

Appendix 1 Antidepressant medications and adjunctive agents

Medication	Therapeutic Class
Antidepressant	
Amitriptyline	TCA
Amoxapine	TCA
Bupropion	Other AD
Bupropion SR	Other AD
Bupropion XL	Other AD
Citalopram	SSRI
Clomipramine	TCA
Desipramine	TCA
Desvenlafaxine	SNRI
Doxepin	TCA
Duloxetine	SNRI
Escitalopram	SSRI
Fluoxetine	SSRI
Fluoxetine weekly	SSRI
Fluvoxamine	SSRI
Imipramine	TCA
Isocarboxazid	MAOI
Levomilnacipran	SNRI
Maprotiline	TCA
Mirtazapine	Other AD
Nefazodone	SSRI
Nortriptyline	TCA
Paroxetine	SSRI
Paroxetine CR	SSRI
Phenelzine	MAOI
Protriptyline	TCA
Selegiline (transdermal patch)	MAOI
Sertraline	SSRI
Tranylcypromine	MAOI
Trazodone	SSRI
Trazodone ER tablets	SSRI
Trimipramine	TCA
Venlafaxine	SNRI
Venlafaxine XR	SNRI
Vilazodone	SSRI
Vortioxetine	SSRI
Adjunctive Agent	
Aripiprazole	Antipsychotic agent
Lithium carbonate	Antimanic agent
Quetiapine	Antipsychotic agent
Combination Antidepressant and Adjunctive Agent	
Fluoxetine/olanzapine	SSRI/Antipsychotic agent

Abbreviations: AD, antidepressant; MAOI, Monoamine Oxidase Inhibitor; SNRI, Serotonin and Norepinephrine Reuptake Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor; TCA, Tricyclic Antidepressant.

Appendix 2 International Classification of Disease (ICD-9) codes for patient selection and subgroup identification

Condition	ICD-9 Code
Major Depressive Disorder	
Major depressive disorder, single episode	296.2
Major depressive disorder, recurrent episode	296.3
Dysthymic disorder	300.4
Depressive disorder, not otherwise specified	311.xx
Anxiety Disorders	
Generalized anxiety disorder	300.02
Panic disorders and phobias	300.01, 300.21, 300.22, 300.23
Obsessive-compulsive disorder	300.3
Post-traumatic stress disorder	309.81
Acute stress disorder	308.3
Anxiety and anxiety, not otherwise specified	300.00, 300.5x, 300.09, 300.20, 300.29, 300.3
Chronic Non-Cancer Pain Disorders	
Fibromyalgia	729.1
Diabetes with neurological manifestations	250.6x, 357.2x
Osteoarthritis	715.xx
Low back pain	721.3x, 722.10, 722.32, 722.52, 722.83, 722.93, 724.02, 724.2-7, 738.5, 739.3, 739.4, 846.xx, 847.2x
Headache (chronic type) and migraine	339.12, 346.xx, 784.0
Neuropathic pain conditions	337.1, 337.2x, 337.9, 344.6, 350.1, 350.2, 354.0, 353.xx, 354.1, 354.2, 354.3, 354.4, 354.5, 354.8, 354.9, 355.0, 355.1, 355.2, 355.3, 355.4, 355.5, 355.6, 355.71, 355.79, 355.8, 355.9, 357.1, 357.3, 357.4, 357.5, 357.6, 357.7, 357.8, 357.9, 721.1, 721.41, 721.42, 721.91, 722.7x, 724.3, 724.4, 729.2
Exclusion Codes	
Pregnancy	630-679
Schizophrenic disorder	295.xx
Bipolar disorder, psychosis related disorders (paranoid states)	296.0-296.1, 296.4-296.9, 297.xx
Other mood disorders	293.83, 301.13
Drug-induced depression	292.84
Depressive type psychosis	298
Alzheimer's disease	331.xx
Parkinson's disease	332.xx
Dementia	290.xx

Appendix 3 Demographic variables, clinical variables, and subgroups by initial antidepressant therapeutic class

	SSRI	Other AD	SNRI	TCA	MAOI	All Classes	P value ^b
Antidepressant class, # prescriptions (%)	387,746 (73%)	71,664 (14%)	57,342 (11%)	11,070 (2%)	85 (^{<} 1%)	527,907 (100%)	
Demographic Variables							
Age, mean (SD)							
Years	37 (18)	39 (17)	42 (15)	41 (18)	45 (16)	38 (17)	^{<} 0.0001
Age Categories, n (%)							
^{<} 18 years	70,557 (18%)	8,624 (12%)	2,550 (4%)	1,559 (14%)	3 (4%)	83,293 (16%)	^{<} 0.001
18-39 years	140,130 (36%)	27,501 (38%)	21,882 (38%)	3,185 (29%)	26 (31%)	192,724 (37%)	
40-65 years	155,381 (40%)	31,432 (44%)	30,123 (53%)	5,546 (50%)	50 (59%)	222,532 (42%)	
^{>} 65 years	21,678 (6%)	4,107 (6%)	2,787 (5%)	780 (7%)	6 (7%)	29,358 (6%)	
Gender, n (%)							
Male	136,980 (35%)	29,911 (42%)	19,148 (33%)	3,606 (33%)	36 (42%)	189,681 (36%)	^{<} 0.001
Female	250,766 (65%)	41,753 (58%)	38,194 (67%)	7,464 (67%)	49 (58%)	338,226 (64%)	
Insurance Claim Source, n (%)							
Medicaid	54,145 (14%)	8,698 (12%)	6,049 (11%)	2,817 (25%)	1 (1%)	71,710 (14%)	^{<} 0.001
Commercial	310,842 (80%)	58,626 (82%)	48,129 (84%)	7,431 (67%)	78 (92%)	425,106 (81%)	
Medicare	22,759 (6%)	4,340 (6%)	3,164 (6%)	822 (7%)	6 (7%)	31,091 (6%)	
Geographical Location, n (%)							
Northeast	54,388 (14%)	9,451 (13%)	7,001 (12%)	1,293 (12%)	10 (12%)	72,143 (14%)	^{<} 0.001
Northcentral	94,703 (24%)	16,619 (23%)	13,989 (24%)	2,017 (18%)	12 (14%)	127,340 (24%)	
South	106,314 (27%)	21,541 (30%)	20,256 (35%)	2,767 (25%)	35 (41%)	150,913 (29%)	
West	73,468 (19%)	14,447 (20%)	9,245 (16%)	2,079 (19%)	26 (31%)	99,265 (19%)	
Unknown	4,728 (1%)	908 (1%)	802 (1%)	97 (^{<} 1%)	1 (1%)	6,536 (1%)	
Missing	54,145 (14%)	8,698 (12%)	6,049 (11%)	2,817 (25%)	1 (1%)	71,710 (14%)	

	SSRI	Other AD	SNRI	TCA	MAOI	All Classes	P value ^b
Antidepressant class, # prescriptions (%)	387,746 (73%)	71,664 (14%)	57,342 (11%)	11,070 (2%)	85 ($<1\%$)	527,907 (100%)	
Health Plan Type, n (%)							
Comprehensive	54,699 (14%)	10,016 (14%)	7,871 (14%)	2,642 (24.0%)	7 (8%)	75,235 (14%)	<0.001
EPO	3,261 ($<1\%$)	622 ($<1\%$)	519 ($<1\%$)	69 ($<1\%$)	2 (2%)	4,473 ($<1\%$)	
HMO	78,453 (20%)	13,804 (19%)	8,946 (16%)	2,297 (21%)	21 (25%)	103,521 (20%)	
POS	28,253 (7%)	5,508 (8%)	4,443 (8%)	704 (6%)	7 (8%)	38,915 (7%)	
PPO	185,067 (48%)	35,019 (49%)	30,740 (54%)	4,473 (40%)	38 (45%)	255,337 (48%)	
POS with Capitation	8,133 (2%)	1,539 (2%)	816 (1%)	282 (3%)	2 (2%)	10,772 (2%)	
CDHP	12,014 (3%)	2,222 (3%)	1,721 (3%)	202 (2%)	5 (6%)	16,164 (3%)	
HDHP	6,245 (2%)	1,106 (2%)	739 (1%)	117 (1%)	1 (1%)	8,208 (2%)	
Missing	11,621 (3%)	1,828 (3%)	1,547 (3%)	284 (3%)	2 (2%)	15,282 (3%)	
Clinical Variables							
MDD Diagnosis Code, n (%)							
Single Episode	53,287 (14%)	10,091 (14%)	7,168 (13%)	1,383 (13%)	13 (15%)	71,942 (14%)	<0.001
Recurrent Episode	66,392 (17%)	15,359 (21%)	11,756 (21%)	2,105 (19%)	40 (47%)	95,652 (18%)	
Dysthymia	49,495 (13%)	8,614 (12%)	7,183 (13%)	1,701 (15%)	9 (11%)	67,002 (13%)	
Depression, NOS	218,572 (56%)	37,600 (53%)	31,235 (55%)	5,881 (53%)	23 (27%)	293,311 (56%)	
CCI (Deyo Modification) in the 12 months pre-IDD, n (%)							
0	309,728 (80%)	57,041 (80%)	44,474 (78%)	7,778 (70%)	68 (80%)	419,089 (79%)	<0.001
1	50,785 (13%)	9,322 (13%)	8,040 (14%)	2,003 (18%)	8 (9%)	70,158 (13%)	
2	13,665 (4%)	2,562 (4%)	2,504 (4%)	635 (6%)	4 (5%)	19,370 (4%)	
3+	13,568 (4%)	2,739 (4%)	2,324 (4%)	654 (6%)	5 (6%)	19,290 (4%)	

	SSRI	Other AD	SNRI	TCA	MAOI	All Classes	P value ^b
Antidepressant class, # prescriptions (%)	387,746 (73%)	71,664 (14%)	57,342 (11%)	11,070 (2%)	85 (<1%)	527,907 (100%)	
Subgroups of Interest							
Comorbid Diagnoses^a, n (%)							
Anxiety Disorder	96,688 (25%)	12,625 (18%)	13,343 (23%)	2,643 (24%)	20 (24%)	125,319 (24%)	<0.001
Chronic Non-Cancer Pain Disorder	84,778 (22%)	16,057 (22%)	17,614 (31%)	5,706 (52%)	15 (18%)	124,170 (24%)	<0.001

Abbreviations: AD, antidepressant; CCI, Charlson Comorbidity Index; CDHP, consumer driven health plan; EPO, exclusive provider organization; HDHP, high deductible health plan; HMO, health maintenance organization; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; NOS, not otherwise specified; POS, point of service; PPO, preferred provider organization; SD, standard deviation; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

^aPercentage does not add to 100% within one therapeutic class because categories (presence of an anxiety or pain disorder) were not mutually exclusive.

^bChi-squared test of independence was undertaken for categorical variables to test equality of proportions when grouped by initial therapeutic class. Analysis of Variance (ANOVA) was undertaken to test equality of means for continuous variables with initial class as the predictor variable.

Appendix 4 Unadjusted and adjusted logistic regression model results at various time-points after IPD^a

	IPD to 3 Months	IPD to 6 Months	IPD to 9 Months	IPD to 12 Months
	Odds Ratio (95% CI) P value ^b	Odds Ratio (95% CI) P value ^b	Odds Ratio (95% CI) P value ^b	Odds Ratio (95% CI) P value ^b
UNADJUSTED ODDS RATIO				
Therapeutic Class				
SSRI	Referent ^c			
Other AD	0.82 (0.80, 0.83) <0.0001	0.78 (0.77, 0.80) <0.0001	0.76 (0.75, 0.77) <0.0001	0.74 (0.72, 0.75) <0.0001
SNRI	1.24 (1.22, 1.26) <0.0001	1.28 (1.27, 1.31) <0.0001	1.31 (1.29, 1.34) <0.0001	1.34 (1.32, 1.37) <0.0001
TCA	0.45 (0.43, 0.47) <0.0001	0.43 (0.41, 0.46) <0.0001	0.47 (0.45, 0.49) <0.0001	0.49 (0.46, 0.52) <0.0001
MAOI	1.29 (0.85, 1.98) 0.2346	1.14 (0.73, 1.79) 0.5576	0.90 (0.55, 1.50) 0.6876	0.82 (0.47, 1.43) 0.4754
ADJUSTED ODDS RATIO				
Therapeutic Class				
SSRI	Referent ^c			
Other AD	0.80 (0.79, 0.81) <0.0001	0.77 (0.75, 0.78) <0.0001	0.74 (0.72, 0.75) <0.0001	0.72 (0.70, 0.73) <0.0001
SNRI	1.20 (1.18, 1.22) <0.0001	1.23 (1.21, 1.25) <0.0001	1.25 (1.22, 1.27) <0.0001	1.27 (1.24, 1.30) <0.0001
TCA	0.46 (0.44, 0.49) <0.0001	0.45 (0.42, 0.47) <0.0001	0.47 (0.45, 0.50) <0.0001	0.49 (0.46, 0.52) <0.0001
MAOI	1.13 (0.74, 1.73) 0.5709	1.0 (0.64, 1.56) 0.9864	0.77 (0.46, 1.28) 0.3087	0.69 (0.40, 1.20) 0.1860
Age Categories				
<18 years	Referent ^c			
18-39 years	0.93 (0.92, 0.95) <0.0001	0.98 (0.96, 1.00) 0.0144	0.99 (0.97, 1.01) 0.2635	1.00 (0.98, 1.03) 0.7441
40-65 years	1.40 (1.37, 1.42) <0.0001	1.55 (1.52, 1.58) <0.0001	1.70 (1.66, 1.73) <0.0001	1.81 (1.77, 1.85) <0.0001
>65 years	1.62 (1.52, 1.73) <0.0001	1.80 (1.68, 1.92) <0.0001	2.04 (1.90, 2.19) <0.0001	2.15 (2.00, 2.32) <0.0001
Gender				
Male	Referent ^c			
Female	1.07 (1.06, 1.08) <0.0001	1.07 (1.06, 1.08) <0.0001	1.06 (1.05, 1.07) <0.0001	1.06 (1.04, 1.07) <0.0001
Insurance Claim Source				
Medicaid	Referent ^c			
Commercial	2.55 (2.48, 2.63) <0.0001	2.42 (2.35, 2.50) <0.0001	2.42 (2.34, 2.50) <0.0001	2.38 (2.29, 2.46) <0.0001
Medicare	2.75 (2.58, 2.92) <0.0001	2.41 (2.25, 2.57) <0.0001	2.44 (2.28, 2.62) <0.0001	2.53 (2.35, 2.73) <0.0001

IPD to 3 Months					IPD to 6 Months					IPD to 9 Months					IPD to 12 Months				
		Odds Ratio (95% CI) P value ^b			Odds Ratio (95% CI) P value ^b			Odds Ratio (95% CI) P value ^b			Odds Ratio (95% CI) P value ^b								
Geographical Location																			
Northeast		Referent ^c																	
Northcentral		0.92 (0.90, 0.94) <0.0001			0.92 (0.90, 0.94) <0.0001			0.90 (0.88, 0.92) <0.0001			0.91 (0.89, 0.93) <0.0001								
South		0.78 (0.76, 0.79) <0.0001			0.77 (0.76, 0.79) <0.0001			0.76 (0.74, 0.77) <0.0001			0.77 (0.75, 0.78) <0.0001								
West		0.96 (0.94, 0.98) <0.0001			0.92 (0.90, 0.93) <0.0001			0.90 (0.88, 0.92) <0.0001			0.90 (0.88, 0.92) <0.0001								
Unknown		0.71 (0.68, 0.75) <0.0001			0.72 (0.68, 0.76) <0.0001			0.71 (0.66, 0.75) <0.0001			0.72 (0.67, 0.76) <0.0001								
Missing		Omitted due to collinearity																	
Health Plan Type																			
Comprehensive		Referent ^c																	
EPO		0.79 (0.74, 0.84) <0.0001			0.83 (0.77, 0.88) <0.0001			0.82 (0.76, 0.89) <0.0001			0.80 (0.74, 0.87) <0.0001								
HMO		0.91 (0.89, 0.93) <0.0001			0.88 (0.85, 0.90) <0.0001			0.87 (0.84, 0.89) <0.0001			0.88 (0.85, 0.90) <0.0001								
POS		0.90 (0.88, 0.93) <0.0001			0.91 (0.89, 0.94) <0.0001			0.89 (0.87, 0.93) <0.0001			0.89 (0.86, 0.93) <0.0001								
PPO		0.90 (0.88, 0.92) <0.0001			0.92 (0.90, 0.94) <0.0001			0.92 (0.90, 0.94) <0.0001			0.93 (0.90, 0.95) <0.0001								
POS with Capitation		0.88 (0.84, 0.92) <0.0001			0.92 (0.88, 0.97) <0.0001			0.89 (0.84, 0.94) <0.0001			0.91 (0.86, 0.96) 0.0001								
CDHP		0.88 (0.85, 0.91) <0.0001			0.89 (0.86, 0.93) <0.0001			0.90 (0.86, 0.94) <0.0001			0.91 (0.87, 0.96) <0.0001								
HDHP		0.94 (0.89, 0.98) 0.0080			0.96 (0.91, 1.01) 0.1093			0.93 (0.88, 0.99) 0.0158			0.94 (0.88, 0.99) 0.0322								
Missing		0.85 (0.81, 0.88) <0.0001			0.88 (0.84, 0.92) <0.0001			0.86 (0.82, 0.90) <0.0001			0.86 (0.82, 0.90) <0.0001								
MDD Diagnosis Code																			
Single Episode		Referent ^c																	
Recurrent Episode		1.00 (0.98, 1.02) 0.9578			0.99 (0.97, 1.02) 0.6035			1.01 (0.99, 1.04) 0.3093			1.02 (1.00, 1.05) 0.0529								
Dysthymia		1.06 (1.04, 1.09) <0.0001			1.05 (1.02, 1.07) <0.0001			1.05 (1.02, 1.07) 0.0002			1.07 (1.04, 1.10) <0.0001								
Depression, NOS		1.03 (1.01, 1.04) 0.0034			1.01 (0.99, 1.03) 0.2073			1.00 (0.98, 1.02) 0.9378			1.02 (1.00, 1.04) 0.0833								
Charlson Comorbidity Index																			
0		Referent ^c																	
1		0.97 (0.95, 0.98) 0.0001			0.98 (0.97, 1.00) 0.0885			1.00 (0.98, 1.02) 0.7786			1.02 (1.00, 1.04) 0.0622								
2		1.01 (0.98, 1.04) 0.5392			1.04 (1.00, 1.07) 0.0234			1.09 (1.05, 1.13) <0.0001			1.11 (1.07, 1.15) <0.0001								
3+		1.00 (0.97, 1.03) 0.9342			1.04 (1.01, 1.08) 0.0117			1.09 (1.05, 1.13) <0.0001			1.11 (1.07, 1.15) <0.0001								

	IPD to 3 Months	IPD to 6 Months	IPD to 9 Months	IPD to 12 Months
	Odds Ratio (95% CI) <i>P</i> value ^b	Odds Ratio (95% CI) <i>P</i> value ^b	Odds Ratio (95% CI) <i>P</i> value ^b	Odds Ratio (95% CI) <i>P</i> value ^b
Comorbid Diagnoses				
Anxiety Disorder (Referent=Presence of disorder) ^c	1.01 (1.00, 1.03) 0.0328	1.05 (1.03, 1.06) <0.0001	1.07 (1.05, 1.08) <0.0001	1.08 (1.07, 1.10) <0.0001
Chronic Non-Cancer Pain Disorder (Referent=Presence of disorder) ^c	0.87 (0.86, 0.89) <0.0001	0.87 (0.86, 0.89) <0.0001	0.88 (0.87, 0.90) <0.0001	0.88 (0.87, 0.90) <0.0001

Abbreviations: AD, antidepressant; CCI, Charlson Comorbidity Index; CDHP, consumer driven health plan; CI, confidence interval; EPO, exclusive provider organization; HMO, health maintenance organization; HDHP, high deductible health plan; IPD, index prescription date; MAOI, Monoamine Oxidase Inhibitor; MDD, major depressive disorder; NOS, not otherwise specified; POS, point of service; PPO, preferred provider organization; SD, standard deviation; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

^aIPD was defined as the first pharmacy claim for an AD medication filled within 60 days before or after a qualifying MDD diagnosis.

^b*P* value of Wald test versus referent category. *P* values of <0.05 are considered statistically significant.

^cReferent category in logistic regression model.