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ORIGINAL RESEARCH

CYP2D6 phenotypes are associated with adverse outcomes related to opioid medications

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Background: Variation in the *CYP2D6* gene may affect response to opioids in both poor and ultrarapid metabolizers, but data demonstrating such associations have been mixed, and the impact of variants on toxicity-related symptoms (e.g., nausea) is unclear. Therefore, we examined the association between *CYP2D6* phenotype and poor pain control or other adverse symptoms related to the use of opioids in a sample of primary care patients.

Materials and methods: We identified all patients in the Mayo Clinic RIGHT Protocol who were prescribed an opioid medication between July 01, 2013 and June 30, 2015, and categorized patients into three phenotypes: poor, intermediate to extensive, or ultrarapid *CYP2D6* metabolizers. We reviewed the electronic health record of these patients for indications of poor pain control or adverse symptoms related to medication use. Associations between phenotype and outcomes were assessed using Chi-square tests and logistic regression.

Results: Overall, 257 (25% of RIGHT Protocol participants) patients received at least one opioid prescription; of these, 40 (15%) were poor metabolizers, 146 (57%) were intermediate to extensive metabolizers, and 71 (28%) were ultrarapid metabolizers. We removed patients that were prescribed a *CYP2D6* inhibitor medication (n=38). After adjusting for age and sex, patients with a poor or ultrarapid phenotype were 2.7 times more likely to experience either poor pain control or an adverse symptom related to the prescription compared to patients with an intermediate to extensive phenotype (odds ratio: 2.68; 95% CI: 1.39, 5.17; *p*=0.003).

Conclusion: Our results suggest that >30% of patients with a poor or ultrarapid *CYP2D6* phenotype may experience an adverse outcome after being prescribed codeine, tramadol, oxycodone, or hydrocodone. These medications are frequently prescribed for pain relief, and ~39% of the US population is expected to carry one of these phenotypes, suggesting that the population-level impact of these gene–drug interactions could be substantial.

Keywords: CYP2D6, opioid, phenotype, adverse effects

Plain language summary

Prescription of opioid pain medications in the USA is very high; between 2011 and 2012, nearly 7% of the adult population was estimated to have taken an opioid in the last 30 days. However, these medications do not control pain in all patients, and some patients are likely to have problems such as vomiting or breathing difficulties after taking an opioid. Characterizing the factors that predict individual patient response to opioid analgesics could help to better target these medications to the patients mostly likely to benefit, while reducing side effects in patients most likely to have problems. The field of pharmacogenomics offers the opportunity to identify patients who carry genetic variants that are likely to impact their response to these medications. Therefore, we studied the impact of variation in the *CYP2D6* gene on patient

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responses to codeine, tramadol, oxycodone, or hydrocodone. Our results suggest that >30% of patients with a poor or ultrarapid *CYP2D6* phenotype may experience an adverse outcome after being prescribed one of these medications. Nearly 40% of the US population is expected to carry one of these phenotypes, suggesting that a large number of people could benefit from more targeted opioid prescribing.

Introduction

Opioid analgesics are effective, commonly prescribed medications used for the management of both acute and chronic pain in patients with many different medical conditions and following many medical procedures.[1,2] Prescription of opioids in the USA is high, and between 2011 and 2012, nearly 7% of the adult population was estimated to have taken an opioid in the last 30 days.[3,4] Opioid use is especially prevalent among older adults; in 2010, an estimated 9% of adults over 65 years took opioid medications.[5] However, these medications do not effectively control pain in all patients.[6–10] In addition, many patients are at high risk of adverse effects due to these medications.[8,10] A meta-analysis of randomized trials found that 80% of patients treated with opioids for chronic, noncancer pain experienced at least one adverse event, with symptoms ranging from mild nausea to life-threatening respiratory depression.[8]

Characterizing the factors that predict individual patient response to opioid analgesics could help to better target prescriptions to the patients mostly likely to benefit from these medications. The field of pharmacogenomics offers the opportunity to identify specific individual characteristics that could predict such responses.[11,12] In particular, the cytochrome P450 2D6 (*CYP2D6*) enzyme is involved in the prodrug conversion of codeine, oxycodone, hydrocodone, and tramadol.[13,14] Patients with an ultrarapid *CYP2D6* phenotype are likely to experience higher systemic levels of the active metabolites of these analgesics upon treatment, while patients with a poor metabolizer *CYP2D6* phenotype will tend to have lower levels.[13,15] Therefore, a patient's *CYP2D6* phenotype may result in reduced efficacy in poor metabolizers.[16]

Conversely, there is some evidence that ultrarapid metabolizers require less pain medication to achieve pain control.[17] These patients may, however, be at a greater risk of respiratory depression at standard doses compared to normal metabolizers.[12,18] However, data demonstrating associations between *CYP2D6* phenotype and poor pain control have been mixed.[13,16] Several studies have indicated that persons with a poor metabolizer phenotype experience less pain relief from

codeine and tramadol,[19–25] but the effect of a poor metabolizer phenotype on pain relief from oxycodone and hydrocodone is less clear.[26–30] In addition, the impact of *CYP2D6* variants on mild, nonlife threatening, adverse reactions associated with opioids (e.g., nausea), and subsequent effects on pain control due to intolerance, has not been routinely studied.[16] A larger study of cancer patients found no differences in pain control, nausea, or tiredness among poor, normal, and ultrarapid metabolizers taking oxycodone.[30] It is not clear, however, whether these results in cancer patients are generalizable to all patients prescribed these medications. Finally, previous studies have focused on a single medication at a time, and it is not clear whether the results of these studies represent the experience of a day-to-day clinical population.

Data regarding the impact of *CYP2D6* phenotypic variation on a general population in real-world clinical practice are limited. To address this gap, we examined the association between *CYP2D6* phenotype and poor pain control or other adverse symptoms related to the use of opioid analgesics among participants in the Mayo Clinic Right Drug, Right Dose, Right Time Protocol (RIGHT Protocol) study.[31] Participants in this study are patients enrolled in the Mayo Clinic general internal medicine practice and could receive opioid prescriptions for a wide range of indications. We used this population to study the association between *CYP2D6* phenotype and opioid prescription outcomes in a real-world clinical setting.

Materials and methods
Setting and study participants

Details of the RIGHT Protocol study have been previously reported.[31] Briefly, 2,000 participants in the Mayo Clinic Biobank were invited to participate in a study of pre-emptive genotyping; 1,013 (51%) agreed to participate.[32] Participants contributed a blood sample that was used to sequence genetic variants in the *CYP2D6* gene that could cause drug–gene interactions with opioid analgesics. At the time of enrollment, participants in the RIGHT study provided written informed consent to allow their PGx genetic data and electronic health record data to be used for research in future PGx studies. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

We used the Rochester Epidemiology Project research infrastructure to identify all patients in the RIGHT Protocol who received an opioid analgesic prescription between 07/01/2013 and 06/30/2015 from a local health care provider.[33,34] Specifically, we identified all RxNorm codes

for prescriptions that included the ingredients codeine, oxycodone, hydrocodone, and tramadol, because the metabolic activation of these medications can be affected by *CYP2D6* variation.[13,14] We excluded formulations intended primarily to treat cough (e.g., guaifenesin/codeine). A complete list of medications considered is shown in Table S1. In addition, we identified all other prescriptions received on the same day. Approximately 25% of the population received one or more prescriptions in addition to the opioid, and the types of other prescriptions are shown in Table S2.

CYP2D6 genotyping
CYP2D6 was genotyped using a custom-designed testing cascade, beginning with the Luminex Tag-It Mutation Detection Kit for Cytochrome P450 2D6 (*CYP2D6* ASPE Kit v2; Luminex Corporation, Austin, TX, USA) and, when needed, followed by a laboratory-developed copy number variation assay and/or sequencing assays.[35]

CYP2D6 phenotyping
Methods for interpreting pharmacogenomic variants have been previously described.[36] Phenotype prediction was binned into four categories in a manner similar to that reviewed by Ingelman-Sundberg and Kirchheiner et al.[37,38] It should be noted that other methodologies for phenotype prediction have been described, and this is a controversial area of pharmacogenomics.[39,40] In particular, there is controversy about where to classify the *CYP2D6*2A* versus other *CYP2D6*2* alleles. There is evidence that the *CYP2D6*2* alleles (except *CYP2D6*2A*) have reduced function, although this is somewhat substrate-dependent.[41–44] However, the c.1584C>G polymorphism found in *CYP2D6*2A* increases protein production, possibly through increased induction, which compensates for the reduced function caused by the other polymorphisms found in the *CYP2D6*2* alleles, resulting in a function similar to and possibly greater than that of *CYP2D6*1*.[45,46]

The classification used in our labs for *CYP2D6* was as follows: ultrarapid, extensive to ultrarapid, extensive, intermediate to extensive, intermediate, poor to intermediate, and poor. For analysis, these categories were further grouped into three phenotype categories: poor (poor and poor to intermediate), intermediate to extensive (intermediate, intermediate to extensive, and extensive), or ultrarapid (extensive to ultrarapid and ultrarapid) *CYP2D6* metabolizers.

Outcomes
All electronic health records (EHRs) were reviewed by a single author (JLS) for indications of poor pain control (e.g.,

note indicating need to change dose or type of drug due to pain) or adverse symptoms related to medication use (e.g., vomiting, nausea, rash, itching, throat swelling, or other indication of adverse reaction attributed to the prescription). All records were reviewed without knowledge of the patient phenotypes.

CYP2D6 inhibitors
Concurrent use of *CYP2D6* inhibitor medications may significantly alter the results of studies that examine outcomes related to the use of opioid medications, because these inhibitors may decrease or prevent the conversion of opioid medications to morphine. Therefore, we identified all patients who were prescribed a medication that was a strong or moderately strong inhibitor of *CYP2D6*. A list of inhibitors that was considered for this study is shown in Table S3. Because most of these prescriptions are intended to be taken long term, we considered persons exposed to a *CYP2D6* inhibitor if the prescription occurred within 1 year prior to the opioid prescription.

Analyses
The frequencies of demographic and medication characteristics were summarized using counts and percentages. Associations between the three assigned phenotype groups (poor, intermediate to extensive, and ultrarapid) and outcomes (poor pain control, adverse reaction or either) were assessed using Chi-square tests for categorical variables. Logistic regression was used to model associations between phenotype group and each outcome and is reported as odds ratios (ORs) and 95% CIs. Multivariable models were used to adjust for age and sex.

Limited sample sizes precluded adjustment for additional variables. However, in separate models, we also adjusted for the type of prescription (codeine or tramadol vs oxycodone or hydrocodone) and the total number of prescriptions in the time frame. Results were similar to models adjusted for age and sex; therefore, only age- and sex-adjusted results are reported.

Finally, we conducted two additional sensitivity analyses. First, to account for potential interactions with medications that are known to inhibit *CYP2D6*, we excluded all persons who were prescribed a *CYP2D6* inhibitor. Second, we repeated our analyses excluding all persons with a *2A/*2A genotype, since, as described above, there is some controversy regarding whether the *2A allele truly has increased activity.

Results
Participant characteristics, including indications and types of prescriptions, are shown in Table 1. A total of 257 (25%)

Table 1 Characteristics of study participants in the RIGHT protocol that received at least one opioid prescription between July 01, 2013 and June 30, 2015

Characteristic	N	%
Sex		
Male	113	44
Female	144	56
Age		
40–64	215	84
65+	42	16
Race		
White	247	96
Black	1	0.4
Asian/Pacific Islander	3	1
Other	6	2
Ethnicity		
Hispanic	2	1
Non-Hispanic	255	99
CYP2D6 phenotype		
Poor metabolizer	40	15
Intermediate to extensive metabolizer	146	57
Ultrarapid metabolizer	71	28
Number of prescriptions[a]		
Codeine	18	7
Oxycodone	167	65
Hydrocodone	63	25
Tramadol	109	42
Total number of prescriptions during the 2-year period		
1	122	48
2	60	23
3	20	8
4+	55	21
Reason for prescription[b]		
Surgery/procedure	131	51
Trauma	21	8
Chronic joint/back pain	75	29
Other	52	20
Prescribed a CYP2D6 inhibitor	38	15

Notes: [a]Participants could receive a prescription for more than one medication during the time frame. [b]Participants could have multiple reasons for a single prescription.

patients received at least one opioid prescription in the 2 year-time period. More women than men received a prescription, and most of those who received a prescription were between 40 and 64 years of age. Among those with an opioid prescription, 57% had an intermediate to extensive metabolizer *CYP2D6* phenotype, whereas 43% had either a poor or ultrarapid phenotype (Table 1). In addition, over half (51%) received their opioid prescription to control pain following surgery or a medical procedure, and 65% of the prescriptions were for oxycodone. Finally, 38 persons were also prescribed a medication that inhibits *CYP2D6* within 1 year of the opioid prescription. Of these persons, 5 were poor metabolizers, 22 were intermediate to extensive metabolizers, and 11 were ultrarapid metabolizers (Table 1). Among

the patients with poor pain control, health care providers increased the dose of the medication or changed the medication type in 19 patients (63%), and recommended further rest or patience for 3 additional patients (10%). In the remainder of the cases, a note indicating that the patient was experiencing poor pain control was present in the record, but the health care provider response was not recorded. Among patients with adverse reactions, most were related to gastrointestinal upset (21; 55%). Itching, rash, or throat swelling were present in 9 (24%) patients, while the remaining patients had a mix of nonspecific reactions (e.g., "extreme withdrawal", dizziness).

Initial analyses indicated that 35% of poor metabolizers and 34% of ultrarapid metabolizers experienced either poor pain control or an adverse symptom following an opioid prescription compared to 18% of intermediate to extensive metabolizers (Table 2). Overall, 19 (17%) participants with a poor or ultrarapid phenotype experienced poor pain control, compared to 11 (8%) intermediate to extensive metabolizers ($p=0.05$). Similarly, 21 (19%) patients with a poor or ultrarapid phenotype experienced an adverse symptom related to the prescribed medication compared to 17 (12%) intermediate to extensive metabolizers ($p=0.25$; Table 2). These results were similar in sensitivity analyses that accounted for persons who were prescribed a *CYP2D6* inhibitor (Table 2). However, associations with poor pain control were attenuated, while associations with adverse reactions were strengthened. Because poor and ultrarapid metabolizers experienced similar rates of both poor pain control and adverse reactions in all analyses, these patients were grouped together into an "extreme phenotype" category for additional analyses.

After adjusting for age and sex, patients with an extreme phenotype were 2.6 times more likely to experience poor pain control related to the prescription and 1.8 times more likely to experience an adverse symptom compared to intermediate to extensive metabolizers (Table 3). However, the association between extreme phenotype and adverse reaction was not statistically significant (OR: 1.77; 95% CI: 0.87, 3.57). Overall, patients with an extreme phenotype were 2.4 times more likely to experience any problem following an opioid prescription than patients with an intermediate to extensive phenotype (OR: 2.40; 95% CI: 1.35, 4.28).

After accounting for persons that were also prescribed a *CYP2D6* inhibitor, the association between extreme phenotype and poor pain control was attenuated and no longer significant. However, the association between extreme phenotype and adverse reaction strengthened and attained significance (Table 3). The associations between an extreme

Table 2 Associations between *CYP2D6* metabolizer status and poor pain control or other adverse reactions following prescription of an opioid medication

CYP2D6 metabolizer status	Poor pain control		Adverse reaction		Any problem[a]	
	n	%	n	%	n	%
All persons						
Poor (N=40)	8	20	7	18	14	35
Intermediate to extensive (N=146)	11	8	17	12	26	18
Ultrarapid (N=71)	11	16	14	20	24	34
Chi-square *p*-value	0.05		0.25		0.01	
Excluding those prescribed a *CYP2D6* inhibitor						
Poor (N=35)	5	14	6	17	11	31
Intermediate to extensive (N=124)	9	7	11	9	19	15
Ultrarapid (N=60)	8	13	13	22	20	33
Chi-square *p*-value	0.29		0.05		0.01	

Notes: [a]Patients could experience both poor pain control and an adverse reaction. If so, they were only counted once as having "any problem".

Table 3 Adjusted odds of poor pain control or other adverse reaction following the prescription of an opioid medication among poor/ultrarapid *CYP2D6* metabolizers compared to intermediate to extensive metabolizers

CYP2D6 metabolizer status	Poor pain control[a]			Adverse reaction[a]			Any problem[a]		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
All patients	2.63	1.19, 5.83	0.02	1.77	0.87, 3.57	0.11	2.40	1.35, 4.28	0.003
Excluded patients prescribed a *CYP2D6* inhibitor	2.15	0.87, 5.32	0.10	2.53	1.12, 5.70	0.03	2.68	1.39, 5.17	0.003
Excluded patients prescribed a CYP2D6 inhibitor and a *2A/*2A genotype	1.74	0.65, 4.66	0.27	2.51	1.07, 5.90	0.03	2.49	1.25, 4.95	0.01
Patients prescribed only oxycodone or hydrocodone, excluding patients prescribed a *CYP2D6* inhibitor and a *2A/*2A genotype	1.71	0.55, 5.30	0.35	2.08	0.67, 6.49	0.21	2.23	0.94, 5.25	0.07

Notes: [a]Results are compared to intermediate to extensive *CYP2D6* metabolizers and are adjusted for age and sex.

phenotype and any problem were unchanged. Additional exclusion of persons with a *2A/*2A genotype did not significantly alter the results (Table 3). Finally, limiting the analysis to only persons prescribed oxycodone and hydrocodone further attenuated the associations; however, results were in the same direction, and were consistent with overall results (Table 3).

Discussion

We found that patients with either a poor or an ultrarapid *CYP2D6* phenotype were more likely to have an EHR note indicating poor pain relief and to experience more adverse medication effects compared to intermediate to extensive metabolizers. Overall, approximately one-third of patients with an extreme *CYP2D6* phenotype experienced problems related to opioid use compared to ~20% of patients with an intermediate to extensive phenotype.

Previous studies have shown that persons with a poor metabolizer *CYP2D6* phenotype are less likely to experience pain relief compared to persons with normal *CYP2D6* phenotypes, particularly following a codeine or tramadol prescription.[19–25] However, data showing a poor analgesic

effect after use of hydrocodone or oxycodone among poor *CYP2D6* metabolizers have been less consistent.[26–30] Our data indicate that persons with a poor metabolizer status were also more likely to have a report of poor pain control in their EHR, and these results are consistent with previous studies.

Research on clinical outcomes in ultrarapid metabolizers is lacking. Expanding the state of the literature, our results indicate that ultrarapid metabolizers also had reports of poor pain control in their records at approximately the same rate as the poor metabolizers. These patients are expected to be at higher risk of drug intoxication or other adverse events, but the lack of pain control has not been emphasized previously. It is not clear why these patients might report lower levels of pain control. However, it is possible that these patients may not tolerate these prescriptions due to a higher rate of adverse symptoms, and are more likely to stop taking these medications. We note, however, that associations between either poor or ultrarapid status and poor pain control were not statistically significant after accounting for the prescription of *CYP2D6* inhibitor medications, but poor pain control was still present more often in those with poor or ultrarapid metabolizer status compared to those with an intermediate to extensive

metabolizer status. Our small number of outcomes makes these estimates unstable, and results must be confirmed in a larger population.

We also found that patients with either a poor or ultrarapid phenotype were more likely to experience an adverse drug effect such as nausea or vomiting compared to those with an intermediate to extensive phenotype. These associations strengthened after accounting for the prescription of *CYP2D6* inhibitor medications. Ultrarapid metabolizers have previously been shown to be at higher risk of life-threatening reactions compared to normal metabolizers when given standard doses of these medications.[47] However, data showing associations between ultrarapid metabolizer status and less severe reactions are limited. Data showing associations between poor metabolizer status and adverse drug reactions are also limited, but one small study with 18 participants suggested that metabolizer status was not associated with adverse reactions to hydrocodone.[19] Our results suggest that persons with an extreme phenotype are more likely to experience adverse drug effects compared to intermediate to extensive metabolizers, and this effect was statistically significant after accounting for the use of *CYP2D6* inhibitor medications.

Strengths and limitations

Strengths of our study included our relatively large sample size for studies that have examined associations between *CYP2D6* phenotypes and response to opioid analgesics. In addition, we had access to patient EHR data and were able to examine these associations in the context of real-life medical care, and were able to examine multiple drugs simultaneously.

Significant limitations of our study include a high potential for misclassification. Specifically, we relied on complete reporting of pain response and adverse drug events through the EHR. Such data may be incompletely reported by patients and recorded by the health care practitioners, and we may have missed adverse events that actually occurred. If there is differential reporting or recording of adverse outcomes by *CYP2D6* phenotype, our results could be biased. First, if persons with an extreme phenotype were less likely to have an adverse outcome reported in their record than those with a normal phenotype, our results will underestimate the true association between extreme phenotype and adverse outcomes. If persons with an extreme phenotype were more likely to have an adverse outcome reported compared to those with a normal phenotype, our results will overestimate the true association. However, both patients and health care providers were unaware of the patient's phenotype at the time of the prescriptions. Therefore, we expect that the most likely

scenario is that adverse events are consistently underreported in the medical records regardless of patient phenotype. If such data are incompletely recorded regardless of phenotype, the result will be an overall reduction in the number of possible outcomes, and our results would be less likely to reach statistical significance, but would not be biased. In fact, it is somewhat surprising that we observed statistically significant associations.

We also lack data regarding medication compliance. If compliance and adverse drug events were reported differentially by *CYP2D6* phenotype, our results may be biased. We expect that persons with a past history of opioid use that they attributed to an adverse event are less likely to actually take their prescription compared to persons who had no problems with the prescription. We also expect that persons with an extreme *CYP2D6* phenotype are more likely in general to have had a poor experience with opioid medications, and these persons would be less likely to take their prescribed medications. Failing to take an opioid may result in poor pain control, and this could account for the unexpected finding that persons with an ultrarapid phenotype seemed to experience poor pain control at about the same rate as poor metabolizers.

Finally, the Luminex kit used for genotyping in this study did not include some alleles that could change the phenotype for some of our participants. Chiefly, the *2A allele (an increased activity allele) harbors some *35 alleles (a normal activity allele). Therefore, some of the *2A alleles may have actually been *35 alleles, and these persons were incorrectly classified as ultrarapid metabolizers rather than as intermediate to extensive metabolizers. Therefore, we excluded all persons with *2A/*2A genotypes in a sensitivity analysis. Results were very similar to including these persons, suggesting that misclassification was not extensive. Future studies, however, will include typing that allows for the detection of *35 alleles. Similarly, intermediate to extensive *CYP2D6* metabolizers may have highly variable phenotypes due to nongenetic factors. Therefore, some of these persons are likely incorrectly classified as not having an extreme phenotype. If these persons experience adverse outcomes at a lower rate than persons in the "extreme" phenotype groups, then our results are an overestimate of the true association. However, if these persons experience adverse outcomes at the same or higher rate as our "extreme" phenotype groups, our results are an underestimate of the true association.

Many of the pain medications identified in this study were prescribed in conjunction with other medications, making it difficult to definitively attribute some events to a single prescription. We also relied on prescription information and do

not know how much or how often the medication was taken. We did account for the prescription of strong or moderately strong *CYP2D6* inhibitor medications, and our results were consistent regardless of whether persons taking these medications were excluded or reclassified. Accounting for these medications substantially strengthened associations between extreme metabolizer status and adverse reactions, indicating that it is important to account for use of these medications in future analyses.

Oxycodone and hydrocodone are predominantly metabolized by *CYP3A4*, and variation in *CYP3A4* function may significantly impact an individual's response to these medications (Yiannakopoulou, 2015 #104). We conducted a subanalysis of persons that were only prescribed oxycodone or hydrocodone, and results were attenuated compared to the overall results (as expected, due to smaller sample sizes). However, all results were still in the same direction, and point estimates were of a similar magnitude, suggesting that variation in *CYP2D6* is still an important factor to consider when considering response to oxycodone and hydrocodone. Finally, while the study sample size was relatively large, the number of outcomes was small, and estimates may not be stable.

Conclusion

In summary, 34% of patients with an extreme *CYP2D6* phenotype experienced an adverse outcome when prescribed codeine, tramadol, oxycodone, or hydrocodone. Opioid medications are frequently prescribed for pain relief, and ~39% of the US population is expected to carry an extreme phenotype (as defined by our study), suggesting that the population-level impact of these gene–drug interactions could be substantial.

Acknowledgments

Disclosure

John L Black III has licensed intellectual property to the companies AssureX Health and OneOme. In addition, he has stock ownership in OneOme. The other authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Ingredient names and RxNorm codes of opioid prescription medications included in the study

RxNorm code	Ingredient name
821601	Acetaminophen/Aspirin/Caffeine/Codeine
689552	Acetaminophen/Aspirin/Caffeine/Codeine/salicylamide
689555	Acetaminophen/Aspirin/Codeine
689561	Acetaminophen/butalbital/Caffeine/Codeine
689563	Acetaminophen/butalbital/Codeine
814657	Acetaminophen/Caffeine/Codeine
817430	Acetaminophen/Caffeine/Codeine/Meprobamate
689568	Acetaminophen/Caffeine/Codeine/salicylamide
817579	Acetaminophen/Codeine
817356	Acetaminophen/Codeine/Ibuprofen
1007238	Aconite/Codeine/Erysimum preparation
690996	Aluminum Hydroxide/Aspirin/Codeine/Magnesium Hydroxide
214237	anhydrous calcium iodide/Codeine
214160	Aspirin/butalbital/Caffeine/Codeine
689511	Aspirin/Caffeine/Codeine
689522	Aspirin/Carisoprodol/Codeine
135095	Aspirin/Codeine
1008493	Benzoate/Codeine
1008060	Butalbital/Caffeine/Codeine
691032	Calcium iodide/Codeine
2670	Codeine
1008110	Codeine/Diclofenac
1008954	Codeine/Erysimum preparation
1007477	Codeine/Ethylmorphine
710303	Codeine/Ibuprofen
214443	Codeine/iodinated glycerol
729517	Codeine/Kaolin
690089	Codeine/Papaverine
1007293	Codeine/Potassium
690096	Codeine/potassium citrate
1007204	Codeine/propyphenazone
690101	Codeine/Pyrilamine
689569	Acetaminophen/Caffeine/dihydrocodeine
151196	Acetaminophen/dihydrocodeine
689783	Acetaminophen/dihydrocodeine/salicylamide
689512	Aspirin/Caffeine/dihydrocodeine
23088	Dihydrocodeine
214183	Acetaminophen/Oxycodone
214256	Aspirin/Oxycodone
484259	Ibuprofen/Oxycodone
1545902	Naloxone/Oxycodone
7804	Oxycodone
689553	Acetaminophen/Aspirin/Caffeine/Hydrocodone
689562	Acetaminophen/butalbital/Caffeine/Hydrocodone
214182	Acetaminophen/Hydrocodone
689515	Aspirin/Caffeine/Hydrocodone
214253	Aspirin/Hydrocodone
5489	Hydrocodone
214627	Hydrocodone/Ibuprofen
352362	Acetaminophen/Tramadol
10689	Tramadol

Table S2 Ingredient name and count of additional prescriptions received on the same day as the opioid prescription

Ingredient RxNorm description	N
Acetominophen	8
Albuterol	2
Amoxicillin or Amoxicillin/Clavulanate	7
Aspirin	3
Azithromycin	2
Bacitracin	1
Benzonatate	1
Cefadroxil	1
Cefdinir	1
Celecoxib	2
Cephalexin	9
Ciprofloxacin/Dexamethasone	1
Ciprofloxacin opthalmic preparation	10
Clindamycin	1
Colchicine	1
Cyclobenzaprine	8
Daptomycin	1
Dexamethasone	3
Diazepam	5
Diclofenac	2
Dicloxacillin	1
Diflunisal	1
Docosanol	1
Docusate	17
Docusate/Sennosides	16
Enoxaparin	4
Erythromycin Base	3
Estrogens, conjugated	3
Fenofibrate	1
Fentanyl	1
Fexofenadine	1
Fluoxetine	1
Furosemide	2
Gabapentin	1
Haloperidol	1
Hydromorphone	1
Indomethacin	2
Insulin Aspart	1
Insulin glargine, hum rec analog	1
Ketoconazole	1
L – Thyroxine	2
Levofloxacin	1
Lidocaine	2
Lisinopril	1
Loratadine/Pseudoephedrine	1
Lorazepam	2
Methylphenidate	1
Metoprolol	1
Metronidazole	2
Miconazole	1
Minocycline	1
Montelukast	2
Morphine	2
Moxifloxacin	1
Naproxen	3
Nortriptyline	1
Omeprazole	3

(*Continued*)

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Table S2 (*Continued*)

Ingredient RxNorm description	N
Ondansetron	11
Oxybutynin	5
Pantoprazole	1
Phenazopyridine	1
Potassium chloride	1
Prednisolone	1
Promethazine	2
Psyllium	1
Rifampin	1
Rivaroxaban	1
Sennoside A & B	2
Sertraline	2
Sildenafil	1
Sulfamethoxazole/Trimethoprim	1
Tadalafil	1
Tamsulosin	8
Trazodone	1
Triamcinolone	2
Vancomycin	1
Warfarin	3
Zolpidem	1

Table S3 Ingredient names and RxNorm codes of strong or moderately strong *CYP2D6* inhibitors included in the study

RxNorm code	Ingredient name
42347	Bupropion
1551467	Bupropion/Naltrexone
407990	Cinacalcet
4493	Fluoxetine
611247	Fluoxetine/olanzapine
32937	Paroxetine
1040053	Dextromethorphan/Quinidine
9068	Quinidine
1007942	Quinidine/Verapamil
1721552	Florfenicol/Mometasone/terbinafine
37801	Terbinafine
72625	Duloxetine
36437	Sertraline