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# The Effect of CYP2D6 Drug-Drug Interactions on Hydrocodone Effectiveness

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## Abstract

**Objectives—**The hepatic cytochrome 2D6 (CYP2D6) is a saturable enzyme responsible for metabolism of approximately 25% of known pharmaceuticals. CYP interactions can alter the efficacy of prescribed medications. Hydrocodone is largely dependent on CYP2D6 metabolism for analgesia, ondansetron is inactivated by CYP2D6, and oxycodone analgesia is largely independent of CYP2D6. The objective was to determine if CYP2D6 medication co-ingestion decreases the effectiveness of hydrocodone.

**Methods—**This was a prospective observational study conducted in an academic U.S. emergency department (ED). Subjects were included if they had self-reported pain or nausea; and were excluded if they were unable to speak English, were less than 18 years of age, had liver or renal failure, or carried diagnoses of chronic pain or cyclic vomiting. Detailed drug ingestion histories for the preceding 48 hours prior to the ED visit were obtained. The patient's pain and nausea were quantified using a 100-millimeter visual analogue scale (VAS) at baseline prior to drug administration and following doses of hydrocodone, oxycodone, or ondansetron. We used a mixed model with random subject effect to determine the interaction between CYP2D6 drug ingestion and study drug effectiveness. Odds ratios (OR) were calculated to compare clinically significant VAS changes between CYP2D6 users and non-users.

**Results—**Two hundred fifty (49.8%) of the 502 subjects enrolled had taken at least one CYP2D6 substrate, inhibitor, or inducing pharmaceutical, supplement, or illicit drug in the 48 hours prior to ED presentation. CYP2D6-drug users were one third as likely to respond to hydrocodone (OR 0.33, 95% CI = 0.1 to 0.8), and more than three times as likely as non-users to respond to ondansetron (OR 3.4, 95% CI = 1.3 to 9.1). There was no significant difference in oxycodone effectiveness between CYP2D6 users and non-users (OR 0.53, 95% CI = 0.3 to 1.1).

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**Conclusions—**CYP2D6 drug-drug interactions appear to change effectiveness of commonly prescribed drugs in the ED. Drug-drug interaction should be considered prior to prescribing CYP2D6 drugs.

## Introduction

The efficacy of many commonly used medications may be altered by variation in metabolism. For example, the analgesic effect of hydrocodone, the most prescribed medication in the United States,[1] is largely dependent upon metabolic activation for analgesic efficacy.[2-4] Hydrocodone is metabolized by the hepatic cytochrome 2D6 (CYP2D6) to hydromorphone. As hydromorphone is approximately five times as potent as hydrocodone, the efficacy of hydrocodone is much higher in patients who have high activity in this metabolic pathway. Conversely, ondansetron is inactivated by CYP2D6; so decreased metabolism by this pathway should increase ondansetron's antiemetic effects.

CYP2D6 metabolizes approximately 25% of known pharmaceuticals.[5] Pharmacokinetic differences have been demonstrated between CYP2D6 genotype subgroups for a range of medications,[6,7] including hydrocodone.[2] While genetic variation accounts for some differences in drug effect, genotype identification does not consistently predict the efficacy or safety of pharmaceuticals.[8,9] This is likely due to the complexity of the human-drug interface; factors upstream and downstream from the encoded enzyme contribute to the ultimately observed clinical effect. For example, CYP2D6 inhibition by drug-drug interaction alters the pharmacokinetics of medication metabolism.[10-12] However, the effect of drug-drug interactions on the effectiveness of medications administered in the emergency department (ED) has not previously been investigated.

The objective of this study was to examine the effect of CYP2D6 drug-drug interactions on CYP2D6-dependent medication effectiveness. Our unifying hypothesis is that the effectiveness of the study drug (hydrocodone, oxycodone, or ondansetron) will be dependent upon CYP2D6-dependent drug use within 48 hours of ED presentation. Furthermore, the effectiveness of hydrocodone will be decreased in patients taking other CY2D6-dependent drugs, the effectiveness of ondansetron will be increased in patients taking CY2D6-dependent drugs, and the effectiveness of oxycodone (which is not primarily metabolized by CYP2D6[12,13]) will not differ between 2D6 users and nonusers. We also explored the association of effectiveness with genotype in a limited number of subjects.

## Methods

### Study Design

This was a prospective observational study. Our local institutional review board approved this study and all subjects provided informed consent.

### Study Setting and Population

The study was conducted in an academic U.S. ED with approximately 72,000 patient visits per year. A convenience sample of ED patients was enrolled between June 4, 2012 and January 25, 2013. Enrollment was performed between the hours of 9 am and 5 pm, as this

has been demonstrated to be the most representative demographic sampling times with the least amount of sampling bias in our ED.[14] Subjects were included if they had self-reported pain or nausea identified during their initial nursing assessments. All pain and nausea complaints were eligible for inclusion; for example ankle sprain, undifferentiated abdominal pain, gastroenteritis, and chemotherapy-related nausea complaints were included. Patients were excluded if they were unable to speak English, younger than 18 years old, had liver or renal failure, or were previously diagnosed with chronic pain (including those who took opioid medications daily) or cyclic vomiting. In patients with dementia or critical illness who were able to comprehend the study and visual analogue scale (VAS) methods (see below), the drug ingestion history was reconciled with the health care proxy. Patients were approached after triage, after initial stabilization, or after initial nursing assessment following ambulance arrival. Detailed medication histories for the preceding 48 hours prior to ED visit were obtained. All prescription, non-prescription, vitamin, herbal supplement, and illicit drugs were captured along with their doses and time since the patient's last dose.

## Study Protocol

**Study Drugs—**Treatment decisions and medication orders were made by the patient's ED provider in the main ED or by symptom-based triage protocols. Patients receiving oxycodone 5 mg (with or without acetaminophen 325 mg), hydrocodone 5 mg/ acetaminophen 500 mg, or ondansetron 4 mg were followed to evaluate medication effectiveness throughout their ED courses. These medications are the three most commonly administered medications in our ED. CYP2D6 activates hydrocodone to hydromorphone,[2] inactivates ondansetron,[15] and plays a minimal role in the analgesic efficacy of oxycodone[12,16,17] (Figure 1).

**Effectiveness Measure—**A 100 mm VAS was used as the assessment tool for both pain and nausea symptoms. This scale has been validated as a reliable tool for a semi-quantitative assessment of acute pain and nausea in a wide variety of ED patients.[18-24]

Patients' pain and nausea were quantified by VAS at baseline prior to medication administration. Repeat VAS scores were obtained between 30 and 90 minutes following hydrocodone, oxycodone, and/or ondansetron administration in the ED. VAS scores were obtained after doses of oxycodone 5 mg, hydrocodone 5 mg, or ondansetron 4 mg. Only single doses of study drugs were followed.

Patients who received more than one study medication throughout their ED stays had serial VAS scores recorded for each medication. A second VAS measurement was not taken if another medication for the same indication was given in the intervening time (example: if morphine was given for pain, or if oxycodone was given after hydrocodone before a repeat VAS could be obtained, these scores were excluded from analysis). Therefore, the analysis included only serial VAS values for each study drug when no additional drugs for the same indication were given between VAS measurements. However, ondansetron could be given to patients for nausea after they received hydrocodone or oxycodone, and serial VAS for both nausea and pain could be followed. If hydrocodone was given followed by oxycodone later in the ED stay, VAS scores could only be included for the first drug if two scores had been

obtained prior to oxycodone administration. If the study drug was repeated during the ED stay, only the first administration was followed for VAS analysis; repeat doses were not analyzed. Intravenous, oral, and sublingual 4 mg ondansetron administrations were captured since all routes have near equivalent bioavailability.[25,26]

**Interaction Identification—**All patient-reported medications were categorized as CYP2D6 substrate, inhibitor, inducer, or not CYP2D6-dependent using the University of Indiana CYP450 Interaction Table.[27] Substrates and inhibitors were considered CYP2D6 enzyme-dependent drugs for the effectiveness analysis. We initially planned on using a scoring system to account for variable effect of substrates, inhibitors, and inducers, although the infrequency of inducers made this distinction irrelevant. The presence of CYP2D6 interaction was considered dichotomous: it was present if the subject had taken an inhibitor or a substrate of the enzyme.

**Genotyping—**Fifty-three patients were randomized for CYP2D6 genotyping by a random number generator after study drug was ordered by the ED provider. Genotyping was provided by LabCorp using the CYP2D6/2C19 Amplichip.[28] Genotyping with the Amplichip accounts for 26 distinct CYP2D6 polymorphisms and allele duplication categorizing the individual's genotype into one of four predicted metabolizer groups: poor metabolizer, intermediate metabolizer, extensive metabolizer, or ultra-rapid metabolizer. The intermediate and extensive groups were combined for clinical effectiveness analysis.

**Adverse Drug Events—**All cases were reviewed for adverse drug events; all symptoms charted by ED providers were abstracted by an ED pharmacist (DH). Naranjo scores[29] were calculated for all possible adverse drug events that occurred after the study drugs were administered. Any symptoms with Naranjo scores 5 or greater were considered probable adverse drug events. 10% of the cases were reviewed by a second investigator (AAM), and the kappa statistic was calculated.

## Outcomes

The primary outcome was clinically significant VAS change between CYP2D6 users and non-users. The secondary outcomes were the overall prevalence of CYP2D6 drug interactions and ΔVAS after study drug administration between CYP2D6 users and non-users in the study population.

## Data Analysis

Descriptive statistics were used to characterize demographic data, the prevalence of CYP2D6 drugs taken, and CYP2D6 drug-drug interactions in the study population. Wilcoxon rank sum was used to compare differences in clinically significant VAS change between CYP2D6 users and non-users. A clinically significant VAS change was considered to be 13 mm for odds ratio analysis.[19] Our a-priori power calculation showed that 33 patients in each group would detect a 13 mm VAS score difference between the groups at a power of 0.8 and a significance of 0.05 using a Wilcoxon rank sum test. We used a mixed model with random subject effect to determine if the interaction between CYP2D6-

dependent drug ingestion within 48 hours of ED presentation and study drug group was significant. Data analysis was performed using JMP 10.

## Results

Five hundred and two out of 655 (76.6%) approached patients consented to enrollment. The overall demographics of the sample were representative of the ED population during the sampling period (Table 1). One hundred forty-six (29.1%) had nausea and/or vomiting, and 468 (93.2%) had pain. Two hundred eighty-six (56.9%) of the patients were enrolled through triage, the remainder were enrolled in the ED after initial stabilization or after ambulance arrival (Figure 2).

### Medication Histories

The median number of all medications, herbals, vitamins, or supplements taken by patients in the 48 hours prior to ED presentation was three (range 0 to 33, interquartile range [IQR] 1 to 6). Two hundred fifty (49.8%) of the 502 subjects enrolled had taken at least one CYP2D6 substrate, inhibitor, or inducing pharmaceutical, supplement, or illicit drug in the 48 hours prior to ED presentation (Figure 3). Of these, 239 (47.6%) had taken substrates, 30 (6.0%) had taken inhibitors, and one (0.2%) had taken an inducer. Sixty-three subjects reported use of illicit drugs, only three reported cocaine use (a CYP2D6 substrate). There was no difference in illicit drug use between groups.

### Effectiveness of Oxycodone, Hydrocodone, and Ondansetron

Oxycodone was administered to a total of 142 patients, hydrocodone to 91 patients, and ondansetron was given to 117 patients. Twenty-nine received both oxycodone and ondansetron, while 12 received both hydrocodone and ondansetron. Four patients received both hydrocodone and oxycodone. Two patients received all three medications while in the ED. One hundred twenty-five of the oxycodone patients, 83 of the hydrocodone patients, and 93 of the ondansetron patients had serial VAS scores obtained. The remainder of the patients were either administered an additional medication for the same indication, or were discharged prior to the second VAS being obtained. There was no difference in timing of the first and second VAS scores between the study drugs (oxycodone, mean 55.5 minutes, 95% CI 52.9 to 58.1 minutes; hydrocodone, mean 57.1 minutes, 95% CI 53.7 to 60.4 minutes; and ondansetron, mean 57.4 minutes, 95% CI = 54.3 to 60.4 minutes).

Overall, oxycodone and hydrocodone had similar effectiveness (mean ΔVAS 24.1, 95% CI = 19.9 to 28.2 vs. 21.5, 95% CI = 16.8 to 26.1, respectively; p = 0.417). There were clinically significant VAS changes in 74 (59.2%) of the oxycodone group, 49 (59.0%) of the hydrocodone group, and 68 (73.1%) of the ondansetron group. There was no difference in effectiveness between those randomized in triage versus those enrolled in the main ED for either oxycodone or hydrocodone (p = 0.431 and 0.368, respectively).

The proportion of subjects having clinically significant responses to ondansetron and hydrocodone differed between subjects taking CYPD26 medications and those not taking CYP2D6 medications. Patients taking CYP2D6 medications were more than three times as likely as non-users to respond to ondansetron (OR 3.4, 95% CI = 1.3 to 9.1) and only one-

third as likely to respond to hydrocodone (OR 0.33, 95% CI = 0.1 to 0.8). There was no significant difference in oxycodone effectiveness between CYP2D6 users and non-users (OR 0.53, 95% CI = 0.3 to 1.1).

The interaction between CYP2D6 drug ingestion within 48 hours of ED presentation was significant (p = 0.0009), indicating that the effect of the CYP2D6-dependent drug ingestion on VAS scores differed by study drug. There was a significant reduction in hydrocodone effectiveness, by VAS change, when patients had co-ingestion of one or more CYP2D6-dependent medications in the 48 hours prior to ED presentation. Conversely, the effectiveness of ondansetron was increased when patients had co-ingested one or more CYP2D6-dependent medications. There was no change in oxycodone effectiveness when controlled for CYP2D6 medication co-ingestion (Table 2).

### Adverse Drug Events

There were no adverse drug events scored as “probable” by the Naranjo scale following oxycodone, hydrocodone, or ondansetron administration. Inter-rater reliability was 1.0 when 10% of the cases were reviewed.

### Genotyping

Fifty three subjects were genotyped for CYP2D6 metabolizer status. Of the 53, 41 (77.3%) were extensive metabolizers, eight (15.1%) were intermediate metabolizers, three (5.7%) were poor metabolizers, and one (1.9%) was an ultra-rapid metabolizer, based on genotype. Forty-eight of these subjects received oxycodone, hydrocodone, or ondansetron while in the ED. Overall, genotype was not predictive of study medication effectiveness, although the few numbers of poor and ultra-rapid metabolizers limited this analysis. When controlled for CYP2D6 interactions, there was a significant association with increased ondansetron effectiveness by VAS change in the intermediate and extensive metabolizer group ($p$ = 0.03). The VAS change in the one ultra-rapid metabolizing patient receiving hydrocodone was only 12 mm. This patient had taken fluoxetine, considered a strong CYP2D6 inhibitor, four hours prior to ED presentation.

## Discussion

In our ED population, the effectiveness of two commonly prescribed drugs metabolized by CYP2D6 was associated with the reported use of other drugs metabolized by this enzyme. The effectiveness of hydrocodone, a drug made more potent by CYP2D6 metabolism, was decreased and the effectiveness of ondansetron, a drug that is inactivated by CYP2D6 metabolism, was increased in the setting of other CYP2D6 substrates and inhibitors. The most plausible mechanism for these observations is that substrate competition for CYP2D6 results in decreased metabolism of the study drug; that this drug-drug interaction alters medication effectiveness.

CYP2D6 drug-drug interactions are common. Almost half of our study population presented to the ED taking one or more substrates or inhibitors of this enzyme. CYP2D6 plays little role in the metabolic conversion of oxycodone in-vivo.[13] While oxycodone analgesia is not generally considered CYP2D6-dependent, a small percentage of oxycodone is metabolized

by CYP2D6 to a more potent metabolite, oxymorphone. Even though we did not find a difference in oxycodone effectiveness between CYP2D6 users and non-users, given Samer et al.'s demonstration of metabolic shunting in the setting of enzyme inhibition,[16] and pharmacokinetic and dynamic alterations due to drug interaction in ultra-rapid metabolizing patients,[30] this represents an important area of future study.

Drug-drug interaction is more likely to occur when efficacy or safety are dependent on a single metabolic pathway with limited metabolic capacity, such as CYP2D6. When metabolism is dependent on a low-capacity enzyme, substrates can saturate enzymatic activity, much like an inhibitor. Substrates may not result in similar enzyme inhibition when high capacity enzymes, such as CYP3A4, are involved. Physicians will find it difficult to know the metabolic fate of all medications they prescribe. Therefore this information is perfectly suited for a computerized program that informs the provider about the expected clinical implication of drug interaction on medications they wish to prescribe.

Overall, the effectiveness of oxycodone and hydrocodone was similar with approximately 60% having clinically significant improvements in pain. This is consistent with prior studies that have identified equivalent effectiveness.[31,32] Our study adds to this information by demonstrating that the proportion of patients achieving clinically significant improvements due to hydrocodone is altered by the presence of drug-drug interactions. While previous studies have suggested that medications prescribed in the ED theoretically interact with the patients' regular medications,[33] our current study found that these interactions result in clinically significant changes in medication effectiveness. One interpretation of these data is that oxycodone should be preferred over hydrocodone due to more consistent clinical effects regardless of drug-drug interactions. It must be acknowledged, however, that a higher delta VAS was observed in CYP non-users given hydrocodone, suggesting that hydrocodone may be preferred in these patients. Routine screening of a patient's medication list and prospective identification of these interactions may result in improved ED medication selection, and affect patient response to medications.

As we were only able to genotype approximately 10% of our research subjects, we cannot make conclusions about the influence of genetics on the effectiveness of medications administered in the ED. However, this project demonstrates the feasibility of enrolling ED patients in a pharmacogenetic study. It is interesting that the one ultra-rapid metabolizer, who would be expected to have increased analgesia from hydrocodone, did not have a clinically significant response and that this occurred in the setting of a CYP2D6 inhibitor. We look forward to following up this observation in future studies.

## Limitations

These data are limited by the nature of self-reported medication ingestion histories and self-reported effectiveness measures for opioid pain medications. While the VAS has been validated in similar patients in the past, all patients experience pain in different ways, and a clinically significant improvement in pain may vary between patients. However Todd et al.[20] and Gallagher et al.[19] both validated 13 mm of change to be clinically significant when compared with Likert pain scales. As patients take more medications, they are more likely to

have more medical problems. These patients may be more likely to be taking opioid medications intermittently, thus minimizing the effectiveness of additional opioids due to tolerance. Forty-eight hours from the time of ED presentation may have been too long of a cut-off for some drugs with short half-lives. This may paradoxically result in increased CYP2D6 enzyme function, thus minimizing effectiveness of hydrocodone. This time period was chosen to accommodate five half lives of a large number of CYP2D6 drugs. Despite this overall inherent bias toward decreased effectiveness, we only observed a decrease in hydrocodone effectiveness.

Exclusion of non-English speaking patients may influence the distribution of the underlying CYP2D6 genotype subgroups. Certain ethnic populations are known to have a higher prevalence of ultra-rapid or poor metabolizer status.[34] However, more than 90% of our ED population speak English and the CYP2D6 genotype distribution closely mirrors the prevalence observed in other European populations.[34] Therefore, we believe this the genotype distribution in our study group is representative of our overall ED cohort. It is possible that prior adverse drug reactions to hydrocodone are associated with an ultra-rapid metabolizer phenotype, which could bias the results toward a more significant effect of CYP2D6 medication interaction. However, we know that only approximately 3% of the general population are ultra-rapid metabolizers, and no one has demonstrated that CYP2D6 genotype subgroup is definitively associated with adverse drug reactions to hydrocodone. Genotyping of only 10% of the cohort has limited the interpretation of the study medication effectiveness stratification by genotype subgroup.

## Conclusions

Users of CYP2D6-dependent drugs were less likely to achieve clinically significant improvement in pain after receiving hydrocodone. Conversely, ondansetron was more likely to result in clinically significant improvement of nausea in CYP2D6 users. There was no change in oxycodone effectiveness in CYP2D6 users and non-users. CYP2D6 drug-drug interactions change effectiveness of commonly prescribed drugs in the ED. Drug-drug interaction should be considered prior to prescribing CYP2D6-dependent drugs.

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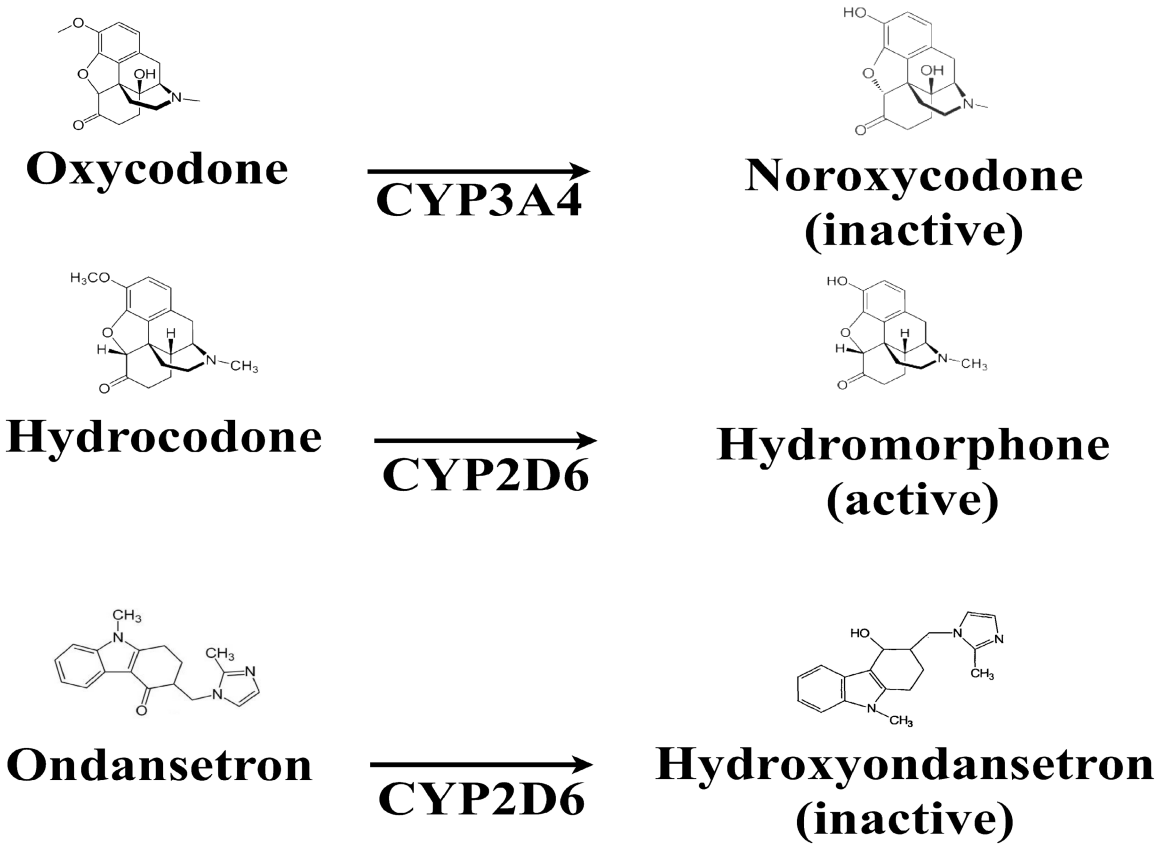


**Figure 1. Primary Metabolic fate of oxycodone, hydrocodone, and ondansetron**

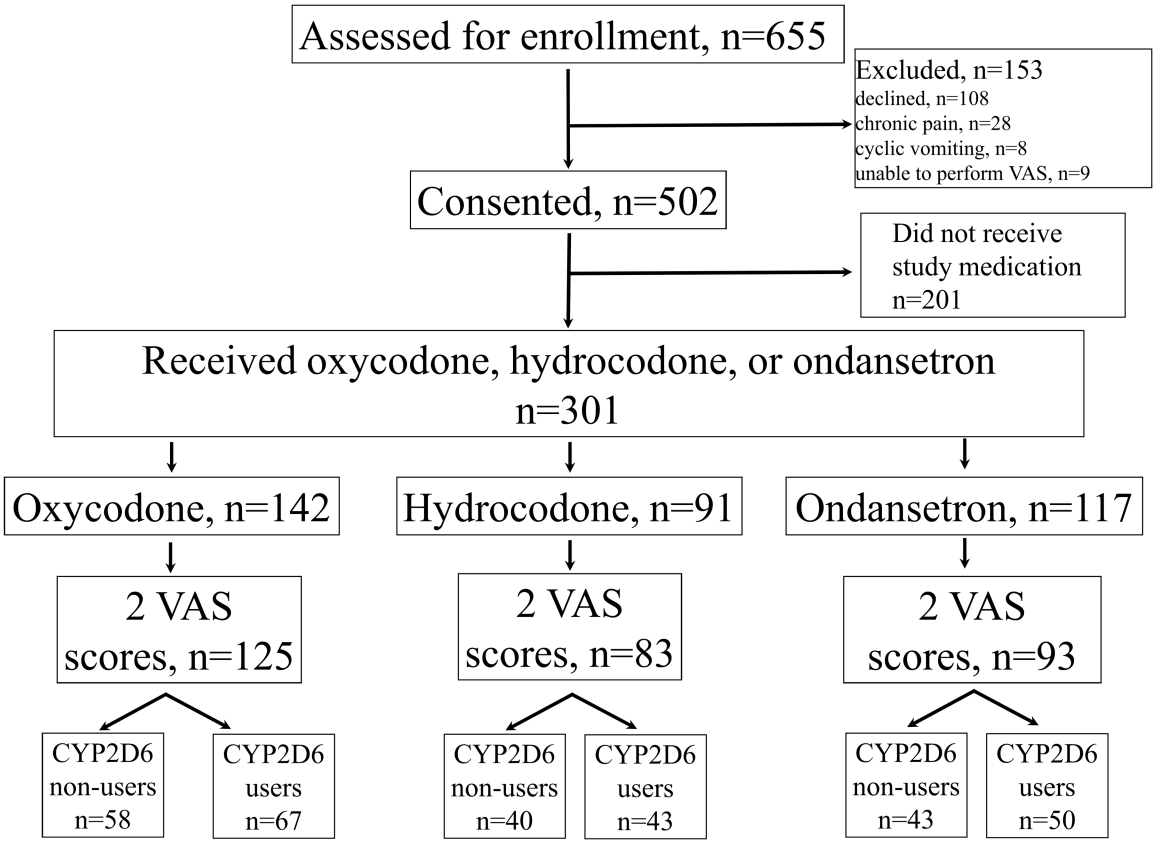


**Figure 2. Patient flow through the protocol and analysis**

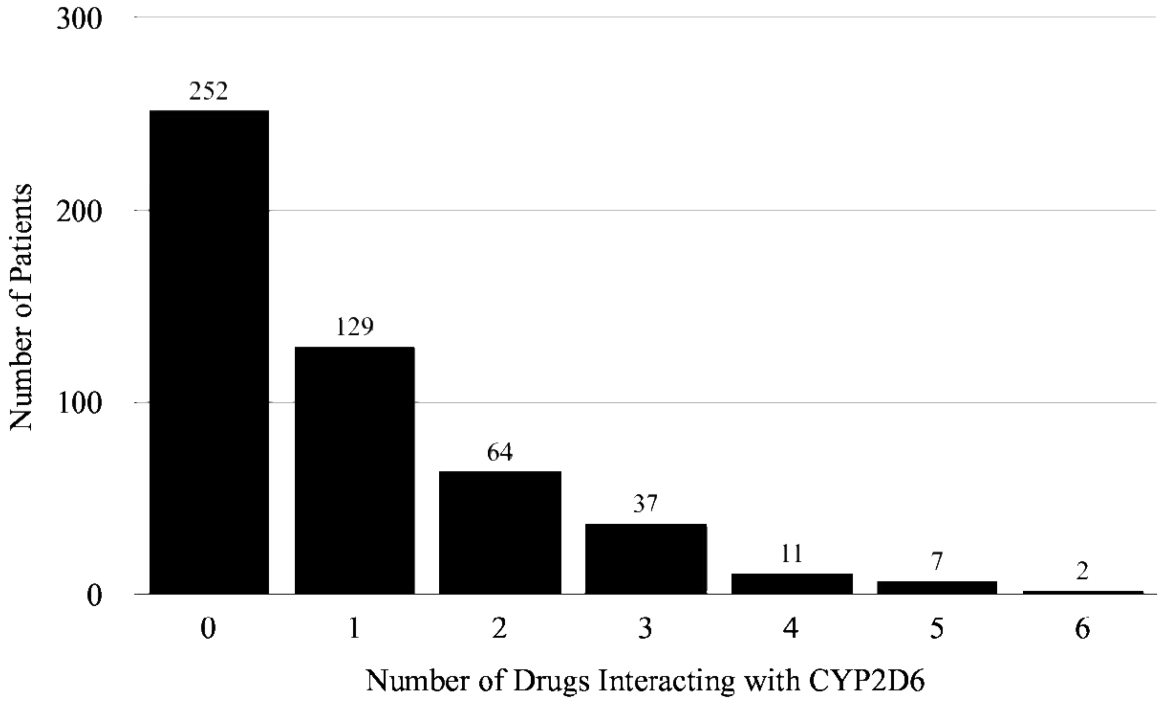


**Figure 3. Number of patients that had taken either 0, 1, 2, 3, 4, 5, or 6 drugs that interact with CYP2D6 within 48 hours of study enrollment**

## Table 1

### Patient Demographics

| Demographic Variable | Total Group n=502 | Oxycodone n=141 | Hydrocodone n=91 | Ondansetron n=116 |
|---|---|---|---|---|
| Mean age, years (range) IQR | 39 (18-89) 22-53.3 | 40 (18-86) 28.5-53 | 38 (18-84) 30-50 | 34 (18-85) 25.25-50.75 |
| Male, n (%) | 198 (39.4) | 62 (44.0) | 35 (38.5) | 33 (28.4) |
| Ethnicity/race, n (%) | | | | |
| Hispanic | 98 (19.5) | 22 (15.6) | 16 (17.6) | 27 (23.3) |
| White | 326 (64.9) | 89 (63.1) | 54 (59.3) | 81 (69.8) |
| African American | 162 (32.3) | 51 (36.2) | 35 (38.5) | 29 (25) |
| Asian | 9 (1.8) | 1 (0.7) | 2 (2.2) | 0 (0) |
| American Indian/ Alaskan Native | 19 (3.8) | 6 (4.3) | 4 (4.4) | 6 (5.2) |
| Hawaiian/ Pacific Islander | 6 (1.2) | 2 (1.4) | 0 (0) | 1 (0.9) |
| Median number of medications taken (range) IQR | 3 (0-33) 1-6 | 3 (0-16) 2-6 | 3 (0-18) 1-7 | 3.5 (0-22) 2-7 |
| Median number of CYP2D6 drugs taken (range) IQR | 0 (0-6) 0-1 | 1 (0-6) 0-2 | 1 (0-5) 0-1 | 1 (0-6) 0-2 |

## Table 2

**Mean delta VAS associated with CYP2D6 drug co-ingestion. Only patients with 2 serial VAS measurements were included in the mixed model analysis**

| Drug | Mean Delta VAS Without CYP2D6 Drug Use | Mean Delta VAS With CYP2D6 Drug Use | Mean Delta VAS Difference | p value |
|---|---|---|---|---|
| Oxycodone n=125 | 28.1 (22.1 to 34.1) | 20.7 (15.1 to 26.3) | 7.4 (-0.8 to 15.6) | 0.0765 |
| Hydrodcodone n=83 | 27.4 (20.0 to 34.8) | 16.4 (9.4 to 23.5) | 10.9 (0.8 to 21.1) | 0.036* |
| Ondansetron n=93 | 21.2 (14.2 to 28.2) | 35.2 (28.7 to 41.7) | -14.0 (-4.4 to -23.6) | 0.0053* |

* significant at the $p<0.05$ level

Data are reported with (95% CI)