Supplemental material

Drug-drug-gene interaction risk among opioid users in the U.S. Department of Veterans Affairs

Catherine Chanfreau-Coffinier, PhD[1*], Sony Tuteja, PharmD MS[2,3*], Leland E. Hull, MD MPH[4,5,6], Sally MacDonald, RN[6,7], Olga Efimova, MD[1], Jill Bates, PharmD MS[8,9], Deepak Voora, MD[8,10], David W. Oslin, MD[2,3], Scott L. DuVall, PhD[1,7], Julie A. Lynch, RN PhD MBA[1,6]

Supplemental Table 1. Drugs queried for the study

Medication	Drug Class	Drug-gene Interaction (s)	Drug-drug interaction	CPIC classification
Codeine	Opioid	*CYP2D6*	-	A
Hydrocodone	Opioid	*CYP2D6*		B
Tramadol	Opioid	*CYP2D6*	-	A
Oxycodone*	Opioid	*CYP2D6*		C
Bupropion	Antidepressant	*CYP2D6*	CYP2D6 inhibitor[1]	n/a
Fluoxetine	Antidepressant	*CYP2D6*	CYP2D6 inhibitor[1]	C
Paroxetine	Antidepressant	*CYP2D6*	CYP2D6 inhibitor[1]	A
Duloxetine	Antidepressant	*CYP2D6*	CYP2D6 inhibitor[2]	C
Fluvoxamine	Antidepressant	*CYP2D6*		A
Sertraline	Antidepressant	*CYP2D6, CYP2C19*		B
Venlafaxine	Antidepressant	*CYP2D6*		B
Escitalopram	Antidepressant	*CYP2C19*		A
Citalopram	Antidepressant	*CYP2C19*		A
Amitriptyline	TCA	*CYP2D6, CYP2C19*		A
Nortriptyline	TCA	*CYP2D6*		A
Desipramine	TCA	*CYP2D6*		B
Imipramine	TCA	*CYP2D6, CYP2C19*		B
Celecoxib	NSAID	*CYP2C9*		A
Ibuprofen	NSAID	*CYP2C9*		A
Flurbiprofen	NSAID	*CYP2C9*		A
Meloxicam	NSAID	*CYP2C9*		A
Piroxicam	NSAID	*CYP2C9*		A
Gabapentin	Neuropathic pain agent	n/a		n/a
Pregabalin	Neuropathic pain agent	n/a		n/a

TCA: tricyclic antidepressant; NSAID: Non-steroidal anti-inflammatory drug; * oxycodone is included in sensitivity analyses only.

[1] strong CYP2D6 inhibitor; [2] moderate CYP2D6 inhibitor

Sources: CPIC guidelines (cpicpgx.org)

Supplemental Table 2: Adjusted Odds Ratios (OR) for the likelihood of chronic opioid use versus non-chronic opioid use among VA Pharmacy patients receiving at least one opioid prescription in Fiscal years 2012-2017

Patient Characteristics	**OR**	**95% CI**
Age (years)	1.013	[1.0130,1.0131]
Female (ref. male)	0.79	[0.78,0.80]
Race/ethnicity (ref. white)		
Black	0.76	[0.75,0.76]
Other	0.89	[0.88,0.90]
Healthcare utilization in year of exposure		
≥ 10 PC visits	1.4	[1.39,1.41]
Inpatient stay	1.27	[1.26,1.28]
Surgery	0.60	[0.59,0.60]
≥ 1 emergency visit	0.50	[0.495,0.503]

N=2,436,626 patients with ≥1 opioid prescription, complete cases only. Chronic opioid use defined as exposure longer than 90 days with more than 10 prescriptions or 120 days- supply. Multivariate logistic model adjusted for year of opioid exposure. All ORs significantly different from 1, P <0.001

Supplemental Table 3: Trends in exposure to CYP2D6 metabolized opioids and co-prescriptions among VA Pharmacy patients receiving at least one opioid prescription in Fiscal years 2012-2017

	FY12		**FY13**		**FY14**		**FY15**		**FY16**		**FY17**	
Patients starting exposure, N	862,588		690,538		660,599		600,728		556,939		489,636	
with co-prescription, N (%)	408,940	47.4%	315,047	45.6%	305,431	46.2%	275,268	45.8%	255,785	45.9%	221,625	45.3%
antidepressants	237,343	27.5%	173,882	25.2%	165,768	25.1%	148,854	24.8%	138,000	24.8%	118,307	24.2%
CYP2D6 inhibitors	104,488	12.1%	74,405	10.8%	70,741	10.7%	64,399	10.7%	63,772	11.5%	56,725	11.6%
TCA	39,935	4.6%	25,874	3.7%	23,190	3.5%	19,181	3.2%	15,866	2.8%	12,270	2.5%
NSAID	189,873	22.0%	147,758	21.4%	136,840	20.7%	118,625	19.7%	107,238	19.3%	90,828	18.6%
neuropathic pain agents	171,207	19.8%	123,688	17.9%	125,826	19.0%	115,245	19.2%	108,820	19.5%	94,136	19.2%

Numbers for the trends presented in Figure 1; opioids impacted by CYP2D6 include codeine, hydrocodone and tramadol based on the 2020 CPIC recommendations.

Patients are assigned to the year of first opioid exposure and counted once over the whole observation period. Co-prescription include the following medications by class:

Antidepressants: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine

CYP2D6 inhibitors, strong or moderate: bupropion, duloxetine, fluoxetine, paroxetine

Tricyclic antidepressants (TCA): amitriptyline, desipramine, imipramine, nortriptyline

NSAID: celecoxib, flurbiprofen, ibuprofen, meloxicam, piroxicam

Neuropathic pain agents: gabapentin, pregabalin

Supplemental Table 4: Concurrent exposure to codeine, hydrocodone or tramadol, and a CYP2D6 metabolized antidepressant or a CYP2D6 inhibitor among VA Pharmacy patients receiving at least one opioid prescription in Fiscal years 2012-2017

Number of unique patients (%)	**All exposed**		**Chronic users**		**Non chronic users**	
	2,436,654		837,660		1,598,994	
Patients with concurrent exposure to an antidepressant metabolized by CYP2D6	684,201	28.08%	349,569	41.73%	334,632	20.93%
Patients with concurrent exposure to a CYP2D6 inhibitor	353,848	14.52%	187,367	22.37%	166,481	10.41%
CY2D6 strong inhibitor	297,233	12.20%	156,544	18.69%	140,689	8.80%
CYP2D6 moderate inhibitor	79,047	3.24%	45,004	5.37%	34,043	2.13%

Percentage within group. All differences between chronic users and non-chronic users significant with $p < 0.0001$

Antidepressants

Strong CYP2D6 inhibitors: bupropion, fluoxetine, paroxetine

Moderate CYP2D6 inhibitors: duloxetine

Supplemental Table 5*:* Definitions of *CYP2D6* Phenotypes

***CYP2D6* Phenotype**	**Projected Prevalence among Veterans***	**Anticipated Impact on Drug Metabolism and Dosing**
Ultrarapid Metabolizer	3.45%	Increased metabolism of opioids such as codeine and oxycodone put patient at increased risk of toxicity
Normal Metabolizer	74.5%	Normal metabolism expected at standard medication dose
Intermediate Metabolizer	7.99%	Normal-lower metabolism expected at standard dose
Poor Metabolizer	5.44%	Decreased metabolism of certain opioids such as codeine, oxycodone, and tramadol may result in decreased efficacy

Additional categories to sum to 100%: NM/UM (1.09%) and indeterminate (7.55%)

* Reference: Chanfreau-Coffinier, C.*, et al.* Projected Prevalence of Actionable Pharmacogenetic Variants and Level A Drugs Prescribed Among US Veterans Health Administration Pharmacy Users. *JAMA Network Open* 2, e195345 (2019).

Supplemental Table 6: Sensitivity analysis for trends in exposure to CYP2D6 metabolized opioids and co-prescriptions among VA Pharmacy patients receiving at least one opioid prescription in Fiscal years 2012-2017

	FY12		**FY13**		**FY14**		**FY15**		**FY16**		**FY17**	
Patients starting exposure, N	956,701		781,214		772,470		730,358		687,751		614,092	
with co-prescription, N (%)	461,003	53.4%	363,787	52.7%	363,317	55.0%	341,673	56.9%	321,680	57.8%	282,706	57.7%
antidepressants	270,776	31.4%	203,816	29.5%	199,576	30.2%	186,650	31.1%	174,945	31.4%	151,245	30.9%
CYP2D6 inhibitors	120,162	12.6%	88,100	11.3%	86,186	11.2%	82,193	11.3%	81,843	11.9%	73,398	12.0%
TCA	47,293	5.5%	31,650	4.6%	29,292	4.4%	25,172	4.2%	21,064	3.8%	16,288	3.3%
NSAID	210,859	24.4%	167,280	24.2%	159,747	24.2%	144,624	24.1%	132,462	23.8%	114,286	23.3%
neuropathic pain agents	198,468	23.0%	148,225	21.5%	154,527	23.4%	148,702	24.8%	142,091	25.5%	124,839	25.5%

Sensitivity analysis for the trends presented in Figure 1 and Supplemental table 3, including oxycodone as one of the opioids impacted by CYP2D6.

Patients are assigned to the year of first opioid exposure and counted once over the whole observation period. Co-prescription include the following medications by class:

Antidepressants: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine

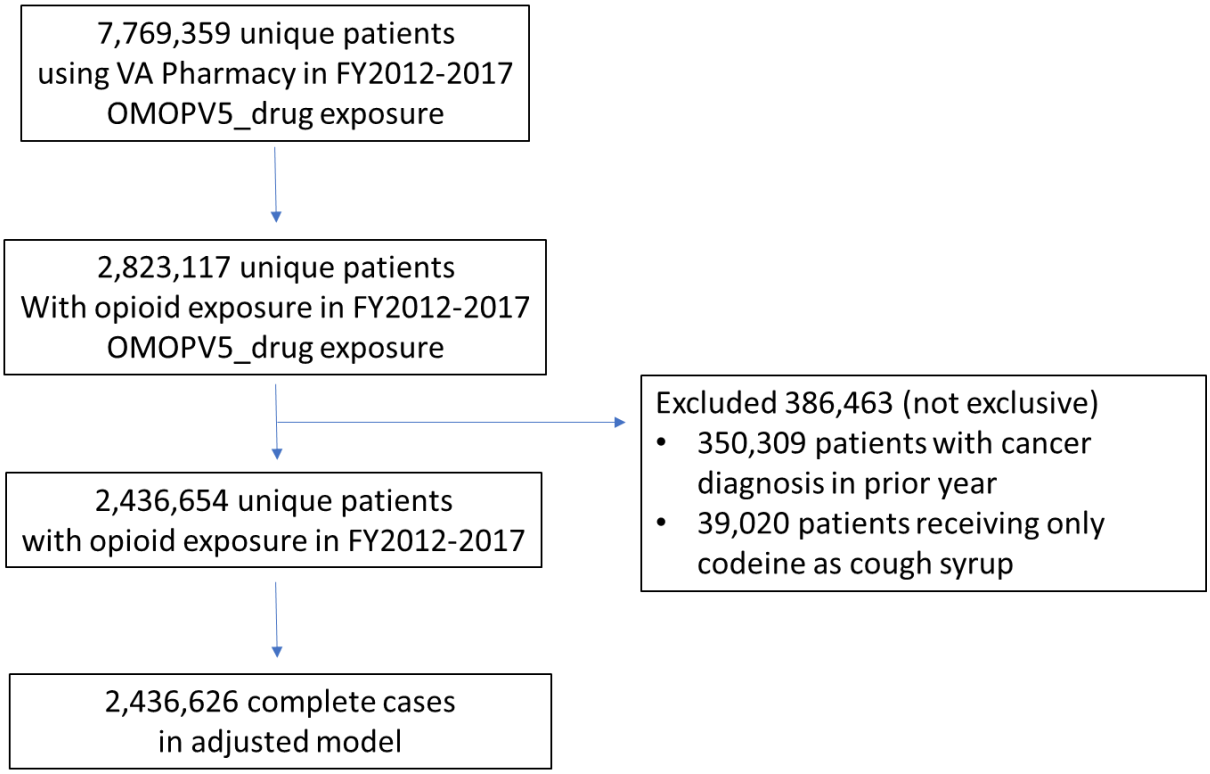
CYP2D6 inhibitors, strong or moderate: bupropion, duloxetine, fluoxetine, paroxetine

Tricyclic antidepressants (TCA): amitriptyline, desipramine, imipramine, nortriptyline

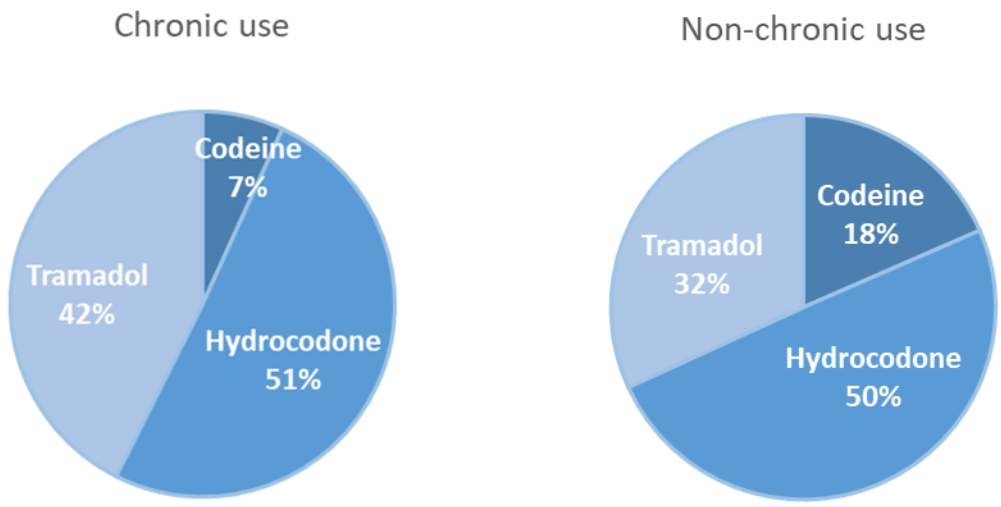
NSAID: celecoxib, flurbiprofen, ibuprofen, meloxicam, piroxicam

Neuropathic pain agents: gabapentin, pregabalin

Supplemental Figure 1: Flow chart for the cohort selection



Supplemental Figure 2: Breakdown of opioids received by VA Pharmacy patients by chronic versus non-chronic use for Fiscal Years 2012-2017



Test for difference in medication distribution by type of opioid use, $p < 0.0001$