

Supplementary Online Content

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eFigure 1. Proportion of Patients with Simultaneous New Use of an Antidepressant and a Benzodiazepine by Age at Antidepressant Treatment Initiation

eFigure 2. Proportion of Antidepressant and Benzodiazepine Simultaneous New Users Who Became Long-term Benzodiazepine Users

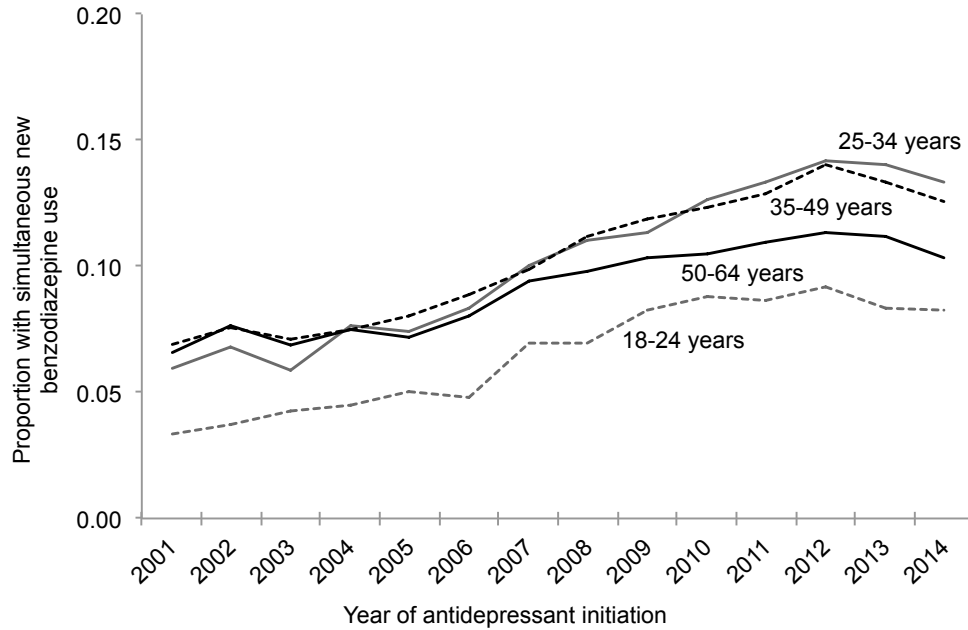
eTable 1. Characteristics of Simultaneous Antidepressant and Benzodiazepine New Users and Non-Simultaneous Antidepressant New Users With Depression and Factors Associated With Simultaneous New Use (Full List of Characteristics)

eTable 2. Details of the Initial Benzodiazepine Prescription Among Antidepressant and Benzodiazepine Simultaneous New Users: Overall and by Selected Physicians

eTable 3. Long-term Benzodiazepine Use Among Simultaneous New Users by Baseline Patient Characteristics and Initial Prescription Details (Full List of Characteristics)

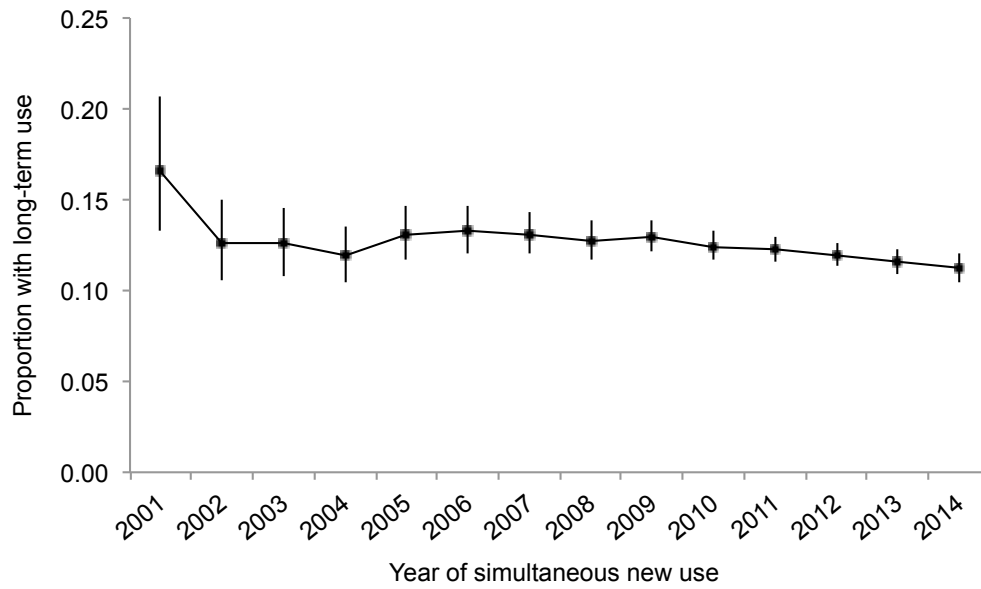
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Proportion of Patients With Simultaneous New Use of an Antidepressant and a Benzodiazepine by Age at Antidepressant Treatment Initiation



Proportions internally standardized (reference year=2012) by sex and region; excluded patients with unknown region (remaining n=755,489)

eFigure 2. Proportion of Antidepressant and Benzodiazepine Simultaneous New Users Who Became Long-term Benzodiazepine Users



Error bars represent the 95% CI; Decreasing error bar size related to increasing sample size in the datasource

eTable 1. Characteristics of Simultaneous Antidepressant and Benzodiazepine New Users and Non-Simultaneous Antidepressant New Users With Depression and Factors Associated With Simultaneous New Use (Full List of Characteristics)^a

	Non-Simultaneous New Users (N=684,110) No. (%)	Simultaneous New Users (N=81,020) No. (%)	Simultaneous New Use		
			Simultaneous New Users, % (95% CI)	Crude RR	Multivariable RR (95% CI)
Male	231,600 (34)	26,079 (32)	10% (10-10)	REF	REF
Female	452,510 (66)	54,941 (68)	11% (11-11)	1.07	1.09 (1.08-1.11)
Age (years), Median (IQR)	39 (29, 49)	39 (30, 49)			
18-24	120,403 (18)	10,140 (13)	8% (8-8)	REF	REF
25-34	144,620 (21)	19,358 (24)	12% (12-12)	1.52	1.59 (1.56-1.63)
35-49	249,217 (36)	32,715 (40)	12% (11-12)	1.49	1.68 (1.64-1.71)
50-64	169,870 (25)	18,807 (23)	10% (10-10)	1.28	1.55 (1.51-1.59)
Year of antidepressant new use					
2001-2004	66,776 (10)	4,844 (6)	7% (7-7)	0.58	0.66 (0.64-0.68)
2005-2008	146,587 (21)	14,101 (17)	9% (9-9)	0.75	0.84 (0.82-0.85)
2009-2012	305,126 (45)	40,426 (50)	12% (12-12)	REF	REF
2013-2014	165,621 (24)	21,649 (27)	12% (11-12)	0.99	0.92 (0.91-0.94)
Initial antidepressant class					
SSRI	474,001 (69)	64,460 (80)	12% (12-12)	REF	REF
SNRI	65,935 (10)	5,554 (7)	8% (8-8)	0.65	0.69 (0.67-0.70)
Bupropion	86,725 (13)	5,667 (7)	6% (6-6)	0.51	0.57 (0.56-0.59)
Other	57,449 (8)	5,339 (7)	9% (8-9)	0.71	0.65 (0.63-0.67)
Depression diagnosis (index diagnosis) ^b					
Not otherwise specified	339,912 (50)	32,443 (40)	9% (9-9)	REF	REF
Major depressive disorder	178,503 (26)	23,466 (29)	12% (11-12)	1.33	1.40 (1.38-1.43)
Other	165,695 (24)	25,111 (31)	13% (13-13)	1.51	1.75 (1.72-1.78)
Inpatient index depression diagnosis	13,144 (2)	2,398 (3)	15% (15-16)	1.47	1.34 (1.29-1.40)
Non-recent depression diagnosis	161,261 (24)	13,328 (16)	8% (8-8)	0.67	0.71 (0.69-0.72)
Physician specialty who provided index depression diagnosis					
Family practice	229,862 (34)	27,350 (34)	11% (11-11)	REF	REF
Psychiatry	86,879 (13)	13,398 (17)	13% (13-14)	1.26	1.32 (1.29-1.35)
Psychologist, therapist	70,953 (10)	6,673 (8)	9% (8-9)	0.81	0.85 (0.83-0.88)
Other specialty	234,533 (34)	26,513 (33)	10% (10-10)	0.96	0.98 (0.96-0.99)
Unknown or multiple physicians	61,883 (9)	7,086 (9)	10% (10-11)	0.97	0.93 (0.91-0.96)
Anxiety disorder diagnosis, recent					
Unspecified anxiety	52,389 (8)	16,651 (21)	24% (24-24)	2.61	2.58 (2.54-2.62)
Generalized anxiety disorder	21,350 (3)	5,705 (7)	21% (21-22)	2.07	1.90 (1.85-1.95)
Panic disorder	4,471 (1)	2,870 (4)	39% (38-40)	3.79	2.67 (2.58-2.76)
PTSD	4,819 (1)	783 (1)	14% (13-15)	1.32	1.14 (1.05-1.22)
OCD, phobic disorder, other anxiety	5,910 (1)	1,465 (2)	20% (19-21)	1.89	1.47 (1.40-1.55)
Non-recent anxiety diagnosis only	23,422 (3)	2,255 (3)	9% (8-9)	0.82	1.11 (1.06-1.15)
Insomnia or sleep disturbance	39,006 (6)	6,618 (8)	15% (14-15)	1.40	1.31 (1.28-1.34)

diagnosis, recent					
Psychiatric co-morbidities					
ADHD	20,452 (3)	1,329 (2)	6% (6-6)	0.57	0.63 (0.59-0.66)
Acute reaction to stress	9,030 (1)	1,936 (2)	18% (17-18)	1.68	1.43 (1.37-1.49)
Adjustment disorder ^c	22,968 (3)	3,086 (4)	12% (11-12)	1.12	1.06 (1.02-1.10)
Other episodic mood disorder	7,088 (1)	678 (1)	9% (8-9)	0.82	0.83 (0.78-0.90)
Treated self-harm	861 (<1)	83 (<1)	9% (7-11)	0.83	0.74 (0.59-0.92)
Psychotherapy, recent					
None recorded	529,351 (77)	64,845 (80)	11% (11-11)	REF	REF
≥1 session	154,759 (23)	16,175 (20)	9% (9-10)	0.87	0.83 (0.81-0.85)
Fall, fracture risk factors					
Fracture (excluding skull)	16,079 (2)	1,959 (2)	11% (10-11)	1.03	1.09 (1.04-1.13)
Bone mineral density scan	18,767 (3)	1,908 (2)	9% (9-10)	0.87	0.92 (0.88-0.97)
Osteoporosis	6,464 (1)	647 (1)	9% (8-10)	0.86	0.95 (0.88-1.03)
Cataracts or glaucoma	19,612 (3)	2,014 (2)	9% (9-10)	0.88	0.92 (0.88-0.96)
Visual disturbance/loss	8,803 (1)	980 (1)	10% (9-11)	0.95	0.95 (0.89-1.00)
Poisoning ^d	4,117 (1)	423 (1)	9% (8-10)	0.88	0.84 (0.76-0.92)
Non-psychiatric co-morbidities					
Cardiac dysrhythmias	17,114 (3)	1,985 (2)	10% (10-11)	0.98	0.95 (0.91-1.00)
Cardiac disorders ^e	25,924 (4)	3,173 (4)	11% (11-11)	1.03	1.06 (1.02-1.10)
Chronic kidney disease	3,670 (1)	362 (<1)	9% (8-10)	0.85	0.95 (0.86-1.05)
Osteoarthritis and allied disorders	30,654 (4)	3,216 (4)	9% (9-10)	0.89	0.94 (0.91-0.97)
Crohn's disease, gastroenteritis	18,352 (3)	2,281 (3)	11% (11-11)	1.05	1.06 (1.02-1.10)
Diabetes	43,589 (6)	4,372 (5)	9% (9-9)	0.85	0.91 (0.88-0.94)
Epilepsy, recurrent seizures	3,458 (1)	321 (<1)	8% (8-9)	0.80	0.80 (0.72-0.89)
Fatigue, malaise	112,920 (17)	11,383 (14)	9% (9-9)	0.84	0.85 (0.84-0.87)
Hearing loss/problem	9,571 (1)	1,014 (1)	10% (9-10)	0.90	0.92 (0.87-0.97)
Hypertension	112,969 (17)	12,640 (16)	10% (10-10)	0.94	0.92 (0.91-0.94)
Hypothyroidism	47,405 (7)	4,941 (6)	9% (9-10)	0.88	0.90 (0.87-0.92)
Overweight, obese	40,729 (6)	4,292 (5)	10% (9-10)	0.89	0.86 (0.84-0.89)
Urinary incontinence	5,125 (1)	515 (1)	9% (8-10)	0.86	0.90 (0.83-0.97)
Outpatient problem-oriented visit, Median (IQR)	4 (2, 6)	3 (2, 6)			
0-1	124,224 (18)	16,077 (20)	11% (11-12)	REF	REF
2-6	399,455 (58)	47,266 (58)	11% (10-11)	0.92	0.94 (0.93-0.96)
>6	160,431 (23)	17,677 (22)	10% (10-10)	0.87	0.91 (0.89-0.93)
Inpatient admission, non-psychiatric related	53,321 (8)	5,719 (7)	10% (9-10)	0.91	0.90 (0.87-0.92)
Count of medications by therapeutic group ^f	3 (1, 5)	3 (1, 5)			
0-1	187,505 (27)	22,702 (28)	11% (11-11)	REF	REF
2-6	390,209 (57)	45,863 (57)	11% (10-11)	0.97	1.02 (1.01-1.04)
>6	106,396 (16)	12,455 (15)	10% (10-11)	0.97	1.11 (1.08-1.13)
Opioid prescription, recent	45,916 (7)	6,006 (7)	12% (11-12)	1.10	1.15 (1.12-1.18)
Region					
Northeast	79,719 (12)	10,466 (13)	12% (11-12)	1.10	1.12 (1.10-1.15)
North Central	192,051 (28)	20,700 (26)	10% (10-10)	0.92	0.99 (0.98-1.01)
South	249,091 (36)	30,291 (37)	11% (11-11)	1.03	1.05 (1.04-1.07)
West	154,927 (23)	18,244 (23)	11% (10-11)	REF	REF
Unknown	8,322 (1)	1,319 (2)	14% (13-14)	1.30	1.28 (1.22-1.35)

Recent refers to measures within 30 days before antidepressant initiation (non-recent: 31-365 days prior); IQR: interquartile range, PTSD: Post traumatic stress disorder, OCD: Obsessive compulsive disorder, ADHD: Attention-deficit/hyperactivity disorder, REF: Reference

^aTable 1 in manuscript is a reduced version of eTable1; Variables removed from full model given independent association with simultaneous new use of 0.952<RR<1.05: Non-recent insomnia/sleep disturbance diagnosis, fall related injury (ICD-

9: E880-E886, E888), fainting/dizziness, gait/lack of coordination, head injury/concussion, dislocation/sprain, other injury, non-psychiatric co-morbidities (anemia, asthma or chronic obstructive pulmonary disease, cerebrovascular disease, gastroesophageal reflux disease, liver disease, migraine/chronic headache, myocardial infarction), psychiatric related inpatient admission

^bIndex depression diagnosis: other includes adults diagnosed with dysthymic disorder, adjustment disorder with depressed mood, or prolonged depressive reaction; not otherwise specified includes adults without a specific diagnosis

^cExcludes ICD-9 309.0x: Adjustment disorder with depressed mood and 309.1x: Prolonged depressive reaction

^dDefined with ICD-9 codes=960-979 (range for poisoning by drugs, medicinals and biological substances)

^eCardiac disorders defined based on Elixhauser cardiac definition

^fCount of therapeutic group excludes day of antidepressant/benzodiazepine initiation

eTable 2. Details of the Initial Benzodiazepine Prescription Among Antidepressant and Benzodiazepine Simultaneous New Users: Overall and by Selected Physicians

	Simultaneous new users (N=81,020)	Diagnosing provider type ^a		
		Psychiatry (N=13,398)	Family practice (N=27,350)	Other (N=40,272)
Initial benzodiazepine prescription ^b	No. (%)	No. (%)	No. (%)	No. (%)
Long-acting agent	20,296 (25)	5,019 (37)	5,907 (22)	9,370 (23)
Days supply, median (IQR)	20 (10, 30)	30 (15, 30)	15 (10, 30)	16 (10, 30)
1-7 days	10,913 (13)	896 (7)	4,117 (15)	5,900 (15)
8-21 days	34,064 (42)	3,549 (26)	13,094 (48)	17,421 (43)
22-35 days	34,640 (43)	8,469 (63)	9,880 (36)	16,291 (40)
>35 days	1,399 (2)	484 (4)	258 (1)	657 (2)
Quantity dispensed, median (IQR)	30 (30, 60)	30 (30, 60)	30 (30, 45)	30 (25, 50)
1-24 pills	18,511 (23)	2,046 (15)	6,452 (24)	10,013 (25)
25-50 pills	41,369 (51)	6,062 (45)	14,895 (54)	20,412 (51)
>50 pills	21,136 (26)	5,290 (39)	6,002 (22)	9,844 (24)
Pills-per-day, median (IQR) ^c	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)
1 pill (<1.5)	25,591 (32)	5,088 (38)	7,774 (28)	12,729 (32)
2 pills (1.5 to <2.5)	26,138 (32)	4,837 (36)	8,633 (32)	12,668 (31)
3+ pills (>2.5)	29,287 (36)	3,473 (26)	10,942 (40)	14,872 (37)
Dose-per-day				
Less than modal dose	18,063 (22)	3,768 (28)	5,187 (19)	9,108 (23)
Modal dose	24,425 (30)	4,644 (35)	7,871 (29)	11,910 (30)
Greater than modal dose	38,528 (48)	4,986 (37)	14,291 (52)	19,251 (48)

^aProvider associated with the index depression diagnosis

^bPatients (n=4) with an index benzodiazepine in a solution form missing days supply, quantity, pills-per-day, dose-per-day; Days supply and quantity values ≤0 were set to the median value (30), days supply values >99 were truncated to 100, and quantity values >200 were truncated to 200. For patients with multiple agents (0.9%) if one agent was long-acting they were classified as initiating on a long-acting agent and we defined modal dose based on the highest modal dose-per-day classification

^cRanges represent calculated values from quantity dispensed/day supply

eTable 3. Long-term Benzodiazepine Use Among Simultaneous New Users by Baseline Patient Characteristics and Initial Prescription Details (Full List of Characteristics)^a

	Non-long term benzodiazepine users (N=54,900)	Long-term benzodiazepine users (N=6,582)	Long-term benzodiazepine use	
	No. (%)	No. (%)	Crude RR	Multivariable RR (95% CI)
Male	17,091 (31)	2,610 (40)	REF	REF
Female	37,809 (69)	3,972 (60)	0.72	0.78 (0.74-0.81)
Age (years), median (IQR)	39 (31, 49)	42 (32, 51)		
18-24	6,806 (12)	706 (11)	REF	REF
25-34	12,740 (23)	1,270 (19)	0.96	1.00 (0.92-1.09)
35-49	22,642 (41)	2,753 (42)	1.15	1.15 (1.07-1.25)
50-64	12,712 (23)	1,853 (28)	1.35	1.27 (1.17-1.38)
Initial antidepressant class				
SSRI	43,993 (80)	4,855 (74)	REF	REF
SNRI	3,661 (7)	607 (9)	1.43	1.19 (1.11-1.29)
Bupropion	3,884 (7)	478 (7)	1.10	1.00 (0.91-1.09)
Other	3,362 (6)	642 (10)	1.61	1.17 (1.08-1.26)
Depression diagnosis (index diagnosis) ^b				
Not otherwise specified	22,134 (40)	2,203 (33)	REF	REF
Major depressive disorder	15,411 (28)	2,744 (42)	1.67	1.19 (1.12-1.26)
Other	17,355 (32)	1,635 (25)	0.95	0.95 (0.90-1.01)
Inpatient index depression diagnosis	1,442 (3)	373 (6)	1.97	1.16 (0.99-1.36)
Physician specialty who provided index depression diagnosis				
Family practice	18,655 (34)	1,675 (25)	REF	REF
Psychiatry	8,661 (16)	1,884 (29)	2.17	1.37 (1.27-1.47)
Psychologist, therapist	4,826 (9)	524 (8)	1.19	1.03 (0.94-1.14)
Other specialty	18,185 (33)	1,968 (30)	1.19	1.08 (1.02-1.15)
Unknown or multiple physicians	4,573 (8)	531 (8)	1.26	1.08 (0.98-1.18)
Short vs. long-acting benzodiazepine ^c				
Short or intermediate-acting	41,820 (76)	4,283 (65)	REF	REF
Long-acting	13,080 (24)	2,299 (35)	1.61	1.28 (1.22-1.34)
Benzodiazepine index days supply ^c	15 (10, 30)	30 (15, 30)		
1-7 days	7,948 (14)	373 (6)	REF	REF
8-21 days	24,154 (44)	1,790 (27)	1.54	1.46 (1.30-1.64)
22-35 days	22,041 (40)	4,103 (62)	3.50	2.91 (2.54-3.33)
>35 days	756 (1)	316 (5)	6.58	4.90 (4.15-5.79)
Initial benzodiazepine dose-per-day ^c				
Less than modal dose	12,147 (22)	1,525 (23)	0.94	0.88 (0.83-0.95)
Modal dose	16,303 (30)	2,193 (33)	REF	REF
Greater than modal dose	26,449 (48)	2,864 (44)	0.82	1.12 (1.06-1.18)
Initial benzodiazepine quantity dispensed ^c	30 (30, 50)	30 (30, 60)		
1-24 pills	13,171 (24)	767 (12)	REF	REF
25-50 pills	28,306 (52)	3,252 (49)	1.87	1.18 (1.08-1.29)
>50 pills	13,422 (24)	2,563 (39)	2.91	1.14 (1.01-1.27)
Anxiety disorder diagnosis, recent				
Generalized anxiety disorder	3,443 (6)	529 (8)	1.27	1.16 (1.07-1.25)
Panic disorder	1,735 (3)	249 (4)	1.18	1.15 (1.02-1.29)
PTSD	496 (1)	75 (1)	1.23	1.08 (0.83-1.39)

OCD, phobic disorder, other anxiety	893 (2)	171 (3)	1.51	1.27 (1.10-1.45)
Non-recent anxiety diagnosis only	1,500 (3)	212 (3)	1.16	1.10 (0.97-1.25)
Insomnia or sleep disturbance diagnosis, recent	4,116 (7)	530 (8)	1.07	1.12 (1.03-1.22)
Non-recent	1,939 (4)	329 (5)	1.37	1.23 (1.11-1.37)
Psychiatric co-morbidities				
ADHD	814 (1)	128 (2)	1.27	1.23 (1.04-1.45)
Acute reaction to stress	1,307 (2)	102 (2)	0.67	0.76 (0.63-0.92)
Adjustment disorder ^d	2,037 (4)	225 (3)	0.93	0.83 (0.71-0.96)
Other episodic mood disorder	426 (1)	75 (1)	1.40	1.10 (0.89-1.35)
Treated self-harm	48 (<1)	*	*	0.95 (0.52-1.74)
Fall, fracture risk factors				
Fracture (excludes skull)	1,285 (2)	210 (3)	1.32	1.16 (1.02-1.32)
Fall injury ^e	290 (1)	34 (1)	0.98	0.90 (0.66-1.23)
Cataracts or glaucoma	1,331 (2)	168 (3)	1.05	0.92 (0.79-1.06)
Visual disturbance/loss	622 (1)	94 (1)	1.23	1.16 (0.97-1.40)
Poisoning ^e	263 (<1)	65 (1)	1.86	1.29 (1.01-1.64)
Non-psychiatric co-morbidities				
Cerebrovascular disease	680 (1)	126 (2)	1.47	1.06 (0.90-1.25)
Chronic kidney disease	236 (<1)	33 (1)	1.15	0.79 (0.57-1.10)
Osteoarthritis and allied disorders	2,037 (4)	344 (5)	1.37	1.13 (1.02-1.26)
Crohn's disease/gastroenteritis	1,475 (3)	218 (3)	1.21	1.12 (0.99-1.27)
Hearing loss/problem	713 (1)	86 (1)	1.01	0.90 (0.74-1.10)
Myocardial infarction	176 (<1)	39 (1)	1.70	1.20 (0.91-1.57)
Overweight, obese	2,743 (5)	290 (4)	0.89	0.85 (0.76-0.95)
Urinary incontinence	338 (1)	36 (1)	0.90	0.84 (0.62-1.14)
Outpatient problem-oriented visits, median (IQR)	4 (2, 6)	3 (2, 6)		
0-1	10,592 (19)	1,548 (24)	REF	REF
2-6	32,327 (59)	3,531 (54)	0.77	0.86 (0.81-0.92)
>6	11,981 (22)	1,503 (23)	0.87	0.83 (0.76-0.90)
Inpatient admission				
Psychiatric-related	1,427 (3)	370 (6)	1.98	1.21 (1.03-1.41)
Non-psychiatric-related	3,801 (7)	503 (8)	1.10	0.93 (0.85-1.02)
Count of medications by therapeutic group ^f	3 (1, 5)	3 (1, 6)		
0-1	15,258 (28)	1,845 (28)	REF	REF
2-6	31,339 (57)	3,548 (54)	0.94	1.02 (0.96-1.08)
>6	8,303 (15)	1,189 (18)	1.16	1.13 (1.04-1.23)
Opioid prescription, recent	3,723 (7)	773 (12)	1.69	1.50 (1.39-1.61)
Year of simultaneous new use				
2001-2004	3,718 (7)	477 (7)	1.05	0.96 (0.88-1.05)
2005-2008	10,360 (19)	1,350 (21)	1.07	1.01 (0.95-1.07)
2009-2012	28,851 (53)	3,500 (53)	REF	REF
2013-2014	11,971 (22)	1,255 (19)	0.88	0.89 (0.84-0.95)
Region				
Northeast	7,039 (13)	849 (13)	1.23	1.17 (1.08-1.27)
North Central	14,092 (26)	1,691 (26)	1.23	1.21 (1.13-1.30)
South	19,917 (36)	2,703 (41)	1.37	1.27 (1.19-1.35)
West	13,039 (24)	1,246 (19)	REF	REF
Unknown	813 (1)	93 (1)	1.18	1.03 (0.84-1.25)

Recent refers to measures within 30 days before antidepressant initiation; IQR: interquartile range, PTSD: Post traumatic stress disorder, OCD: Obsessive compulsive disorder, ADHD: Attention-deficit/hyperactivity disorder, REF: Reference

*Not displayed due to small number

^aTable 3 in manuscript is a reduced version of eTable3; Restricted to patients with 6-months of enrollment (n=61,482); Variables removed from full model given independent association with long-term use 0.952<RR<1.05: Non-recent depression diagnosis, recent unspecified anxiety diagnosis, recent psychotherapy session, bone mineral density scan,

fainting/dizziness, gait/lack of coordination, osteoporosis, head injury/concussion, dislocation/sprain, other injury, non-psychiatric co-morbidities (anemia, asthma/chronic obstructive pulmonary disease, cardiac dysrhythmia and disorder, gastroesophageal reflux disease, diabetes, epilepsy/recurrent seizures, fatigue/malaise, hypertension, hypothyroidism, liver disease, migraine/chronic headache); One person was excluded from multivariable analysis who initiated on a benzodiazepine in solution form

^bIndex depression diagnosis: other includes adults diagnosed with dysthymic disorder, adjustment disorder with depressed mood, or prolonged depressive reaction; not otherwise specified includes adults without a specific diagnosis

^cDays supply and quantity values ≤ 0 were set to the median value (30), days supply values >99 were truncated to 100, and quantity values >200 were truncated to 200. For patients with multiple agents (0.9%) if one agent was long-acting they were classified as initiating on a long-acting agent and we defined modal dose based on the highest modal dose-per-day classification

^dExcludes ICD-9 309.0x: Adjustment disorder with depressed mood and 309.1x: Prolonged depressive reaction

^eDefined with ICD-9 codes=960-979 (range for poisoning by drugs, medicinals and biological substances)

^fCount of therapeutic group excludes day of antidepressant/benzodiazepine initiation