticoids & Thiazide Diuretics	11,212	7.31	2.59	2.08	3.22	1.20E-17	4.00E-17
Anticonvulsants & Opioids	9,695	12.58	3.79	3.17	4.54	4.40E-48	3.10E-47
PPI & Nitrates	8,589	9.90	2.02	1.63	2.50	1.50E-10	3.30E-10
Anticonvulsants & Loop Diuretics	8,566	13.42	2.88	2.39	3.47	4.00E-29	2.30E-28
Inhaled Glucocorticoids & PPI	8,525	6.22	2.10	1.60	2.75	8.10E-08	1.50E-07
Benzodiazepine & Thiazide Diuretics	8,214	7.79	3.03	2.37	3.88	1.20E-18	4.20E-18
Oral Glucocorticoids & PPI	7,847	10.20	2.73	2.19	3.41	4.30E-19	1.60E-18
SSRI/SNRI & Benzodiazepine	*7,752*	*15.87*	*4.50*	*3.76*	*5.38*	*6.40E-61*	*5.10E-60*
PPI & TCA	7,680	5.08	1.84	1.35	2.53	1.40E-04	2.10E-04
H2RA & Loop Diuretics	6,880	13.81	2.73	2.23	3.34	3.10E-22	1.30E-21
H2RA & SSRI/SNRI	6,279	12.10	2.19	1.74	2.74	1.20E-11	2.80E-11
Antiparkinson Agents & Thiazide Diuretics	6,278	8.28	2.78	2.11	3.65	2.40E-13	5.90E-13
CAAH & Loop Diuretics	6,147	6.34	1.82	1.33	2.49	2.10E-04	3.20E-04
PPI & H2RA	6,039	6.79	2.23	1.64	3.03	3.00E-07	5.60E-07
Sedative Hypnotics & Opioids	*5,905*	*15.41*	*4.90*	*3.98*	*6.02*	*3.50E-51*	*2.70E-50*
PPI & Benzodiazepine	5,691	9.14	2.97	2.26	3.91	5.40E-15	1.50E-14
SSRI/SNRI & Antiparkinson Agents	5,266	16.90	3.57	2.89	4.41	3.10E-32	2.00E-31
Inhaled Glucocorticoids & Loop Diuretics	5,204	11.72	2.47	1.92	3.18	2.30E-12	5.60E-12
Inhaled Glucocorticoids & SSRI/SNRI	4,871	13.34	3.29	2.58	4.21	1.30E-21	5.40E-21
SSRI/SNRI & TCA	4,519	9.74	3.16	2.35	4.25	2.70E-14	7.20E-14
Oral Glucocorticoids & SSRI/SNRI	4,482	16.29	3.67	2.92	4.63	2.50E-28	1.40E-27
TZD & Loop Diuretics	4,463	9.63	3.48	2.58	4.70	4.00E-16	1.20E-15
Oral Glucocorticoids & Loop Diuretics	4,323	12.49	2.45	1.87	3.20	5.80E-11	1.30E-10
PPI & TZD	4,212	9.26	3.91	2.86	5.36	2.20E-17	7.20E-17
Sedative Hypnotics & Loop Diuretics	4,177	16.04	3.36	2.64	4.28	6.30E-23	2.90E-22
H1 Blockers & Thiazide Diuretics	4,138	7.49	2.49	1.75	3.54	4.20E-07	7.70E-07
SSRI/SNRI & Nitrates	4,029	16.38	2.50	1.96	3.19	1.50E-13	3.80E-13
PPI & Antiparkinson Agents	3,797	14.49	3.44	2.63	4.48	1.10E-19	4.10E-19
PPI & CAAH	3,721	6.45	1.88	1.26	2.81	2.00E-03	2.80E-03
Oral Glucocorticoids & Opioids	3,581	16.20	4.46	3.44	5.77	1.10E-29	6.60E-29
PPI & SGAP	3,504	29.97	2.94	2.42	3.57	9.80E-28	5.20E-27
H2RA & Opioids	3,404	14.98	3.69	2.80	4.86	1.70E-20	6.70E-20
Thiazide Diuretics & SGAP	3,352	22.97	3.65	2.92	4.58	1.60E-29	9.40E-29
TCA & Loop Diuretics	3,224	8.69	2.29	1.58	3.32	1.20E-05	2.10E-05
Benzodiazepine & Opioids	3,139	15.61	4.50	3.40	5.96	1.10E-25	5.70E-25
TCA & Opioids	3,118	14.75	5.05	3.78	6.75	6.90E-28	3.70E-27
SGAP & Loop Diuretics	2,999	24.01	2.22	1.76	2.81	1.80E-11	4.20E-11
TZD & SSRI/SNRI	2,934	11.93	3.84	2.75	5.35	2.30E-15	6.60E-15
Anticonvulsants & Sedative Hypnotics	2,831	9.19	2.98	2.03	4.39	2.60E-08	5.10E-08
PPI & H1 Blockers	2,655	13.18	3.53	2.53	4.92	9.80E-14	2.60E-13
Anticonvulsants & TCA	2,548	5.50	1.84	1.09	3.11	2.20E-02	2.80E-02
SSRI/SNRI & CAAH	2,469	10.13	2.33	1.57	3.45	2.50E-05	4.30E-05
Nitrates & Opioids	2,383	18.04	4.02	2.98	5.43	1.10E-19	4.10E-19
Antiparkinson Agents & Loop Diuretics	2,369	16.04	2.96	2.15	4.08	2.80E-11	6.40E-11
H2RA & Anticonvulsants	2,279	8.78	1.93	1.25	3.00	3.30E-03	4.60E-03
Benzodiazepine & Loop Diuretics	2,172	21.18	4.61	3.45	6.17	6.00E-25	3.00E-24
Anticonvulsants & SGAP	2,134	16.40	2.27	1.62	3.16	1.50E-06	2.60E-06
Inhaled Glucocorticoids & Oral Glucocorticoi	2,091	11.48	3.33	2.23	4.97	4.10E-09	8.30E-09

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eTable 7 continued

H2RA & Nitrates	**1,950**	**11.79**	**2.30**	**1.52**	**3.46**	**7.10E-05**	**1.10E-04**
Antiparkinson Agents & Opioids	**1,949**	**18.47**	**4.90**	**3.53**	**6.80**	**2.10E-21**	**8.50E-21**
Antiparkinson Agents & SGAP	**1,909**	**17.81**	**2.97**	**2.12**	**4.17**	**2.90E-10**	**6.20E-10**
Inhaled Glucocorticoids & Opioids	**1,894**	**10.03**	**3.02**	**1.92**	**4.74**	**1.50E-06**	**2.60E-06**
Anticonvulsants & Antiparkinson Agents	**1,874**	**16.55**	**4.04**	**2.84**	**5.75**	**1.00E-14**	**2.70E-14**
CAAH & Opioids	**1,865**	**11.26**	**3.67**	**2.39**	**5.64**	**2.60E-09**	**5.40E-09**
TCA & Sedative Hypnotics	1,767	<11	1.74	0.87	3.49	1.20E-01	1.40E-01
Oral Glucocorticoids & Anticonvulsants	**1,599**	**20.01**	**5.75**	**4.06**	**8.14**	**6.20E-23**	**2.90E-22**
Benzodiazepine & Sedative Hypnotics	**1,532**	**8.49**	**3.14**	**1.82**	**5.42**	**3.70E-05**	**6.10E-05**
Oral Glucocorticoids & Sedative Hypnotics	**1,515**	**<11**	**2.09**	**1.13**	**3.89**	**2.00E-02**	**2.60E-02**
Anticonvulsants & Nitrates	**1,480**	**9.46**	**1.93**	**1.14**	**3.27**	**1.40E-02**	**1.80E-02**
H2RA & Sedative Hypnotics	**1,458**	**<11**	**1.98**	**1.07**	**3.69**	**3.00E-02**	**3.80E-02**
Anticonvulsants & Benzodiazepine	**1,407**	**10.66**	**3.09**	**1.86**	**5.13**	**1.30E-05**	**2.20E-05**
TZD & Opioids	**1,395**	**15.05**	**6.23**	**4.06**	**9.56**	**6.10E-17**	**1.90E-16**
H1 Blockers & Loop Diuretics	**1,327**	**17.33**	**3.59**	**2.38**	**5.41**	**9.50E-10**	**2.00E-09**
TZD & Anticonvulsants	**1,282**	**8.58**	**4.21**	**2.33**	**7.60**	**1.90E-06**	**3.30E-06**
Muscle Relaxers & Opioids	**1,271**	**14.16**	**6.50**	**4.09**	**10.32**	**2.20E-15**	**6.40E-15**
Oral Glucocorticoids & H2RA	**1,243**	**11.26**	**2.90**	**1.72**	**4.90**	**7.00E-05**	**1.10E-04**
Inhaled Glucocorticoids & Sedative Hypnotics	1,242	<11	1.28	0.53	3.08	5.80E-01	6.20E-01
SSRI/SNRI & H1 Blockers	**1,241**	**22.56**	**4.64**	**3.20**	**6.73**	**5.40E-16**	**1.60E-15**
Inhaled Glucocorticoids & Anticonvulsants	1,220	<11	1.32	0.59	2.94	5.00E-01	5.40E-01
Opioids & SGAP	**1,219**	**32.00**	**3.60**	**2.63**	**4.94**	**1.60E-15**	**4.70E-15**
H2RA & TCA	1,210	<11	1.93	0.92	4.05	8.30E-02	1.00E-01
Inhaled Glucocorticoids & H2RA	**1,184**	**<11**	**2.81**	**1.51**	**5.22**	**1.10E-03**	**1.60E-03**
Anticonvulsants & CAAH	1,183	<11	**2.12**	**1.06**	**4.24**	**3.40E-02**	**4.30E-02**
H2RA & SGAP	**1,140**	**23.69**	**2.21**	**1.52**	**3.23**	**3.90E-05**	**6.40E-05**
H1 Blockers & Opioids	**1,139**	**21.07**	**5.76**	**3.86**	**8.61**	**1.10E-17**	**3.70E-17**
Sedative Hypnotics & SGAP	**1,030**	**28.15**	**4.17**	**2.89**	**6.00**	**1.80E-14**	**4.90E-14**
TCA & Benzodiazepines	**1,006**	**<11**	**3.36**	**1.75**	**6.46**	**2.80E-04**	**4.20E-04**
Sedative Hypnotics & Nitrates	**1,002**	**11.98**	**2.55**	**1.45**	**4.49**	**1.20E-03**	**1.70E-03**
Barbiturates & Thiazide Diuretics	**967**	**<11**	**2.65**	**1.33**	**5.31**	**5.80E-03**	**8.00E-03**
Sedative Hypnotics & Antiparkinson Agents	**844**	**<11**	**3.60**	**1.93**	**6.69**	**5.30E-05**	**8.60E-05**
Muscle Relaxers & Thiazide Diuretics	844	<11	2.22	0.83	5.91	1.10E-01	1.30E-01
Oral Glucocorticoids & TCA	808	<11	1.93	0.80	4.63	1.40E-01	1.60E-01
SSRI/SNRI & Barbiturates	799	<11	1.57	0.71	3.51	2.70E-01	3.10E-01
Thiazide Diuretics & FGAP	**797**	**<11**	**2.98**	**1.49**	**5.97**	**2.00E-03**	**2.80E-03**
CAAH & Nitrates	778	<11	1.97	0.94	4.13	7.40E-02	9.00E-02
Inhaled Glucocorticoids & Nitrates	775	<11	1.68	0.76	3.75	2.00E-01	2.30E-01
Antiparkinson Agents & FGAP	**768**	**19.53**	**5.44**	**3.27**	**9.03**	**6.00E-11**	**1.30E-10**
TZD & Nitrates	**766**	**<11**	**4.04**	**2.10**	**7.77**	**2.80E-05**	**4.70E-05**
H2RA & Benzodiazepine	**762**	**<11**	**3.24**	**1.68**	**6.22**	**4.30E-04**	**6.40E-04**
H2RA & TZD	755	<11	1.87	0.60	5.81	2.80E-01	3.10E-01
H2RA & CAAH	748	<11	1.40	0.53	3.73	5.00E-01	5.40E-01
Sedative Hypnotics & CAAH	**696**	**<11**	**2.65**	**1.19**	**5.91**	**1.70E-02**	**2.20E-02**
Anticonvulsants & Barbiturates	**692**	**23.13**	**7.38**	**4.52**	**12.07**	**1.50E-15**	**4.50E-15**
Oral Glucocorticoids & Benzodiazepine	**681**	**19.09**	**5.43**	**3.15**	**9.35**	**1.10E-09**	**2.30E-09**
TZD & Sedative Hypnotics	**675**	**<11**	**4.55**	**2.17**	**9.54**	**6.20E-05**	**9.80E-05**
SSRI/SNRI & FGAP	**675**	**22.22**	**3.49**	**2.10**	**5.80**	**1.30E-06**	**2.30E-06**
Inhaled Glucocorticoids & TCA	668	<11	2.50	1.04	6.01	4.10E-02	5.20E-02
Inhaled Glucocorticoids & Benzodiazepine	**665**	**<11**	**3.91**	**1.96**	**7.83**	**1.20E-04**	**1.80E-04**
Benzodiazepine & SGAP	**661**	**49.95**	**6.91**	**4.91**	**9.74**	**2.00E-28**	**1.10E-27**
TZD & TCA	655	<11	1.45	0.36	5.82	6.00E-01	6.40E-01
Oral Glucocorticoids & Nitrates	653	<11	2.10	1.00	4.40	5.00E-02	6.30E-02
TCA & Antiparkinson Agents	**618**	**<11**	**2.99**	**1.34**	**6.66**	**7.40E-03**	**1.00E-02**
TCA & Nitrates	615	<11	1.83	0.76	4.39	1.80E-01	2.10E-01
PPI & Barbiturates	**602**	**<11**	**2.85**	**1.28**	**6.35**	**1.00E-02**	**1.30E-02**
PPI & Muscle Relaxers	591	<11	2.02	0.65	6.25	2.20E-01	2.50E-01
H2RA & Antiparkinson Agents	581	<11	1.93	0.87	4.29	1.10E-01	1.30E-01
H2RA & H1 Blockers	**551**	**<11**	**2.59**	**1.17**	**5.78**	**2.00E-02**	**2.60E-02**
PPI & FGAP	542	<11	1.82	0.87	3.82	1.10E-01	1.30E-01
Sedative Hypnotics & H1 Blockers	528	<11	1.45	0.47	4.51	5.20E-01	5.60E-01
Anticonvulsants & H1 Blockers	**524**	**<11**	**4.37**	**2.18**	**8.74**	**3.10E-05**	**5.20E-05**
TCA & SGAP	518	<11	1.03	0.33	3.19	9.60E-01	9.60E-01
Benzodiazepine & Antiparkinson Agents	**496**	**<11**	**5.23**	**2.72**	**10.06**	**7.20E-07**	**1.30E-06**
Nitrates & SGAP	492	<11	1.69	0.88	3.25	1.20E-01	1.40E-01
Oral Glucocorticoids & Antiparkinson Agents	**486**	**<11**	**3.41**	**1.62**	**7.15**	**1.20E-03**	**1.70E-03**

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eTable 7 continued

TCA & CAAH	**480**	**<11**	**3.23**	**1.35**	**7.77**	**8.70E-03**	**1.20E-02**
Benzodiazepine & Nitrates	467	<11	2.14	0.89	5.15	8.90E-02	1.10E-01
TZD & CAAH	**462**	**<11**	**3.83**	**1.44**	**10.20**	**7.30E-03**	**1.00E-02**
Oral Glucocorticoids & CAAH	441	<11	1.10	0.28	4.39	8.90E-01	9.00E-01
FGAP & SGAP	**440**	**24.97**	**4.80**	**2.65**	**8.67**	**2.10E-07**	**3.90E-07**
Benzodiazepine & CAAH	**426**	**<11**	**3.92**	**1.76**	**8.72**	**8.40E-04**	**1.20E-03**
Inhaled Glucocorticoids & TZD	**424**	**<11**	**4.40**	**1.65**	**11.72**	**3.10E-03**	**4.40E-03**
Antiparkinson Agents & Nitrates	406	<11	0.92	0.23	3.67	9.00E-01	9.00E-01
Inhaled Glucocorticoids & Antiparkinson Age	**384**	**<11**	**4.47**	**2.01**	**9.96**	**2.50E-04**	**3.80E-04**
Barbiturates & Loop Diuretics	**381**	**<11**	**4.86**	**2.61**	**9.03**	**6.00E-07**	**1.10E-06**
SSRISNRI & Muscle Relaxers	366	<11	2.89	0.93	8.95	6.60E-02	8.10E-02
TZD & SGAP	366	<11	1.81	0.58	5.62	3.00E-01	3.30E-01
H1 Blockers & Nitrates	360	<11	2.11	0.79	5.62	1.40E-01	1.60E-01
FGAP & Loop Diuretics	**357**	**33.61**	**5.27**	**2.99**	**9.29**	**8.80E-09**	**1.80E-08**
Inhaled Glucocorticoids & SGAP	354	<11	1.36	0.51	3.62	5.40E-01	5.80E-01
Inhaled Glucocorticoids & CAAH	339	<11	0.00	0.00	0.00	7.50E-01	7.80E-01
TCA & FGAP	**322**	**<11**	**6.14**	**2.76**	**13.68**	**8.80E-06**	**1.50E-05**
CAAH & SGAP	287	<11	0.39	0.06	2.79	3.50E-01	3.90E-01
Oral Glucocorticoids & H1 Blockers	**277**	**<11**	**7.94**	**3.97**	**15.87**	**4.80E-09**	**9.60E-09**
Antiparkinson Agents & CAAH	**273**	**<11**	**5.13**	**2.31**	**11.43**	**6.20E-05**	**9.80E-05**
Oral Glucocorticoids & SGAP	**267**	**<11**	**2.77**	**1.32**	**5.82**	**7.00E-03**	**9.60E-03**
TCA & H1 Blockers	267	<11	2.10	0.52	8.39	3.00E-01	3.30E-01
Oral Glucocorticoids & TZD	260	<11	1.48	0.21	10.51	7.00E-01	7.40E-01
Inhaled Glucocorticoids & H1 Blockers	**252**	**<11**	**8.34**	**3.98**	**17.51**	**2.00E-08**	**4.00E-08**
Benzodiazepine & H1 Blockers	**249**	**<11**	**4.25**	**1.60**	**11.34**	**3.80E-03**	**5.30E-03**
TZD & Antiparkinson Agents	249	<11	1.45	0.20	10.28	7.10E-01	7.40E-01
Anticonvulsants & FGAP	**227**	**<11**	**4.40**	**1.83**	**10.57**	**9.40E-04**	**1.40E-03**
Muscle Relaxers & Loop Diuretics	214	<11	1.53	0.22	10.89	6.70E-01	7.10E-01
Anticonvulsants & Muscle Relaxers	212	<11	3.80	0.95	15.18	5.90E-02	7.30E-02
Sedative Hypnotics& Muscle Relaxers	207	<11	0.00	0.00	0.00	8.50E-01	8.70E-01
Opioids & FGAP	**202**	**<11**	**6.18**	**2.94**	**12.97**	**1.50E-06**	**2.60E-06**
Barbiturates & Opioids	**198**	**<11**	**8.16**	**3.89**	**17.12**	**2.90E-08**	**5.60E-08**
TZD & H1 Blockers	197	<11	3.77	0.94	15.06	6.10E-02	7.50E-02
H1 Blockers & CAAH	196	<11	2.89	0.72	11.54	1.30E-01	1.50E-01
H2RA & FGAP	172	<11	1.73	0.43	6.90	4.40E-01	4.80E-01
H1 Blockers & SGAP	160	<11	2.31	0.74	7.16	1.50E-01	1.70E-01
Barbiturates & Antiparkinson Agents	**157**	**<11**	**4.08**	**1.31**	**12.65**	**1.50E-02**	**2.00E-02**
Sedative Hypnotics& FGAP	**147**	**<11**	**5.01**	**1.88**	**13.36**	**1.30E-03**	**1.90E-03**
H1 Blockers & Antiparkinson Agents	**143**	**<11**	**4.68**	**1.51**	**14.52**	**7.50E-03**	**1.00E-02**
TCA & Muscle Relaxers	131	<11	0.00	0.00	0.00	8.80E-01	8.90E-01
TZD & Benzodiazepine	**129**	**<11**	**13.43**	**5.04**	**35.80**	**2.10E-07**	**3.90E-07**
Barbiturates & Sedative Hypnotics	127	<11	3.92	0.98	15.67	5.30E-02	6.60E-02
Benzodiazepine & Barbiturates	126	<11	2.96	0.42	21.05	2.80E-01	3.10E-01
TCA & Barbiturates	**107**	**<11**	**10.53**	**3.40**	**32.66**	**4.60E-05**	**7.50E-05**
Inhaled Glucocorticoids & Barbiturates	105	<11	0.00	0.00	0.00	8.70E-01	8.80E-01
FAD pairs with <100PY	**-**	**-**	**2.67**	**1.66**	**4.29**	**5.40E-05**	**8.70E-05**
3+FAD	**-**	**-**	**4.58**	**4.43**	**4.73**	**0.00E+00**	**0.00E+00**
0 Non-FAD	**-**	**-**					
1 Non-FAD	**-**	**-**	**0.94**	**0.91**	**0.97**	**1.20E-04**	**1.80E-04**
2 Non-FAD	**-**	**-**	**0.84**	**0.82**	**0.87**	**1.20E-23**	**5.80E-23**
3+ Non-FAD	**-**	**-**	**0.75**	**0.72**	**0.77**	**4.80E-80**	**5.20E-79**

Exposure indicator variables for fracture associated drug (FAD) use reflect person days with any of 21 individual FADs and 210 possible two-way combination of these drugs (included as a specific exposure in most cases, but aggregated to "FAD pairs with <100 PY" if cohort specific observation < 100 person years). "3+FAD" is an indicator variable for person days with three-or-more FADs. The reference exposure was zero FADs. Non-FADs are 552 drug ingredients that are not FADs aggregated into status of receipt of any 1 non-FAD expsoure (1 Non-FAD), 2 concurrent non-FAD exposures (2 Non-FAD) or 3+ Non-FAD exposure classified for each person, for each day of observation. Medicaid eligibility and Medicare Part D low income subsidy are two poverty indicators. Long-term care is defined as 50% or more of annual prescriptions dispensed by a long-term care pharmacy. The three categories of drugs protective of fracture are: 1. osteoporosis treatments: oral and injected bisphosphonates, calcitonin, denosumab, parathyroid hormone, 2. Estrogens- systemic estrogens, selective estrogen receptor modulators, and 3. beta-blockers. SSRI/SNRI = combined drug group of selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors. PPI= proton pump inhibitors, FGAP = first generation antipsychotic. SGAP = second generation antipsychotic. TCA= tricyclic antidepressants. H2RA is Histamine-2 Receptor Antagonists. TZD = Thiazolidinediones. H1 Blockers = 1st Generation Antihistamines. CAAH = Central Acting Antihypertensives. Sedative Hypnotics include only non-benzodiazepine drugs. The Tobacco/Chronic Obstructive Lung Disease is an aggregate indicator of these diagnoses. Bold if False Discovery Rate corrected P value < 0.05. Italicized if population-level impact criteria were met.

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eTable 8. Cox Proportional Hazard Model Output: Hip Fracture Risk Associated With Fracture-Associated Drugs Among Men

In 20% Medicare sample, person-years of exposure and crude fracture rate per exposure group, adjusted for sociodemographic factors, comorbidities, non-fracture-associated drug use (person-years, 4 160 502).

			Cox Regression Model (Hip Fracture n = 12,317)				
Parameter	Person Years	Fracture Rate (# Fracture per 1000 PY)	Hazard Ratio (HR)	Lower 95% Confidence Interval	Higher 95% Confidence Interval	p-value	False Discovery Rate p-value
Age (reference 67-69)							
Age 70-74	-	-	**1.19**	**1.12**	**1.27**	**9.60E-08**	**3.00E-07**
Age 75-79	-	-	**1.84**	**1.72**	**1.96**	**1.10E-77**	**2.50E-76**
Age 80-84	-	-	**2.98**	**2.80**	**3.18**	**1.00E-248**	**4.00E-247**
Age 85+	-	-	**5.29**	**4.96**	**5.64**	**0.00E+00**	**0.00E+00**
Race/Ethnicity (reference white)							
Black	-	-	**0.56**	**0.51**	**0.61**	**6.20E-38**	**7.90E-37**
Hispanic	-	-	**0.71**	**0.65**	**0.77**	**5.40E-16**	**3.30E-15**
Asian	-	-	**0.52**	**0.45**	**0.59**	**1.80E-23**	**1.20E-22**
Other	-	-	0.92	0.77	1.08	3.00E-01	3.70E-01
Low Income Subsidy	-	-	**1.18**	**1.08**	**1.28**	**1.20E-04**	**2.60E-04**
Original Medicare eligibility (%)							
Disability	-	-	1.03	0.33	3.18	9.70E-01	9.70E-01
Aged	-	-	0.87	0.28	2.71	8.10E-01	9.00E-01
Long term care	-	-	**1.43**	**1.36**	**1.51**	**9.90E-43**	**1.50E-41**
Dual eligible	-	-	**0.85**	**0.78**	**0.93**	**2.70E-04**	**5.70E-04**
Chronic Conditions							
Osteoporosis/Osteopenia	-	-	**4.44**	**4.12**	**4.78**	**0.00E+00**	**0.00E+00**
Dementia	-	-	**3.74**	**3.55**	**3.94**	**0.00E+00**	**0.00E+00**
Obesity	-	-	0.94	0.87	1.02	1.20E-01	1.60E-01
Depression	-	-	**1.23**	**1.16**	**1.31**	**3.60E-12**	**1.60E-11**
Serious Mental Illness	-	-	**1.34**	**1.23**	**1.45**	**8.50E-13**	**4.10E-12**
Alcohol Abuse	-	-	**1.69**	**1.48**	**1.93**	**2.40E-14**	**1.30E-13**
Tobacco/Chronic Lung Disease	-	-	**2.52**	**2.41**	**2.63**	**0.00E+00**	**0.00E+00**
Diabetes	-	-	**0.87**	**0.83**	**0.90**	**6.60E-13**	**3.30E-12**
Liver Disease	-	-	1.07	0.96	1.19	2.10E-01	2.70E-01
Pancreatic Disease	-	-	**0.88**	**0.80**	**0.96**	**4.80E-03**	**8.10E-03**
Inflammatory Bowel Disease	-	-	0.99	0.87	1.12	8.50E-01	9.30E-01
Rheumatologic Disease	-	-	0.98	0.93	1.04	5.70E-01	6.50E-01
Spinal Cord Disease or Injury	-	-	1.09	1.00	1.19	4.40E-02	6.10E-02
Serious Neurologic Disease	-	-	1.01	0.97	1.06	6.20E-01	6.90E-01
Parkinson's/Huntington's Disease	-	-	**1.09**	**1.01**	**1.16**	**1.80E-02**	**2.70E-02**
Seizure Disorder	-	-	**0.90**	**0.85**	**0.96**	**1.70E-03**	**3.10E-03**
Congestive Heart Failure	-	-	**1.06**	**1.02**	**1.11**	**4.60E-03**	**7.80E-03**
Coronary Artery Disease	-	-	**0.91**	**0.87**	**0.95**	**4.40E-06**	**1.10E-05**
Cerebrovascular Disease	-	-	1.03	0.99	1.08	1.80E-01	2.30E-01
Peripheral Vascular Disease	-	-	1.01	0.97	1.05	5.90E-01	6.70E-01
Traumatic Brain Injury	-	-	**1.29**	**1.19**	**1.39**	**1.10E-10**	**4.30E-10**
Amputee	-	-	**1.36**	**1.19**	**1.55**	**6.40E-06**	**1.60E-05**
Estrogen	-	-	0.52	0.22	1.25	1.40E-01	1.80E-01
Osteoporosis medications	-	-	**0.86**	**0.75**	**0.97**	**1.60E-02**	**2.50E-02**
Beta Blockers	-	-	**1.28**	**1.23**	**1.33**	**2.80E-31**	**2.70E-30**
Single FAD Exposures							
Thiazide Diuretics	**356,819**	**1.74**	**1.65**	**1.51**	**1.81**	**5.80E-28**	**4.70E-27**
Proton Pump Inhibitors (PPI)	**165,092**	**2.51**	**1.89**	**1.70**	**2.09**	**1.90E-32**	**2.20E-31**
Loop Diuretics	**87,781**	**5.72**	**2.77**	**2.51**	**3.06**	**1.80E-88**	**5.20E-87**
SSRI/SNRI	**61,141**	**5.74**	**2.96**	**2.64**	**3.32**	**2.30E-78**	**5.90E-77**
Opioids	**47,153**	**5.41**	**3.83**	**3.36**	**4.36**	**3.90E-91**	**1.30E-89**
Anticonvulsants	**38,090**	**4.17**	**2.66**	**2.26**	**3.13**	**5.30E-32**	**5.80E-31**
Thiazolidinediones (TZD)	**35,171**	**2.33**	**2.48**	**1.99**	**3.10**	**1.10E-15**	**6.50E-15**
Nitrates	**32,805**	**3.17**	**1.80**	**1.48**	**2.19**	**6.30E-09**	**2.10E-08**
Sedative Hypnotics	**29,598**	**2.03**	**1.51**	**1.17**	**1.95**	**1.70E-03**	**3.10E-03**
Inhaled Glucocorticoids	**28,431**	**2.64**	**1.92**	**1.52**	**2.41**	**3.20E-08**	**1.00E-07**
Oral Glucocorticoids	**24,530**	**3.71**	**2.50**	**2.03**	**3.09**	**1.10E-17**	**6.80E-17**
H2 Receptor Antagonists (H2RA)	**24,328**	**2.84**	**1.84**	**1.44**	**2.33**	**6.80E-07**	**1.90E-06**
Anti Parkinson's Agents	**18,174**	**8.58**	**4.23**	**3.57**	**5.01**	**1.30E-62**	**2.70E-61**
Benzodiazepine	**11,556**	**2.25**	**1.62**	**1.10**	**2.38**	**1.50E-02**	**2.30E-02**
Tricyclic Antidepressants (TCA)	9,848	2.03	1.55	1.00	2.40	5.20E-02	7.20E-02
Central Acting Antihypertensives (CAAH)	9,276	2.16	1.59	1.03	2.48	3.80E-02	5.40E-02
2nd Generation Antispychotics (SGAP)	**9,002**	**11.55**	**2.53**	**2.07**	**3.08**	**6.80E-20**	**4.30E-19**
1st Generation Antihistamines (H1 Blockers)	5,108	3.13	1.70	1.04	2.77	3.50E-02	5.00E-02
Barbiturates	2,841	<11	1.78	0.89	3.56	1.10E-01	1.50E-01
1st Generation Antipsychotics (FGAP)	**1,644**	**7.91**	**2.73**	**1.58**	**4.71**	**3.10E-04**	**6.40E-04**
Muscle Relaxers	1,591	<11	1.65	0.53	5.13	3.80E-01	4.50E-01

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Appendix Table 8 Continued

Concurrent Exposure to 2 FADs							
PPI & Thiazide Diuretics	**50,082**	**1.88**	**1.77**	**1.44**	**2.18**	**6.20E-08**	**2.00E-07**
PPI & Loop Diuretics	***16,398***	***7.56***	***3.15***	***2.62***	***3.78***	***1.40E-34***	***1.70E-33***
SSRI/SNRI & Thiazide Diuretics	**15,502**	**3.48**	**2.51**	**1.92**	**3.29**	**2.60E-11**	**1.10E-10**
PPI & SSRI/SNRI	***14,657***	***8.73***	***3.94***	***3.29***	***4.72***	***2.00E-50***	***3.50E-49***
TZD & Thiazide Diuretics	**13,126**	**2.44**	**3.00**	**2.11**	**4.25**	**8.50E-10**	**3.00E-09**
Thiazide Diuretics & Opioids	**12,391**	**5.57**	**4.98**	**3.92**	**6.33**	**4.20E-39**	**5.70E-38**
Thiazide Diuretics & Loop Diuretics	***10,358***	***6.47***	***4.18***	***3.28***	***5.34***	***1.80E-30***	***1.60E-29***
PPI & Opioids	***9,930***	***7.25***	***4.97***	***3.92***	***6.29***	***1.60E-40***	***2.30E-39***
Anticonvulsants & Thiazide Diuretics	**9,928**	**3.32**	**2.81**	**1.99**	**3.97**	**4.20E-09**	**1.40E-08**
Nitrates & Loop Diuretics	***8,944***	***7.94***	***3.45***	***2.71***	***4.37***	***3.30E-24***	***2.40E-23***
Thiazide Diuretics & Nitrates	**7,784**	**3.08**	**2.11**	**1.41**	**3.16**	**2.90E-04**	**6.10E-04**
H2RA & Thiazide Diuretics	**7,677**	**2.47**	**2.18**	**1.39**	**3.42**	**7.40E-04**	**1.50E-03**
PPI & Anticonvulsants	**7,433**	**5.38**	**2.94**	**2.15**	**4.02**	**1.70E-11**	**7.10E-11**
Sedative Hypnotics & Thiazide Diuretics	**7,333**	**2.05**	**1.83**	**1.10**	**3.04**	**2.00E-02**	**3.00E-02**
PPI & Nitrates	**7,229**	**3.60**	**1.87**	**1.27**	**2.76**	**1.50E-03**	**2.90E-03**
CAAH & Thiazide Diuretics	**7,042**	**2.13**	**2.07**	**1.25**	**3.44**	**5.00E-03**	**8.30E-03**
SSRI/SNRI & Loop Diuretics	***6,777***	***12.54***	***3.72***	***2.98***	***4.63***	***8.90E-32***	***9.20E-31***
Inhaled Glucocorticoids & Thiazide Diuretics	**6,751**	**2.67**	**2.35**	**1.48**	**3.75**	**3.00E-04**	**6.20E-04**
PPI & Sedative Hypnotics	**6,112**	**3.76**	**2.84**	**1.88**	**4.28**	**6.70E-07**	**1.90E-06**
Opioids & Loop Diuretics	***5,652***	***13.80***	***6.93***	***5.52***	***8.70***	***2.70E-62***	***5.20E-61***
Inhaled Glucocorticoids & PPI	**5,557**	**3.96**	**2.72**	**1.79**	**4.14**	**3.10E-06**	**7.90E-06**
Anticonvulsants & Opioids	**5,262**	**8.17**	**5.43**	**4.01**	**7.35**	**6.80E-28**	**5.40E-27**
Oral Glucocorticoids & Thiazide Diuretics	5,060	2.37	**1.92**	**1.09**	**3.39**	**2.40E-02**	**3.60E-02**
Anticonvulsants & Loop Diuretics	**5,013**	**7.58**	**3.16**	**2.29**	**4.36**	**3.00E-12**	**1.30E-11**
Anticonvulsants & SSRI/SNRI	**4,717**	**7.00**	**3.00**	**2.12**	**4.23**	**4.90E-10**	**1.80E-09**
Oral Glucocorticoids & PPI	**4,543**	**6.38**	**3.81**	**2.64**	**5.50**	**9.50E-13**	**4.40E-12**
SSRI/SNRI & SGAP	***4,445***	***15.52***	***3.57***	***2.80***	***4.55***	***6.30E-25***	***4.70E-24***
SSRI/SNRI & Opioids	***4,443***	***13.28***	***6.26***	***4.83***	***8.12***	***1.90E-43***	***3.10E-42***
SSRI/SNRI & Sedative Hypnotics	**4,192**	**8.35**	**5.12**	**3.67**	**7.16**	**1.00E-21**	**6.70E-21**
PPI & TZD	**4,077**	**2.94**	**3.04**	**1.72**	**5.36**	**1.30E-04**	**2.80E-04**
Antiparkinson Agents & Thiazide Diuretics	**3,634**	**6.88**	**4.63**	**3.11**	**6.88**	**3.80E-14**	**2.00E-13**
TZD & Loop Diuretics	**3,589**	**6.41**	**5.11**	**3.38**	**7.71**	**8.80E-15**	**5.00E-14**
PPI & H2RA	3,446	<11	1.86	0.93	3.71	8.10E-02	1.10E-01
Sedative Hypnotics & Opioids	**3,347**	**5.97**	**4.39**	**2.82**	**6.81**	**4.80E-11**	**1.90E-10**
Inhaled Glucocorticoids & Loop Diuretics	**3,311**	**7.25**	**3.22**	**2.15**	**4.81**	**1.40E-08**	**4.60E-08**
H2RA & Loop Diuretics	**3,268**	**6.43**	**2.86**	**1.86**	**4.40**	**1.70E-06**	**4.50E-06**
PPI & Antiparkinson Agents	**2,964**	**8.43**	**3.48**	**2.34**	**5.18**	**7.40E-10**	**2.60E-09**
SSRI/SNRI & Antiparkinson Agents	**2,963**	**15.86**	**5.81**	**4.33**	**7.80**	**9.20E-32**	**9.20E-31**
Oral Glucocorticoids & Loop Diuretics	**2,900**	**12.07**	**5.08**	**3.64**	**7.11**	**2.00E-21**	**1.30E-20**
TCA & Thiazide Diuretics	2,882	<11	1.52	0.63	3.66	3.50E-01	4.20E-01
Benzodiazepine & Thiazide Diuretics	**2,875**	**4.52**	**3.88**	**2.25**	**6.69**	**1.10E-06**	**2.90E-06**
PPI & Benzodiazepine	**2,634**	**4.56**	**3.17**	**1.80**	**5.59**	**6.90E-05**	**1.50E-04**
CAAH & Loop Diuretics	**2,560**	**5.86**	**3.90**	**2.35**	**6.49**	**1.50E-07**	**4.50E-07**
SSRI/SNRI & Benzodiazepine	**2,462**	**11.78**	**7.12**	**4.93**	**10.28**	**1.20E-25**	**9.20E-25**
Sedative Hypnotics & Loop Diuretics	**2,346**	**10.66**	**4.56**	**3.07**	**6.77**	**5.20E-14**	**2.70E-13**
H2RA & SSRI/SNRI	**2,263**	**10.17**	**3.70**	**2.45**	**5.59**	**4.80E-10**	**1.80E-09**
PPI & TCA	2,143	<11	1.38	0.52	3.69	5.20E-01	6.00E-01
SSRI/SNRI & Nitrates	**2,045**	**10.76**	**3.89**	**2.56**	**5.93**	**2.50E-10**	**9.50E-10**
Oral Glucocorticoids & Opioids	**1,877**	**6.93**	**4.43**	**2.57**	**7.65**	**9.20E-08**	**2.90E-07**
Antiparkinson Agents & Loop Diuretics	**1,798**	**21.14**	**6.67**	**4.82**	**9.23**	**2.70E-30**	**2.40E-29**
H2RA & Opioids	**1,797**	**10.02**	**6.21**	**3.90**	**9.88**	**1.30E-14**	**7.30E-14**
PPI & SGAP	**1,715**	**13.99**	**2.51**	**1.68**	**3.76**	**8.20E-06**	**2.00E-05**
Benzodiazepine & Opioids	**1,699**	**8.83**	**6.40**	**3.85**	**10.64**	**8.60E-13**	**4.10E-12**
TZD & SSRI/SNRI	**1,683**	**8.91**	**6.21**	**3.73**	**10.32**	**2.00E-12**	**9.20E-12**
Nitrates & Opioids	**1,679**	**8.93**	**5.00**	**3.01**	**8.32**	**5.50E-10**	**2.00E-09**
H2RA & Nitrates	**1,627**	**<11**	**2.90**	**1.51**	**5.59**	**1.40E-03**	**2.70E-03**
Inhaled Glucocorticoids & Oral Glucocorticoids	1,615	<11	1.42	0.53	3.78	4.90E-01	5.70E-01
Anticonvulsants & Sedative Hypnotics	1,524	<11	1.36	0.44	4.21	6.00E-01	6.80E-01
Inhaled Glucocorticoids & SSRI/SNRI	**1,514**	**7.27**	**3.16**	**1.75**	**5.73**	**1.40E-04**	**3.00E-04**
Oral Glucocorticoids & SSRI/SNRI	**1,408**	**9.94**	**3.91**	**2.31**	**6.62**	**3.80E-07**	**1.10E-06**
H2RA & Anticonvulsants	**1,399**	**<11**	**2.82**	**1.46**	**5.44**	**1.90E-03**	**3.40E-03**
Antiparkinson Agents & SGAP	**1,367**	**15.36**	**3.43**	**2.23**	**5.29**	**2.40E-08**	**7.90E-08**
Anticonvulsants & SGAP	**1,343**	**11.17**	**2.54**	**1.52**	**4.23**	**3.50E-04**	**7.20E-04**
PPI & CAAH	**1,341**	**<11**	**2.98**	**1.34**	**6.65**	**7.50E-03**	**1.20E-02**
Anticonvulsants & Antiparkinson Agents	**1,292**	**10.06**	**4.05**	**2.34**	**7.00**	**5.60E-07**	**1.60E-06**
TZD & Anticonvulsants	**1,231**	**<11**	**4.11**	**1.71**	**9.88**	**1.60E-03**	**3.00E-03**
H1 Blockers & Thiazide Diuretics	1,228	<11	1.76	0.57	5.45	3.30E-01	4.00E-01
TZD & Opioids	**1,202**	**<11**	**4.21**	**1.75**	**10.14**	**1.30E-03**	**2.50E-03**
Anticonvulsants & Nitrates	1,198	<11	1.61	0.60	4.30	3.40E-01	4.10E-01
Thiazide Diuretics & SGAP	**1,170**	**11.11**	**3.74**	**2.17**	**6.46**	**2.20E-06**	**5.70E-06**
Inhaled Glucocorticoids & Opioids	**1,154**	**<11**	**4.53**	**2.26**	**9.08**	**2.00E-05**	**4.80E-05**
SGAP & Loop Diuretics	**1,139**	**23.70**	**3.56**	**2.43**	**5.21**	**7.20E-11**	**2.80E-10**
Antiparkinson Agents & Opioids	**1,085**	**11.06**	**5.52**	**3.12**	**9.74**	**4.00E-09**	**1.40E-08**
Muscle Relaxers & Opioids	**1,058**	**<11**	**5.42**	**2.43**	**12.08**	**3.60E-05**	**8.30E-05**
TCA & Opioids	**1,057**	**<11**	**5.97**	**2.98**	**11.96**	**4.60E-07**	**1.30E-06**
TZD & Nitrates	**1,057**	**<11**	**3.84**	**1.60**	**9.24**	**2.70E-03**	**4.70E-03**
PPI & H1 Blockers	**1,053**	**<11**	**4.46**	**2.23**	**8.93**	**2.40E-05**	**5.70E-05**
Anticonvulsants & TCA	1,022	<11	2.07	0.67	6.42	2.10E-01	2.70E-01
SSRI/SNRI & TCA	992	<11	1.83	0.59	5.69	2.90E-01	3.60E-01
Benzodiazepine & Loop Diuretics	985	<11	2.27	0.94	5.47	6.70E-02	9.10E-02
Oral Glucocorticoids & Anticonvulsants	**908**	**<11**	**3.62**	**1.62**	**8.07**	**1.70E-03**	**3.10E-03**

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Appendix Table 8 Continued

Sedative Hypnotics & Nitrates	874	<11	1.76	0.57	5.46	3.30E-01	4.00E-01
Benzodiazepine & Sedative Hypnotics	850	<11	2.70	0.87	8.38	8.60E-02	1.20E-01
TCA & Loop Diuretics	**844**	**<11**	**3.31**	**1.37**	**7.95**	**7.60E-03**	**1.20E-02**
Inhaled Glucocorticoids & H2RA	824	<11	2.07	0.67	6.43	2.10E-01	2.70E-01
Oral Glucocorticoids & Sedative Hypnotics	**805**	**<11**	**3.94**	**1.64**	**9.48**	**2.20E-03**	**3.80E-03**
H2RA & Sedative Hypnotics	784	<11	2.69	1.01	7.17	4.80E-02	6.70E-02
CAAH & Opioids	772	<11	0.95	0.13	6.78	9.60E-01	9.70E-01
Inhaled Glucocorticoids & Anticonvulsants	769	<11	**2.96**	**1.11**	**7.90**	**3.00E-02**	**4.40E-02**
Inhaled Glucocorticoids & Sedative Hypnotics	**743**	**<11**	**4.53**	**1.88**	**10.89**	**7.50E-04**	**1.50E-03**
Barbiturates & Thiazide Diuretics	**736**	**<11**	**4.04**	**1.68**	**9.71**	**1.80E-03**	**3.20E-03**
Anticonvulsants & Barbiturates	**701**	**<11**	**10.03**	**5.38**	**18.69**	**3.90E-13**	**2.00E-12**
Anticonvulsants & Benzodiazepine	**697**	**<11**	**3.78**	**1.42**	**10.08**	**8.00E-03**	**1.30E-02**
Inhaled Glucocorticoids & Nitrates	696	<11	**2.95**	**1.10**	**7.86**	**3.10E-02**	**4.50E-02**
H2RA & TZD	**691**	**<11**	**3.65**	**1.18**	**11.34**	**2.50E-02**	**3.70E-02**
Oral Glucocorticoids & H2RA	684	<11	**2.99**	**1.12**	**7.97**	**2.90E-02**	**4.30E-02**
TZD & Sedative Hypnotics	**653**	**<11**	**5.96**	**2.23**	**15.91**	**3.60E-04**	**7.30E-04**
TCA & Sedative Hypnotics	653	<11	**3.42**	**1.10**	**10.62**	**3.30E-02**	**4.80E-02**
SSRI/SNRI & CAAH	**623**	**<11**	**3.81**	**1.58**	**9.16**	**2.90E-03**	**5.00E-03**
Sedative Hypnotics & Antiparkinson Agents	**596**	**<11**	**5.51**	**2.47**	**12.28**	**3.10E-05**	**7.20E-05**
Oral Glucocorticoids & Nitrates	**576**	**<11**	**4.07**	**1.69**	**9.79**	**1.70E-03**	**3.10E-03**
Oral Glucocorticoids & Antiparkinson Agents	**534**	**<11**	**8.65**	**4.64**	**16.13**	**1.20E-11**	**5.10E-11**
H2RA & SGAP	**525**	**22.87**	**4.59**	**2.60**	**8.11**	**1.50E-07**	**4.50E-07**
Antiparkinson Agents & FGAP	**516**	**<11**	**4.01**	**1.50**	**10.70**	**5.60E-03**	**9.20E-03**
PPI & Barbiturates	507	<11	2.76	0.89	8.55	7.90E-02	1.10E-01
Anticonvulsants & CAAH	507	<11	1.23	0.17	8.73	8.40E-01	9.20E-01
H1 Blockers & Loop Diuretics	**489**	**<11**	**6.41**	**3.20**	**12.84**	**1.60E-07**	**4.80E-07**
Antiparkinson Agents & Nitrates	**475**	**<11**	**5.37**	**2.55**	**11.30**	**9.40E-06**	**2.30E-05**
Sedative Hypnotics & SGAP	**473**	**<11**	**3.90**	**1.94**	**7.81**	**1.30E-04**	**2.80E-04**
H2RA & Antiparkinson Agents	466	<11	2.20	0.71	6.83	1.70E-01	2.20E-01
Benzodiazepine & Antiparkinson Agents	**462**	**<11**	**3.99**	**1.28**	**12.40**	**1.70E-02**	**2.60E-02**
Opioids & SGAP	**439**	**<11**	**4.83**	**2.59**	**8.99**	**7.10E-07**	**1.90E-06**
H1 Blockers & Opioids	**433**	**<11**	**4.85**	**1.82**	**12.92**	**1.60E-03**	**3.00E-03**
Inhaled Glucocorticoids & TZD	408	<11	2.50	0.35	17.75	3.60E-01	4.30E-01
CAAH & Nitrates	**401**	**<11**	0.00	0.00	0.00	9.30E-01	9.70E-01
H2RA & TCA	379	<11	1.74	0.25	12.38	5.80E-01	6.60E-01
TZD & TCA	373	<11	2.69	0.38	19.09	3.20E-01	3.90E-01
Benzodiazepine & Nitrates	368	<11	1.26	0.18	8.98	8.10E-01	9.00E-01
H2RA & Benzodiazepine	365	<11	1.64	0.23	11.68	6.20E-01	6.90E-01
SSRI/SNRI & Barbiturates	**344**	**<11**	**5.34**	**2.00**	**14.26**	**8.20E-04**	**1.60E-03**
Oral Glucocorticoids & Benzodiazepine	**338**	**<11**	**9.70**	**4.03**	**23.35**	**3.90E-07**	**1.10E-06**
Muscle Relaxers & Thiazide Diuretics	331	<11	2.98	0.42	21.16	2.80E-01	3.50E-01
Benzodiazepine & SGAP	**323**	**<11**	**4.73**	**1.96**	**11.38**	**5.30E-04**	**1.10E-03**
Barbiturates & Loop Diuretics	**314**	**<11**	**10.07**	**5.23**	**19.40**	**5.00E-12**	**2.20E-11**
Inhaled Glucocorticoids & Benzodiazepine	311	<11	1.95	0.27	13.82	5.10E-01	5.90E-01
TCA & Nitrates	**303**	**<11**	0.00	0.00	0.00	9.30E-01	9.70E-01
Oral Glucocorticoids & TZD	**297**	**<11**	0.00	0.00	0.00	9.40E-01	9.70E-01
H2RA & CAAH	**295**	**<11**	0.00	0.00	0.00	9.30E-01	9.70E-01
SSRI/SNRI & H1 Blockers	**290**	**<11**	**6.19**	**2.57**	**14.90**	**4.70E-05**	**1.10E-04**
TCA & Benzodiazepines	**287**	**<11**	**11.87**	**4.45**	**31.67**	**7.70E-07**	**2.10E-06**
TZD & CAAH	**287**	**<11**	**7.04**	**1.76**	**28.17**	**5.80E-03**	**9.50E-03**
SSRI/SNRI & FGAP	**285**	**<11**	**3.88**	**1.46**	**10.36**	**6.70E-03**	**1.10E-02**
TCA & Antiparkinson Agents	283	<11	4.28	1.07	17.15	4.00E-02	5.70E-02
Inhaled Glucocorticoids & Antiparkinson Agents	**282**	**<11**	0.00	0.00	0.00	9.30E-01	9.70E-01
Nitrates & SGAP	**279**	**<11**	**3.07**	**1.28**	**7.39**	**1.20E-02**	**1.90E-02**
PPI & Muscle Relaxers	**275**	**<11**	0.00	0.00	0.00	9.50E-01	9.70E-01
TZD & Antiparkinson Agents	**264**	**<11**	**9.58**	**3.08**	**29.75**	**9.30E-05**	**2.10E-04**
Thiazide Diuretics & FGAP	**263**	**<11**	0.00	0.00	0.00	9.30E-01	9.70E-01
Sedative Hypnotics & CAAH	260	<11	2.79	0.39	19.84	3.00E-01	3.70E-01
Oral Glucocorticoids & TCA	**237**	**<11**	0.00	0.00	0.00	9.40E-01	9.70E-01
H2RA & H1 Blockers	236	<11	2.04	0.29	14.48	4.80E-01	5.60E-01
FGAP & SGAP	235	<11	**3.74**	**1.21**	**11.63**	**2.20E-02**	**3.30E-02**
PPI & FGAP	**212**	**<11**	**7.42**	**3.09**	**17.87**	**7.70E-06**	**1.90E-05**
H1 Blockers & Nitrates	207	<11	2.15	0.30	15.24	4.50E-01	5.30E-01
TZD & SGAP	**203**	**<11**	**5.07**	**1.63**	**15.75**	**5.00E-03**	**8.30E-03**
Inhaled Glucocorticoids & TCA	**201**	**<11**	0.00	0.00	0.00	9.50E-01	9.70E-01
Anticonvulsants & H1 Blockers	**198**	**<11**	**5.32**	**1.33**	**21.29**	**1.80E-02**	**2.70E-02**
TCA & SGAP	**189**	**<11**	0.00	0.00	0.00	9.30E-01	9.70E-01
Barbiturates & Antiparkinson Agents	**184**	**<11**	**6.22**	**1.55**	**24.93**	**9.80E-03**	**1.50E-02**
Oral Glucocorticoids & CAAH	**183**	**<11**	0.00	0.00	0.00	9.50E-01	9.70E-01
Inhaled Glucocorticoids & SGAP	183	<11	2.26	0.56	9.05	2.50E-01	3.10E-01
Sedative Hypnotics & H1 Blockers	**182**	**<11**	0.00	0.00	0.00	9.50E-01	9.70E-01
Inhaled Glucocorticoids & CAAH	**176**	**<11**	**8.71**	**2.18**	**34.86**	**2.20E-03**	**3.80E-03**
Anticonvulsants & FGAP	156	<11	4.22	1.05	16.93	4.20E-02	5.90E-02
Oral Glucocorticoids & H1 Blockers	144	<11	4.11	0.58	29.21	1.60E-01	2.10E-01
Barbiturates & Opioids	**143**	**<11**	0.00	0.00	0.00	9.50E-01	9.70E-01
TCA & CAAH	**140**	**<11**	0.00	0.00	0.00	9.60E-01	9.70E-01
Benzodiazepine & CAAH	**137**	**<11**	0.00	0.00	0.00	9.60E-01	9.70E-01
Antiparkinson Agents & CAAH	130	<11	3.19	0.45	22.68	2.50E-01	3.10E-01
Inhaled Glucocorticoids & H1 Blockers	128	<11	4.48	0.63	31.85	1.30E-01	1.70E-01
TZD & Benzodiazepine	**126**	**<11**	**17.98**	**4.49**	**71.98**	**4.40E-05**	**1.00E-04**
TZD & H1 Blockers	122	<11	6.41	0.90	45.55	6.30E-02	8.60E-02
FGAP & Loop Diuretics	**117**	**<11**	0.00	0.00	0.00	9.30E-01	9.70E-01
Oral Glucocorticoids & SGAP	**113**	**<11**	0.00	0.00	0.00	9.30E-01	9.70E-01
Anticonvulsants & Muscle Relaxers	**111**	**<11**	0.00	0.00	0.00	9.70E-01	9.70E-01

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Appendix Table 8 Continued

FAD pairs with <100PY	-	-	**2.43**	**1.38**	**4.30**	**2.10E-03**	**3.70E-03**
3+FAD	-	-	**5.41**	**5.08**	**5.76**	**0.00E+00**	**0.00E+00**
0 Non-FAD	-	-	1.00	-	-	-	-
1 Non-FAD	-	-	**0.91**	**0.85**	**0.97**	**3.20E-03**	**5.50E-03**
2 Non-FAD	-	-	**0.86**	**0.80**	**0.91**	**2.20E-06**	**5.70E-06**
3+ Non-FAD	-	-	**0.72**	**0.68**	**0.76**	**4.90E-29**	**4.20E-28**

Exposure indicator variables for fracture associated drug (FAD) use reflect person days with any of 21 individual FADs and 210 possible two-way combination of these drugs (included as a specific exposure in most cases, but aggregated to "FAD pairs with <100 PY" if cohort specific observation < 100 person years). "3+FAD" is an indicator variable for person days with three-or-more FADs. The reference exposure was zero FADs. Non-FADs are 552 drug ingredients that are not FADs aggregated into status of receipt of any 1 non-FAD expsoure (1 Non-FAD), 2 concurrent non-FAD exposures (2 Non-FAD) or 3+ Non-FAD exposure classified for each person, for each day of observation. Medicaid eligibility and Medicare Part D low income subsidy are two poverty indicators. Long-term care is defined as 50% or more of annual prescriptions dispensed by a long-term care pharmacy. The three categories of drugs protective of fracture are: 1. osteoporosis treatments: oral and injected bisphosphonates, calcitonin, denosumab, parathyroid hormone, 2. Estrogens-systemic estrogens, selective estrogen receptor modulators, and 3. beta-blockers. SSRI/SNRI = combined drug group of selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors. PPI= proton pump inhibitors, FGAP = first generation antipsychotic. SGAP = second generation antipsychotic. TCA= tricyclic antidepressants. H2RA is Histamine-2 Receptor Antagonists. TZD = Thiazolidinediones. H1 Blockers = 1st Generation Antihistamines. CAAH = Central Acting Antihypertensives. Sedative Hypnotics include only non-benzodiazepine drugs. The Tobacco/Chronic Obstructive Lung Disease is an aggregate indicator of these diagnoses. Bold if False Discovery Rate corrected P value < 0.05. Italicized if population-level impact criteria were met.

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