

SUPPLEMENTARY MATERIAL

Table S1a: Medications considered to be PIMs for this analysis based on modified AGS Beers Criteria®

Medication	ATC	Medication	ATC	Medication	ATC	Medication	ATC
Androgens or Estrogens		Benzodiazepines continued		Drugs with anti-cholinergic properties continued		NSAID without use of PPI continued	
Methyltestosterone	G03BA02	Oxazepam	N05BA04	Imipramine	N06AA02	Naproxen	M01AE02
Testosterone	G03BA03	Clorazepate	N05BA05	Clomipramine	N06AA04	Ketoprofen	M01AE03
Estradiol	G03CA03	Lorazepam	N05BA06	Trimipramine	N06AA06	Fenoprofen	M01AE04
Estriol	G03CA04	Alprazolam	N05BA12	Amitriptyline	N06AA09	Oxaprozin	M01AE12
Estrone	G03CA07	Meprobamate	N05BC01	Nortriptyline	N06AA10	Meclofenamate	M01AG04
Conjugated estrogens	G03CA57	Flurazepam	N05CD01	Protriptyline	N06AA11	Mefenamic acid	M01AG04
Tibolone	G03CX01	Estazolam	N05CD04	Doxepin >6 mg/day	N06AA12	Nabumetone	M01AX01
Antipsychotics		Triazolam	N05CD05	Amoxapine	N06AA17	Naproxen	M02AA12
Chlorpromazine	N05AA01	Temazepam	N05CD07	Paroxetine	N06AB05	Diflunisal	N02BA11
Perphenazine	N05AB03	Quazepam	N05CD10	Diphenhydramine (oral)	R06AA02	Other pain medications	
Prochlorperazine	N05AB04	Zolpidem	N05CF02	Clemastine	R06AA04	Indomethacin	M01AB01
Trifluoperazine	N05AB06	Zaleplon	N05CF03	Carbinoxamine	R06AA08	Ketorolac, includes parenteral	M01AB15
Periciazine	N05AC01	Eszopiclone	N05CF04	Doxylamine	R06AA09	Meperidine	N02AB02
Ziprasidone	N05AE04	Cardiovascular		Dimenhydrinate	R06AA52	PPIs without use of NSAID	
Olanzapine	N05AH03	Amiodarone	C01BD01	Brompheniramine	R06AB01	Omeprazole	A02BC01
Quetiapine	N05AH04	Dronedarone	C01BD07	Chlorpheniramine	R06AB02	Pantoprazole	A02BC02
Amisulpride	N05AL05	Isoxsuprine	C04AA01	Dexchlorpheniramine	R06AB02	Lansoprazole	A02BC03
Lithium	N05AN01	Nifedipine, immediate release	C08CA05	Dexbrompheniramine	R06AB06	Rabeprazole	A02BC04
Risperidone	N05AX08	Other endocrine		Pyrilamine	R06AC01	Esomeprazole	A02BC05
Aripiprazole	N05AX12	Megestrol	G03AC05	Promethazine	R06AD02	Dexlansoprazole	A02BC06
Antithrombotics		Growth hormone	H01AC01	Meclizine	R06AE05	Skeletal muscle relaxants	
Dipyridamole, oral short acting (does not apply to the extended-release combination with aspirin)	B01AC07	Megestrol	L02AB01	Cyproheptadine	R06AX02	Carisoprodol	M03BA02
Barbiturates		Drugs with anti-cholinergic properties		Tripolidine	R06AX07	Methocarbamol	M03BA03
Methylbarbital	N03AA01	Homatropine (excludes ophthalmic)	A03AA07	Gastrointestinal		Chlorzoxazone	M03BB03
Phenobarbital	N03AA02	Propantheline	A03AB05	Metoclopramide	A03FA01	Orphenadrine	M03BC01
Pentobarbital	N05CA01	Atropine (excludes ophthalmic)	A03BA01	Mineral oil, given orally	A06AA01	Cyclobenzaprine	M03BX08
Amobarbital	N05CA02	Hyoscyamine	A03BA03	Desmopressin	H01BA02	Sulfonyleureas, long acting	
Secobarbital	N05CA06	Belladonna alkaloids	A03BB01	NSAID without use of PPI		Glyburide	A10BB01
Benzodiazepines		Methylscopolamine	A03BB03	Sulindac	M01AB02	Chlorpropamide	A10BB02
Clonazepam	N03AE01	Clidinium-chlordiazepoxide	A03CA02	Tolmetin	M01AB03	Glimepiride	A10BB12
Diazepam	N05BA01	Scopolamine	A04AD01	Diclofenac	M01AB05		
Chlordiazepoxide (alone or in combination with amitriptyline or clidinium)	N05BA02	Trihexyphenidyl	N04AA01	Etodolac	M01AB08		
		Benzotropine (oral)	N04AC01	Piroxicam	M01AC01		
		Hydroxyzine	N05BB01	Meloxicam	M01AC06		
		Desipramine	N06AA01	Ibuprofen	M01AE01		

Table S1b: Medications not included as PIMs based on modified 2019 AGS Beers Criteria®

Medication	ATC	Reason not prescribed
Nitrofurantoin	J01XE01	Insufficient prescribing information
Digoxin for first-line treatment of atrial fibrillation or of heart failure	C01AA05	Insufficient prescribing information
Disopyramide	C01BA03	Insufficient prescribing information
Reserpine (>0.1 mg/day)	C02AA02	
Methyldopa	C02AB	
Clonidine for first-line treatment of hypertension	C02AC01	
Guanfacine	C02AC02	
Prazosin	C02CA01	Insufficient prescribing information
Doxazosin	C02CA04	
Terazosin	G04CA03	
Insulin sliding scale	A10A	Insufficient prescribing information

Table S2: Baseline PIMs prevalence by medication class, based on modified 2019 AGS Beers Criteria®

PIMs medication class (descending order of prevalence)	N (% of participants with at least one PIM)
PPIs	4054 (54.8%)
NSAIDs	1281 (17.3%)
Benzodiazepines	1260 (17.0%)
Androgens & estrogens	874 (11.8%)
Drugs with anticholinergic properties	857 (11.6%)
Antipsychotics	277 (3.8%)
Cardiovascular medications	180 (2.4%)
Other pain medication	110 (1.5%)
Sulfonylureas	109 (1.5%)
Gastrointestinal	43 (0.6%)
Skeletal muscle relaxants	34 (0.5%)
Barbituates	4 (<0.1%)
Other endocrine	3 (<0.1%)

Table S3: Risk of disability and hospitalization outcomes by baseline PIMs exposure, based on modified 2019 AGS Beers Criteria® in participants who experienced both events

	No PIM (n=11,718)		PIM (n=7,396)		Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI) ^a
	N	Rate per 1000 person years (95% CI)	N	Rate per 1000 person years (95% CI)		
First event						
Hospitalization AND disability	131	2.52 (2.12, 3.00)	159	5.00 (4.26, 5.81)	1.96 (1.60, 2.50)	1.65 (1.30, 2.10)
Hospitalization followed by disability	94	1.81 (1.48, 2.21)	104	3.25 (2.68, 3.95)	1.78 (1.35, 2.35)	1.54 (1.15, 2.05)
Disability followed by hospitalization	37	0.71 (1.52, 0.98)	55	1.72 (1.32, 2.24)	2.40 (1.58, 3.64)	1.92 (1.25, 2.96)

^a Adjusted for sex, age, country, years of education (<12y, vs 12y+), frailty, average gait speed, hypertension, diabetes, and the presence of depression.

Table S4: Assessment of interaction between Cox models for PIMs and Polypharmacy

	HR ^a : PIM	HR ^a : Polypharmacy	HR ^a : Interaction	p for Interaction
Loss of disability-free survival	0.96 (0.87, 1.06)	1.33 (1.20, 1.48)	1.07 (0.89, 1.33)	0.43
Death	0.85 (0.72, 1.01)	1.32 (1.09, 1.60)	1.02 (0.78, 1.34)	0.87
Incident disability	1.38 (1.05, 1.81)	1.76 (1.28, 2.41)	0.86 (0.57, 1.30)	0.47
Dementia	0.85 (0.68, 1.07)	0.93 (0.69, 1.23)	1.28 (0.87, 1.88)	0.21
Incident Hospitalisation	1.23 (1.16, 1.30) ^b	1.48 (1.36, 1.60) ^c	0.86 (0.77, 0.94)	0.003

^a Cox model included: PIM, Polypharmacy (baseline), PIMxPolypharmacy interaction, sex, age, country, years of education, frailty, average gait speed, hypertension, diabetes, and the presence of depression.

^b For people with PIM and not polypharmacy, the expected rate of Hospitalization is 23% higher than amongst people without PIM, all other variables held constant. For people with PIM and Polypharmacy, the expected rate of hospitalization is $1.23 \times 0.86 = 5.3\%$ higher than amongst people without PIM (95%CI 0.96, 1.14), all other variables held constant.

^c For those with Polypharmacy and not PIM, the estimated hospitalization rate is 48% higher, compared to those without polypharmacy (95%CI: 1.36, 1.60). For those with Polypharmacy and PIM, the estimated hospitalization rate is $1.48 \times 0.86 = 26.6\%$ higher, compared to those without polypharmacy (95%CI for HR: 1.17, 1.36).

Table S5 – Risk of primary endpoint, death, dementia, disability and hospitalisation outcomes by baseline PIMs medication category exposure based on modified 2019 AGS Beers Criteria®

	Number of pts with event, rate per 1000 PY and 95% CI				Adjusted Hazard Ratio (95% CI) ^a
	No PIM [^]		PIM [^]		
Primary Endpoint^b					
Androgens and estrogens	1776	21.6 (20.6, 22.6)	59	15.2 (11.8, 19.7)	1.01 (0.77, 1.32)
Anticholinergics	1730	21.0 (20.1, 22.0)	105	27.5 (22.7, 33.3)	1.17 (0.97, 1.47)
Antipsychotics	1795	21.2 (20.2, 22.2)	40	32.3 (23.7, 44.0)	1.45 (1.06, 1.99)
Benzodiazepines	1689	20.9 (20.0, 21.9)	146	27.5 (23.4, 32.3)	1.11 (0.94, 1.32)
Cardiovascular	1808	21.2 (20.2, 22.2)	27	35.2 (24.2, 51.4)	1.35 (0.92, 1.98)
NSAID	1697	21.2 (20.2, 22.2)	138	23.5 (19.9, 27.8)	1.13 (0.95, 1.34)
Other pain medications	1819	21.3 (20.3, 22.3)	16	32.6 (20.0, 53.2)	1.04 (0.63, 1.71)
PPI	1442	21.2 (20.1, 22.3)	393	21.9 (19.9, 24.2)	0.96 (0.86, 1.07)
Death					
Androgens and estrogens	1019	12.1 (11.3, 12.8)	33	8.4 (6.0, 11.8)	1.11 (0.77, 1.58)
Anticholinergics	1000	11.8 (11.1, 12.6)	52	13.2 (10.0, 17.3)	1.04 (0.79, 1.38)
Antipsychotics	1034	11.9 (11.2, 12.6)	18	13.9 (8.8, 22.0)	1.18 (0.74, 1.90)
Benzodiazepines	979	11.8 (11.1, 12.6)	73	13.3 (11.6, 16.7)	1.01 (0.80, 1.29)
Cardiovascular	1038	11.9 (11.2, 12.6)	14	17.2 (10.2, 29.1)	1.13 (0.67, 1.92)
NSAID	975	11.8 (11.1, 12.6)	77	12.8 (10.2, 16.0)	1.07 (0.85, 1.35)
Other pain medications	1041	11.8 (11.1, 12.6)	11	21.8 (12.1, 39.4)	1.22 (0.67, 2.21)
PPI	849	12.1 (11.3, 13.0)	203	11.04 (9.6, 12.7)	0.85 (0.73, 0.99)
Disability					
Androgens and estrogens	400	5.5 (4.9, 6.0)	12	3.5 (2.0, 6.1)	0.88 (0.49, 1.57)
Anticholinergics	381	5.2 (4.7, 5.7)	31	9.4 (6.6, 13.4)	1.4 (0.96, 2.02)
Antipsychotics	396	5.2 (4.7, 5.8)	16	14.7 (9.0, 24.1)	1.96 (1.17, 3.28)
Benzodiazepines	366	5.1 (4.6, 5.6)	46	10.0 (7.5, 13.3)	1.38 (1.01, 1.89)
Cardiovascular	406	5.3 (4.8, 5.9)	6	8.7 (3.9, 19.3)	1.00 (0.44, 2.26)
NSAID	379	5.3 (4.8, 5.8)	33	6.4 (4.5, 9.0)	1.21 (0.85, 1.73)
Other pain medications	406	5.3 (4.8, 5.9)	6	14.0 (6.3, 31.1)	1.27 (0.55, 2.94)
PPI	291	4.8 (4.3, 5.4)	121	7.6 (6.4, 9.1)	1.34 (1.07, 1.67)
Dementia					
Androgens and estrogens	557	6.9 (6.4, 7.5)	18	4.7 (3.0, 7.5)	0.93 (0.57, 1.49)
Anticholinergics	544	6.8 (6.2, 7.4)	31	8.3 (5.8, 11.8)	1.11 (0.77, 1.60)
Antipsychotics	563	6.7 (6.2, 7.4)	12	9.7 (5.5, 17.1)	1.43 (0.81, 2.55)
Benzodiazepines	533	6.7 (6.2, 7.3)	42	8.1 (6.0, 10.9)	1.03 (0.75, 1.41)
Cardiovascular	565	6.8 (6.2, 7.3)	10	13.3 (7.1, 24.8)	1.77 (0.95, 3.32)
NSAID	532	6.8 (6.2, 7.4)	43	7.5 (5.6, 10.1)	1.11 (0.81, 1.51)
Other pain medications	575	6.9 (6.3, 7.4)	0	0	-
PPI	462	6.9 (6.3, 7.6)	113	6.4 (5.3, 7.3)	0.89 (0.72, 1.10)
Incident Hospitalization					
Androgens and estrogens	7078	106.2 (103.8, 108.7)	363	120.6 (108.8, 133.7)	1.22 (1.09, 1.36)
Anticholinergics	7031	105.2 (102.8, 107.7)	410	144.8 (131.5, 160.0)	1.3 (1.17, 1.44)
Antipsychotics	7309	106.4 (104.0, 108.9)	132	139.8 (117.9, 165.8)	1.18 (0.99, 1.40)
Benzodiazepines	6935	106.0 (103.6, 108.6)	506	119.6 (109.7, 130.5)	1.03 (0.93, 1.13)
Cardiovascular	7367	106.7 (104.3, 109.2)	74	118.5 (94.4, 148.8)	1.07 (0.85, 1.35)
NSAID	6828	104.6 (102.1, 107.1)	613	140.3 (129.6, 151.8)	1.34 (1.23, 1.46)
Other pain medications	7391	106.7 (104.3, 109.2)	50	137.6 (104.3, 181.6)	1.16 (0.87, 1.53)
PPI	5656	101.5 (98.9, 104.2)	1785	128.1 (122.3, 134.2)	1.18 (1.12, 1.25)

[^] In this table PIM refers to the specific PIM indicated by the row e.g. No PIM vs PIM for the Androgen and estrogens row means no exposure vs exposure to Androgens and estrogens that fit the PIMs definition. Exposure to other PIMs is ignored;

^a Adjusted for sex, age, country, years of education, frailty, average baseline gait speed, hypertension, diabetes, and the presence of depression; ^b Composite of death from any cause, incident dementia or incident disability; Gastrointestinal, Other hypnotics, Skeletal muscle relaxants, Sulfonylureas, Genitourinary, barbiturates, meprobamate and other endocrine (e.g. thyroid, growth hormone and megestrol) not presented to due lack of events.

Table S6: Risk of cause of death from specific causes by baseline PPI use considered to be potentially inappropriate based on modified 2019 AGS Beers Criteria ®

	No PPI use considered to be PIM		PPI considered to be PIM		Adjusted HR ^a (95% CI)
	N	Rate per 1000 person years (95% CI)	N	Rate per 1000 person years (95% CI)	
Cancer Related	411	5.9 (5.3, 6.5)	104	5.7 (4.7, 6.8)	0.89 (0.72, 1.11)
Cardiovascular Death	56	0.8 (0.6, 1.0)	16	0.9 (0.5, 1.4)	1.00 (0.57, 1.76)
Clinically Significant Bleeding Death	11	0.2 (0.09, 0.3)	7	0.4 (0.2, 0.8)	1.71 (0.63, 4.65)
Coronary Heart Disease Death	79	1.1 (0.9, 1.4)	17	0.9 (0.6, 1.5)	0.77 (0.46, 1.31)
Stroke Death	59	0.8 (0.7, 1.1)	4	0.2 (0.1, 0.6)	0.23 (0.09, 0.70)
Other Death	210	3.0 (2.6, 3.4)	53	2.9 (2.2, 3.8)	0.92 (0.70, 1.24)
Unadjudicated	23	0.33 (0.2, 0.5)	2	0.11(0.03, 0.4)	0.54 (0.13, 2.34)
Total	849	12.1 (11.3, 13.0)	203	11.0 (9.6, 12.7)	0.85 (0.73, 0.995)

^a *Adjusted for sex, age, country, years of education, frailty, average baseline gait speed, hypertension, diabetes, and the presence of depression.*