ORIGINAL ARTICLE

Urinary metabolic ratio of pain management and substance abuse treatment drugs: Drug–drug interactions

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ABSTRACT

We present data showing that the urinary metabolic ratio (MR) of metabolite to parent drug can be used to estimate the drug–drug interactions (DDIs) of pain management and substance abuse treatment medications with other coadministered drugs. We quantitatively measure 18 drugs and their phase I metabolites and monitor the effects of 14 interfering drugs on their MRs. The 18 drugs include dextromethorphan, oxycodone, hydrocodone, tramadol, morphine, buprenorphine, fentanyl, clonazepam, alprazolam, quetiapine, carisoprodol, tapentadol, ketamine, methadone, impramine, and amitriptyline. The 14 interfering drugs include fluoxetine, paroxetine, bupropion, citalopram, sertraline, venlafaxine, duloxetine, risperidone, trazodone, aripiprazole, cyclobenzaprine, amphetamine, and tetrahydrocannabinol. Some of these interfering drugs are inhibitors of either the CYP2D6, CYP3A4/5, or CYP2C19 pathways. By using the urinary MR of metabolite/parent drug, we observed patterns of inhibition and enhancement due to DDIs. Using the MR reference intervals of the 18 drug pairs established in an earlier study, and the current DDI system, we can alert providers of unusual metabolism caused by DDIs. This will help providers do better prescribing or review more closely all medications and supplements patients are taking, thus avoiding underdosing or potential medication adverse reactions.

INTRODUCTION

Drug–drug interactions (DDIs) occur when two or more drugs react with each other. A primary mechanism through which drug interactions can occur involves effects on the cytochrome P450 (CYP) enzymes that alter the metabolism of prescription drugs.[1] These interactions may make the prescription drug less effective or cause unexpected side effects.[2] One study estimated that these interactions could account for 1 percent of hospitalizations and 2-5 percent of hospital admissions in the elderly.[3] Previous studies have focused on cardiovascular or human immunodeficiency virus drugs. We wish to establish if DDIs could affect our patient population who are being treated for substance abuse or pain management. We noted that a significant number of these patients were being treated for depression as they were positive for various serotonin-norepinephrine reuptake inhibitors (SNRIs), and other drugs used to treat depression. This drug category includes fluoxetine, paroxetine, bupropion, citalopram, sertraline, venlafaxine, duloxetine, risperidone, trazodone, haloperidol, and aripiprazole. A significant number of our patients were also positive for amphetamine, cyclobenzaprine, and tetrahydrocannabinol (THC). Amphetamine is used to treat attention-deficit disorder, cyclobenzaprine is a muscle relaxant, and THC is used to treat pain. Some of these drugs are potent inhibitors of either the CYP2D6 or CYP3A4/5 or CYP2C19 pathways.[4-22]

One method of alerting caregivers to DDIs is to attach the Elsevier database information to the urine drug test report to warn them that the patient is at risk for a severe or mild DDI.[16,21] We are concerned that these drugs may affect the metabolism of the pain

and substance abuse treatment medications. We propose that the metabolism effect can be observed by examining changes in the metabolic ratios (MRs) present in our 2 million definitive drug tests that quantitatively measure the parent drug and its metabolite.[23-25] Metabolic ratio, defined as the ratio of the metabolite to its parent drug, reflects the ability of the CYP450 pathway to process the drug. When MRs are compared in the presence or absence of these inhibitory drugs, a define change in the MR should be observed.

We examined the following interfering drugs and metabolic pairs to be tested for metabolic effects. The metabolite/parent drug pairs that were considered are those described in Table 1. The interfering drugs for DDIs examined in this study are those listed in Table 2. As shown in other studies, the urinary metabolites of drugs such as dextromethorphan can be used to show inhibitory effects on drug metabolism.[26] If the listed antidepressants act as metabolic inhibitors, the expected result will be a decrease in the MR of these pairs in the presence of the inhibitors.

METHODS

Populations

We used the same population as in the determination of the MR reference interval from an earlier paper. This was a retrospective study of specimens submitted to Precision Diagnostics for urine drug testing. Specimens came from pain physician clinics and rehabilitation facilities across the 50 United States states and the District of Columbia.[67] We used data from specimens collected between January 2, 2020, and September 30, 2024, which totaled ~2.2 million observations from 581,614 patients. No exclusion criteria were applied in the initial selection of the patients, and repeats were excluded. We assigned unique patient identifiers and specimen numbers to deidentify data. Our control population is defined as those specimens with none of the interfering drugs present (Table 2). A subsequent test population for a given DDI are those specimens positive for the parent drug and the given DDI but no other DDIs. For the MRs of oxymorphone/oxycodone, hydromorphone/hydrocodone, and hydromorphone/morphine, data were collected from specimens of patients prescribed the parent drug, while excluding those with prescribed oxymorphone or hydromorphone. This study was approved by Aspire IRB (Santee, California).

Table 1. Table of metabolite–parent drug pairs and associated CYP metabolizing enzymes

Metabolite–parent drug pair	CYP metabolizing enzyme
Dextrorphan/dextromethorphan	CYP2D6[18,27]
Oxymorphone/oxycodone	CYP2D6[28]
Hydromorphone/hydrocodone	CYP2D6[29]
O-Desmethyltramadol/tramadol	CYP2D6, CYP3A4[30]
Hydromorphone/morphine	CYP2D6[31,32]
Norbuprenorphine/buprenorphine	CYP3A4/5[33]
Norfentanyl/fentanyl	CYP3A4/5[34]
Noroxycodone/oxycodone	CYP3A4/5[28]
Norhydrocodone/hydrocodone	CYP3A4/5[35]
7-Aminoclonazepam/clonazepam	CYP3A4/5[36]
α-Hydroxyalprazolam/alprazolam	CYP3A4/5, CYP2C9[37]
Norquetiapine/quetiapine	CYP3A4/5, CYP2D6[38,39]
Meprobamate/carisoprodol	CYP2C19[40]
N-Desmethyltapentadol/tapentadol	CYP2C9, CYP2C19, CYP2D6[41]
Norketamine/ketamine	CYP3A4, CYP2B6, CYP2C9[42]
EDDP/methadone	CYP3A4, CYP2B6, CYP2D6, CYP2C19[43]
Desipramine/imipramine	CYP2C19, CYP1A2, CYP3A4, CYP2D6[44,45]
Nortriptyline/amitriptyline	CYP2C19, CYP2D6, CYP2C9, CYP3A4, CYP2C8[46,47]

EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.

Analytical method

Quantitative urine drug testing was performed using a clinically validated LC–MS/MS method.[23] Briefly, a Shimadzu 20-XR series binary pump systems, well-plate autosampler, and thermostatted column oven paired with a Sciex 6500/6500+ mass spectrometer were used for the analysis of all

Table 2. Table of interfering (drug–drug interaction [DDI]) drugs (and metabolites) and associated CYP metabolizing enzymes

DDI drugs	CYP metabolizing enzyme
Fluoxetine (norfluoxetine)	CYP2D6[48,49]
Paroxetine	CYP2D6, CYP3A4[48,49]
Bupropion (hydroxybupropion)	CYP2B6[50]
Citalopram (N-desmethylcitalopram)	CYP3A4, CYP2C19, CYP2D6[14,48,49,51]
Sertraline	CYP2C9, CYP2C19, CYP2D6, CYP3A4[48,49,52,53]
Venlafaxine	CYP2D6, CYP3A4[54,55]
Duloxetine	CYP2D6, CYP1A2[12,56]
Risperidone (9-hydroxyrisperidone)	CYP2D6, CYP3A4[15,57]
Trazodone (trazodone-metabolite)	CYP3A4, CYP2D6[58,59]
Haloperidol	CYP3A4[60]
Aripiprazole (dehydroaripiprazole)	CYP3A4, CYP2D6[61,62]
Cyclobenzaprine	CYP3A4, CYP1A2, CYP2D6[63,64]
Amphetamine	CYP2D6[65]
THC (THCA)	CYP2C9, CYP2C19, CYP3A4[66]
THC: tetrahydrocannabinol.	

Table 3. Minimum cutoff values for detection of the parent drug and metabolite

Parent drug	Cutoff (ng/mL)	Metabolite	Cutoff (ng/mL)
Alprazolam	5	α-Hydroxyalprazolam	5
Amitriptyline	10	Nortriptyline	10
Buprenorphine	5	Norbuprenorphine	5
Carisoprodol	10	Meprobamate	100
Clonazepam	5	7-Aminoclonazepam	5
Dextromethorphan	5	Dextrorphan	5
Fentanyl	1	Norfentanyl	2
Hydrocodone	5	Hydromorphone	5
		Norhydrocodone	10
Imipramine	5	Desipramine	5
Ketamine	2	Norketamine	2
Methadone	50	EDDP	100
Morphine	50	Hydromorphone	5
Oxycodone	10	Oxymorphone	10
		Noroxycodone	25
Quetiapine	5	Norquetiapine	25
Tapentadol	2	N-Desmethyltapentadol	25
Tramadol	25	O-Desmethyltramadol	10
EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.			

drugs. Chromatographic separation was achieved using a methanol–formic acid–water gradient on a 50 × 4.6 mm, 2.6 µm Kinetex phenyl-hexyl column (Phenomenex, Torrance, California) kept at 40 °C. Samples were prepared by the "dilute and shoot" method and hydrolyzed with β-glucuronidase prior to analysis. Thus, calculated concentrations represent the sum total of both free and conjugated forms. Results were analyzed using Indigo Bio Automation Ascent software (Indianapolis, Indiana), using a 4-point calibration curve with linear fit and $1/x^2$ weighting. Calibrators were deemed acceptable if they were within 20 percent of expected concentrations and with R^2 value greater than 0.98. The inter-assay coefficient of variation (CV) of all analytes at the lower limit of quantitation (cutoff values) were evaluated to be within 20 percent (most were within 10 percent CV). Tables 3 and 4 list the minimum cutoff values for detection of the parent drug and metabolites, and the interfering (DDI) drugs, respectively. For some drugs, such as fluoxetine, bupropion, risperidone, trazodone, aripiprazole, citalopram, and THC, we detected their metabolites to signify the presence of the parent drugs, with metabolites listed respectively as follows: norfluoxetine, hydroxybupropion, 9-hydroxyrisperidone, trazodone-metabolite, dehyroaripiprazole, N-desmethylcitalopram, and THCA (Table 4).

Data and statistical analysis

Metabolic ratio was calculated for the control and DDI-test populations, using urinary concentrations

Table 4. Minimum cutoff values for the detection of the interfering (DDI) drugs

DDI drugs	Cutoff (ng/mL)
Fluoxetine (norfluoxetine)	10
Paroxetine	5
Bupropion (hydroxybupropion)	10
Citalopram (N-desmethylcitalopram)	10
Sertraline	10
Venlafaxine	2
Duloxetine	10
Risperidone (9-hydroxyrisperidone)	5
Trazodone (trazodone-metabolite)	20
Haloperidol	5
Aripiprazole (dehydroaripiprazole)	20
Cyclobenzaprine	5
Amphetamine	25
THC (THCA)	25

THC: tetrahydrocannabinol.

of the analytes in ng/mL, ie, metabolite concentration divided by parent drug concentration. The MR values were then log-transformed for analysis. A two-sample *t*-test was used to assess statistically significant differences, ie, the log-MR mean of samples with an interfering drug was compared against the log-MR mean of the control samples. A critical p-value of 0.05 was set as the threshold, with p-values less than 0.05 considered statistically significant. No adjustment to p-values was made, since we did not make multiple comparisons. The aim of comparisons was not to discern the presence of any effect among the interfering drugs, but to discern how the presence of an interfering drug affects the MR of the control population.

We also measured effect size using Hedges' g, which normalizes the difference in means with respect to the pooled standard deviation (SD) of two populations. For our study, Hedges' g is the difference between the log-MR mean of the DDI population (M_1) and the log-MR mean of the population filtered for DDIs (M_2), divided by the pooled standard deviation (SD^{pooled}).[68,69] The pooled SD is calculated as follows:

$$SD^{pooled} = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 + 1)s_2^2}{n_1 + n_2 - 2}},$$

where n_1 and s_1^2 are the sample size and variance of the first population, n^2 and s_2^2 are the sample size and variance of the second population. Hedges' g is then calculated as follows:

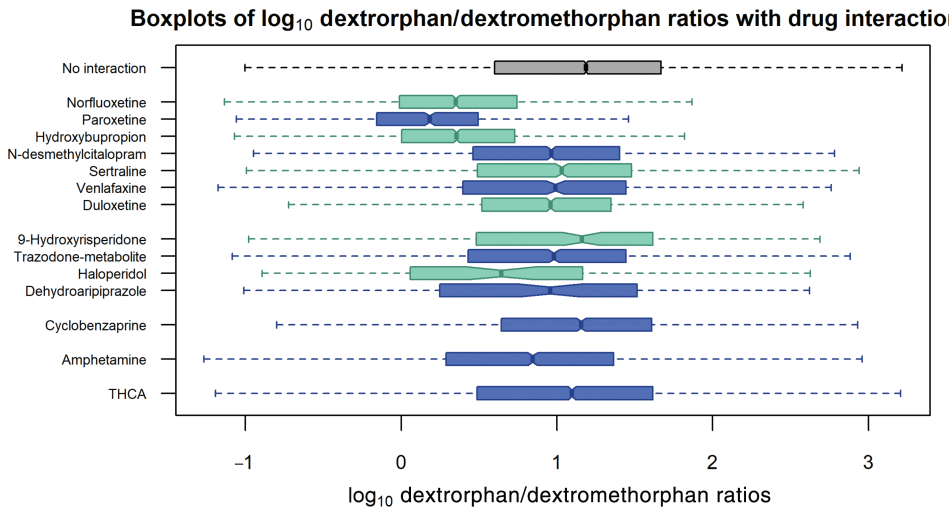
$$g = \frac{M_1 - M_2}{SD^{pooled}}.$$

A correction factor of $\left(\frac{N-3}{N-2.25}\right) \times \sqrt{\frac{N-2}{N}}$ is multiplied by g to account for inflated bias in the case of low sample sizes, where $n = n_1 + n_2 < 50$. A rule of thumb for interpreting g, from Cohen,[70,71] is counting 0.2 as a small effect, 0.5 as a medium effect, and >0.8 as a large effect. However, these interpretations should be used with caution, as the analysis here concerns log-MR values: A seemingly small effect under log values may appear large when considered in the arithmetic space. The negative sign indicates a decrease in the MR, and vice versa.

Data extraction, MR calculations, statistical analysis and Hedges' g calculations were performed in RStudio using the R language.[72,73] Graphs were generated using base R and the ggplot package.

RESULTS

Figures 1-18 show the MRs (log-transformed) for each of the metabolite/parent drug pairs under examined DDIs. The control population, defined as those with no interfering drugs present, is designated as "No interaction," while subsequent DDI-test populations are designated based on the presence of the interfering drug. For example, "Norfluoxetine" indicates patient samples positive for norfluoxetine and reflect the effect of fluoxetine (parent drug) on the MR. In each boxplot, the box depicts the interquartile range (IQR) of the log-MR data, with the lower and upper boundaries representing the first and third quartiles, respectively. The line inside the box represents the median MR, and the whiskers extending from the box show the minimum and maximum values. The accompanying table contains the median, mean, SD, IQR, number of patients, number of observations, p-value and Hedges' g for the log-MR of the control and each of the DDI-test groups. With a sufficiently large sample size, a



(a)

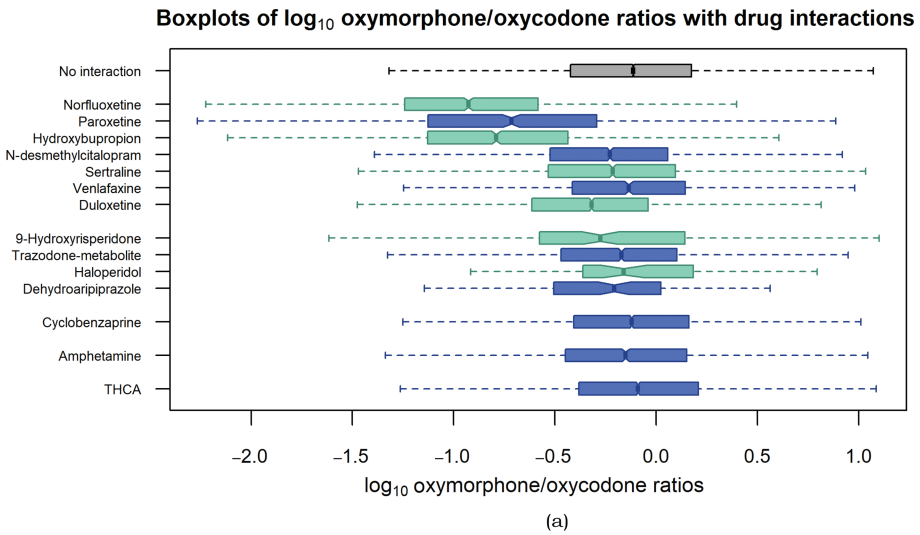
DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	1.19	1.07	0.83	(0.6, 1.67)	18,250	26,342	NA	NA
Norfluoxetine	0.35	0.37	0.60	(–0.01, 0.74)	1,777	2,682	<0.001	–0.85
Paroxetine	0.18	0.18	0.51	(–0.16, 0.49)	594	915	<0.001	–1.10
Hydroxybupropion	0.36	0.37	0.55	(0, 0.73)	1,958	2,922	<0.001	–0.86
N-desmethylcitalopram	0.96	0.88	0.77	(0.46, 1.4)	2,006	2,827	<0.001	–0.23
Sertraline	1.03	0.92	0.81	(0.49, 1.48)	1,305	1,765	<0.001	–0.17
Venlafaxine	0.99	0.90	0.79	(0.4, 1.44)	634	862	<0.001	–0.21
Duloxetine	0.96	0.88	0.70	(0.52, 1.35)	1,617	2,152	<0.001	–0.23
9-Hydroxyrisperidone	1.16	1.03	0.83	(0.48, 1.62)	173	231	0.52	–0.04
Trazodone-metabolite	0.98	0.89	0.80	(0.43, 1.44)	1,420	1,956	<0.001	–0.22
Haloperidol	0.64	0.58	0.79	(0.07, 1.16)	51	66	<0.001	–0.58
Dehydroaripiprazole	0.96	0.85	0.87	(0.26, 1.5)	85	104	0.01	–0.27
Cyclobenzaprine	1.16	1.05	0.79	(0.64, 1.61)	2,125	2,737	0.26	–0.02
Amphetamine	0.84	0.82	0.79	(0.29, 1.36)	2,230	2,855	<0.001	–0.30
THCA	1.10	1.00	0.85	(0.49, 1.62)	3,571	4,757	<0.001	–0.08

(b)

Figure 1. Boxplots and table of statistics for dextrorphan/dextromethorphan log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of dextrorphan/dextromethorphan log-ratios, filtered for DDIs. (b) Table of statistics for dextrorphan/dextromethorphan log-ratios, filtered for DDIs.

significant p-value can result even when differences between two groups are very small. Thus, to fully understand the results, we also report Hedges' g, which is a statistical measure of effect size, or the magnitude of difference between two groups.[74] Table 5 summarizes these estimated DDI effects on the MRs, based on observed statistically significant differences between control and DDI group ($p < 0.05$). The symbol "–" indicates an inhibitory effect on metabolism, "+" indicates enhanced metabolism, while "0" indicates no effect on metabolism.

These results illustrate patterns in DDI influence. We observed the strong inhibitory effect of fluoxetine, paroxetine, and bupropion on the metabolism of dextromethorphan, oxycodone, hydrocodone, and tramadol. In this case, the MRs of dextrorphan/dextromethorphan, oxymorphone/oxycodone, hydromorphone/hydrocodone, and O-desmethyltramadol/tramadol significantly decreased in the presence of these drugs, with Hedges' $g > 0.8$ indicating large effect (Figures 1-4). These are processed in large part by the CYP2D6 pathway. Fluoxetine, paroxetine, and bupropion also decreased MR of hydromorphone/morphine, with small, measured effect (Hedges' $g \leq 0.2$) (Figure 5). Fluoxetine and bupropion moderately/



(a)

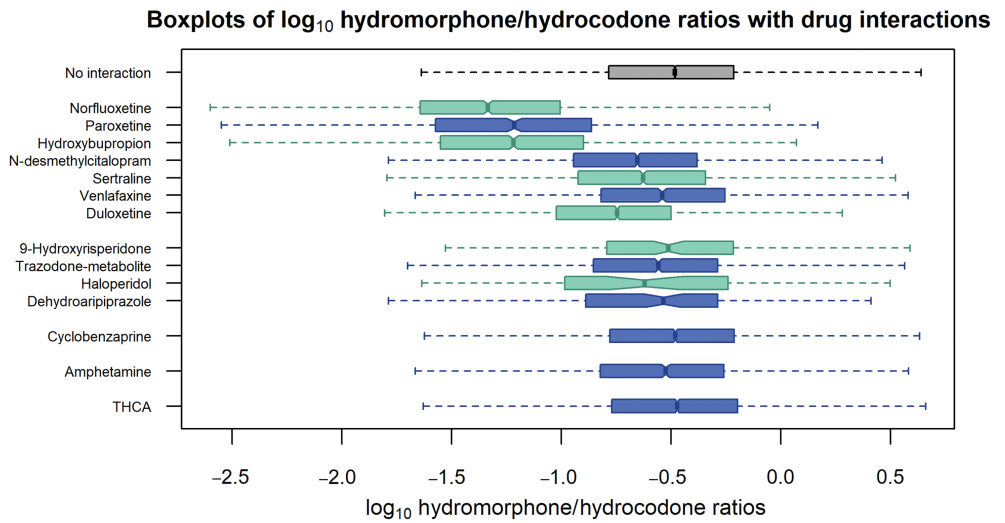
DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	−0.11	−0.18	0.66	(−0.42, 0.18)	32,833	71,363	NA	NA
Norfluoxetine	−0.93	−0.92	0.56	(−1.24, −0.58)	1,368	2,410	<0.001	−1.10
Paroxetine	−0.72	−0.72	0.59	(−1.13, −0.29)	508	974	<0.001	−0.81
Hydroxybupropion	−0.79	−0.78	0.54	(−1.13, −0.43)	1,338	2,405	<0.001	−0.90
N-desmethylcitalopram	−0.23	−0.26	0.53	(−0.52, 0.06)	2,699	4,862	<0.001	−0.12
Sertraline	−0.21	−0.25	0.58	(−0.53, 0.09)	1,876	3,354	<0.001	−0.10
Venlafaxine	−0.13	−0.14	0.51	(−0.41, 0.14)	1,042	1,923	<0.001	0.07
Duloxetine	−0.32	−0.35	0.52	(−0.61, −0.04)	3,585	6,469	<0.001	−0.25
9-Hydroxyrisperidone	−0.28	−0.25	0.57	(−0.57, 0.14)	108	164	0.13	−0.10
Trazodone-metabolite	−0.17	−0.20	0.53	(−0.47, 0.1)	2,157	3,709	0.02	−0.03
Haloperidol	−0.16	−0.19	0.64	(−0.36, 0.18)	51	63	0.93	−0.01
Dehydroaripiprazole	−0.21	−0.28	0.50	(−0.5, 0.02)	78	122	0.03	−0.15
Cyclobenzaprine	−0.12	−0.15	0.56	(−0.41, 0.16)	5,890	10,221	<0.001	0.05
Amphetamine	−0.15	−0.21	0.67	(−0.45, 0.15)	1,649	2,722	0.06	−0.04
THCA	−0.09	−0.13	0.62	(−0.38, 0.21)	7,007	13,654	<0.001	0.08

(b)

Figure 2. Boxplots and table of statistics for oxymorphone/oxycodone log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of oxycodone/oxymorphone log-ratios, filtered for DDIs. (b) Table of statistics for oxymorphone/oxycodone log-ratios, filtered for DDIs.

weakly decreased MR of α-hydroxyalprazolam/alprazolam (Hedges' g of 0.63 and 0.34, respectively) (Figure 11), while fluoxetine weakly decreased MR of meprobamate/carisoprodol (Hedges' g < 0.2) (Figure 13). Fluoxetine, paroxetine, and bupropion also enhanced the metabolism of some drugs. In this case, the MRs of norbuprenorphine/buprenorphine (Figure 6), noroxycodone/oxycodone (Figure 8), norhydrocodone/hydrocodone (Figure 9), norquetiapine/quetiapine (Figure 12), 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)/methadone (Figure 16), and nortriptyline/amitriptyline (Figure 18) slightly increased in the presence of these drugs; however, the measured effects were relatively small (Hedges' g < 0.2-0.29). The MR of desipramine/imipramine also increased in the presence of these drugs, with Hedges' g > 0.5-0.8 indicating large effect (Figure 17); however, only the effect of bupropion was statistically significant. MRs of the remaining drug pairs were not affected by fluoxetine, paroxetine, and bupropion. These were norfentanyl/fentanyl (Figure 7), 7-aminoclonazepam/clonazepam (Figure 10), meprobamate/carisoprodol (Figure 13), N-desmethyltapentadol/tapentadol (Figure 14), and norketamine/ketamine (Figure 15).

We observe the weak inhibitory effects of citalopram, sertraline, venlafaxine, duloxetine, trazodone,



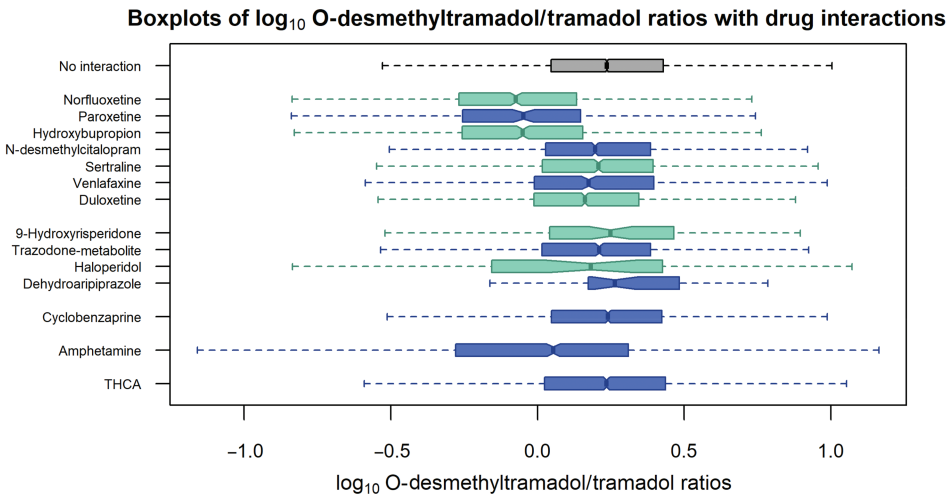
(a)

DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	−0.48	−0.52	0.50	(−0.78, −0.21)	33,747	71,509	NA	NA
Norfluoxetine	−1.33	−1.31	0.53	(−1.64, −1)	1,504	2,626	<0.001	−1.60
Paroxetine	−1.21	−1.21	0.51	(−1.57, −0.86)	671	1,157	<0.001	−1.40
Hydroxybupropion	−1.22	−1.20	0.49	(−1.55, −0.9)	1,472	2,558	<0.001	−1.40
N-desmethylcitalopram	−0.65	−0.67	0.47	(−0.94, −0.38)	3,431	6,216	<0.001	−0.31
Sertraline	−0.63	−0.65	0.49	(−0.92, −0.34)	2,324	4,150	<0.001	−0.26
Venlafaxine	−0.54	−0.56	0.50	(−0.82, −0.25)	1,219	2,180	<0.001	−0.08
Duloxetine	−0.75	−0.76	0.45	(−1.02, −0.5)	3,898	7,126	<0.001	−0.49
9-Hydroxyrisperidone	−0.51	−0.52	0.48	(−0.79, −0.22)	112	189	0.90	0.01
Trazodone-metabolite	−0.56	−0.58	0.49	(−0.85, −0.29)	2,185	3,577	<0.001	−0.12
Haloperidol	−0.62	−0.63	0.59	(−0.98, −0.25)	38	50	0.20	−0.22
Dehydroaripiprazole	−0.54	−0.61	0.45	(−0.88, −0.29)	80	132	0.03	−0.17
Cyclobenzaprine	−0.48	−0.51	0.49	(−0.78, −0.21)	6,112	10,523	0.16	0.02
Amphetamine	−0.52	−0.54	0.51	(−0.82, −0.26)	1,381	2,223	0.05	−0.04
THCA	−0.47	−0.50	0.50	(−0.77, −0.2)	5,891	10,668	<0.001	0.05

(b)

Figure 3. Boxplots and table of statistics for hydromorphone/hydrocodone log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of hydromorphone/hydrocodone log-ratios, filtered for DDIs. (b) Table of statistics for hydromorphone/hydrocodone log-ratios, filtered for DDI.

and aripiprazole on the metabolism of dextromethorphan, oxycodone, hydrocodone, tramadol, and morphine. The MRs of dextrorphan/dextromethorphan, oxymorphone/oxycodone, hydromorphone/hydrocodone, O-desmethyltramadol/tramadol, and hydromorphone/morphine decreased slightly in the presence of these drugs; except for the moderate effect on hydrocodone (Hedges' g = 0.49), the measured effects were relatively small (Hedges' g < 0.25). Duloxetine, trazodone, and aripiprazole did not affect the metabolism of morphine to hydromorphone. Risperidone and haloperidol did not affect the metabolism of oxycodone (oxymorphone), hydrocodone (hydromorphone), tramadol, and morphine. Risperidone also did not affect the metabolism of dextromethorphan, while haloperidol moderately decreased MR of dextrorphan/dextromethorphan (Hedges' g = 0.58). Risperidone significantly increased MR of norketamine/ketamine (Hedges' g = 1.30), while venlafaxine moderately decreased MR of norketamine/ketamine (Hedges' g = 0.38). Citalopram, sertraline, venlafaxine, duloxetine, risperidone, trazodone, haloperidol, and aripiprazole weakly enhanced the metabolism of the



(a)

DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	0.24	0.23	0.32	(0.05, 0.43)	17,376	29,705	NA	NA
Norfluoxetine	–0.07	–0.06	0.34	(–0.27, 0.13)	698	1,034	<0.001	–0.91
Paroxetine	–0.05	–0.05	0.33	(–0.25, 0.15)	224	306	<0.001	–0.89
Hydroxybupropion	–0.05	–0.05	0.33	(–0.26, 0.15)	700	1,005	<0.001	–0.88
N-desmethylcitalopram	0.20	0.20	0.31	(0.03, 0.39)	1,702	2,565	<0.001	–0.09
Sertraline	0.21	0.21	0.30	(0.02, 0.39)	1,046	1,599	<0.001	–0.08
Venlafaxine	0.17	0.19	0.31	(–0.01, 0.4)	523	763	<0.001	–0.14
Duloxetine	0.16	0.16	0.30	(–0.01, 0.35)	1,779	2,598	<0.001	–0.22
9-Hydroxyrisperidone	0.25	0.24	0.31	(0.04, 0.47)	59	93	0.69	0.04
Trazodone-metabolite	0.21	0.21	0.30	(0.01, 0.39)	1,250	1,867	<0.001	–0.08
Haloperidol	0.18	0.16	0.41	(–0.16, 0.43)	34	37	0.27	–0.24
Dehydroaripiprazole	0.26	0.32	0.25	(0.17, 0.48)	27	42	0.02	0.28
Cyclobenzaprine	0.24	0.23	0.31	(0.05, 0.42)	2,686	3,903	0.70	–0.01
Amphetamine	0.05	0.01	0.43	(–0.28, 0.31)	1,341	1,687	<0.001	–0.67
THCA	0.24	0.23	0.33	(0.02, 0.44)	2,886	4,130	0.32	–0.02

(b)

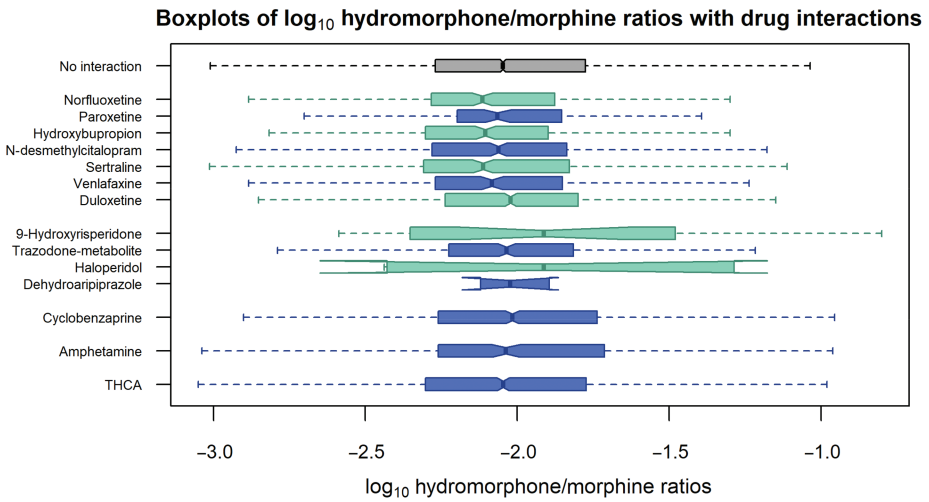
Figure 4. Boxplots and table of statistics for O-desmethyltramadol/tramadol log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of O-desmethyltramadol/tramadol log-ratios, filtered for DDIs. (b) Table of statistics for O-desmethyltramadol/tramadol log-ratios, filtered for DDI.

remaining drugs. These include buprenorphine, fentanyl, oxycodone (noroxycodone), hydrocodone (norhydrocodone), and clonazepam. The measured DDI effects were relatively small (Hedges' g ≤ 0.1-0.3), except for the moderate effects of haloperidol on the metabolism of fentanyl (Hedges' g = 0.41), and aripiprazole on clonazepam (Hedges' g < 0.43). The metabolism of carisoprodol, tapentadol, and imipramine were not affected by most interfering drugs in this study.

Cyclobenzaprine weakly affected the metabolism of most drugs, with Hedges' g ranging from 0.02 to 0.3, indicating very small to small effects. Amphetamine decreased MR of dextrorphan/dextromethorphan and O-desmethyltramadol/tramadol, with small to moderate effects (Hedges' g of 0.30 and 0.67, respectively). Amphetamine enhanced the metabolism of remaining drugs, with effects ranging from very small to moderate (Hedges' g < 0.04-0.4). The overall DDI effect of THC is enhanced metabolism, with measured effects ranging from very small to moderate (Hedges' g < 0.04-0.4).

DISCUSSION

Our hypothesis is that the MR reflects the activity of the metabolic pathway converting the drug. Urinary concentrations of a drug and its metabolite



(a)

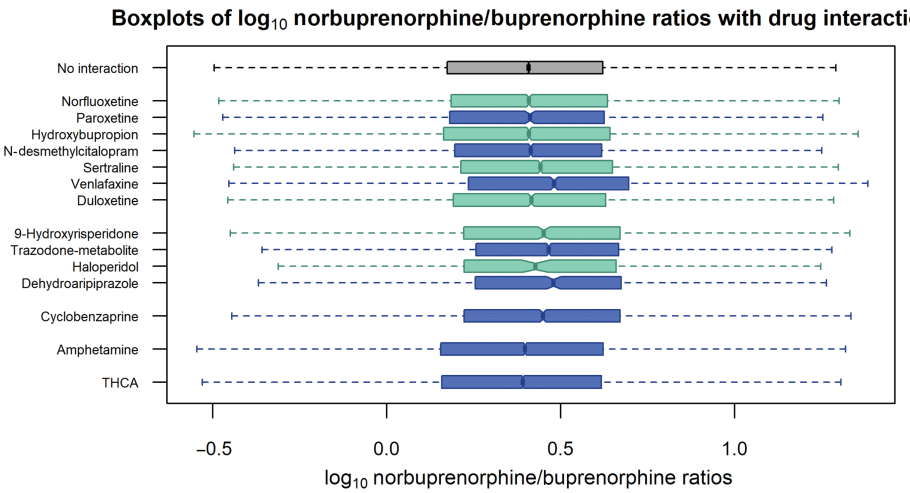
DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	−2.05	−1.97	0.50	(−2.27, −1.78)	4,205	8,418	NA	NA
Norfluoxetine	−2.12	−2.06	0.42	(−2.28, −1.88)	214	395	<0.001	−0.17
Paroxetine	−2.07	−2.05	0.33	(−2.2, −1.85)	86	163	0.005	−0.15
Hydroxybupropion	−2.11	−2.08	0.37	(−2.3, −1.9)	213	391	<0.001	−0.21
N-desmethylcitalopram	−2.06	−2.03	0.40	(−2.28, −1.84)	404	703	<0.001	−0.11
Sertraline	−2.11	−2.04	0.48	(−2.31, −1.83)	302	536	0.002	−0.13
Venlafaxine	−2.08	−2.02	0.40	(−2.27, −1.85)	194	341	0.02	−0.10
Duloxetine	−2.02	−1.97	0.42	(−2.24, −1.8)	729	1,293	0.82	−0.01
9-Hydroxyrisperidone	−1.91	−1.86	0.50	(−2.35, −1.48)	14	25	0.29	0.22
Trazodone-metabolite	−2.03	−1.98	0.45	(−2.23, −1.82)	327	572	0.86	−0.01
Haloperidol	−1.91	−1.52	1.24	(−2.35, −1.39)	6	6	0.42	0.90
Dehydroaripiprazole	−2.02	−2.00	0.42	(−2.12, −1.89)	5	5	0.89	−0.06
Cyclobenzaprine	−2.02	−1.95	0.47	(−2.26, −1.74)	780	1,453	0.14	0.04
Amphetamine	−2.04	−1.93	0.56	(−2.26, −1.72)	220	376	0.12	0.09
THCA	−2.05	−1.98	0.54	(−2.3, −1.77)	947	1,748	0.36	−0.03

(b)

Figure 5. Boxplots and table of statistics for hydromorphone/morphine log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of hydromorphone/morphine log-ratios, filtered for DDIs. (b) Table of statistics for hydromorphone/morphine log-ratios, filtered for DDIs.

reflect the end result of drug metabolism and thus offer a way to test this hypothesis. Some of the SNRI class of antidepressants are known to be strong inhibitors of the CYP2D6 metabolic pathway of drugs. We examined MRs to determine the possible effects of these SNRI antidepressants. Our logic was that if there was inhibition of the CYP2D6 or other CYP pathways, this would be reflected by changes in the MR. If the metabolism was not affected by these SNRI drugs, then there should be no change in the MR in the presence or absence of these inhibitors. The metabolic pathways of the chosen drug pairs in this study are well described, and it was expected that those drugs processed by the CYP2D6 pathway would be affected, and those metabolites not processed by this pathway would not be affected.

The data show that fluoxetine, paroxetine, and bupropion are powerful inhibitors of the CYP2D6 pathway. The MRs of dextrorphan/dextromethorphan, oxymorphone/oxycodone, hydromorphone/hydrocodone, and O-desmethyltramadol/tramadol largely decreased in the presence of these DDIs, indicating strong inhibition of metabolism. These drug pairs are processed in large part by CYP2D6. Data are consistent with previous studies that showed fluoxetine, paroxetine, and bupropion are



(a)

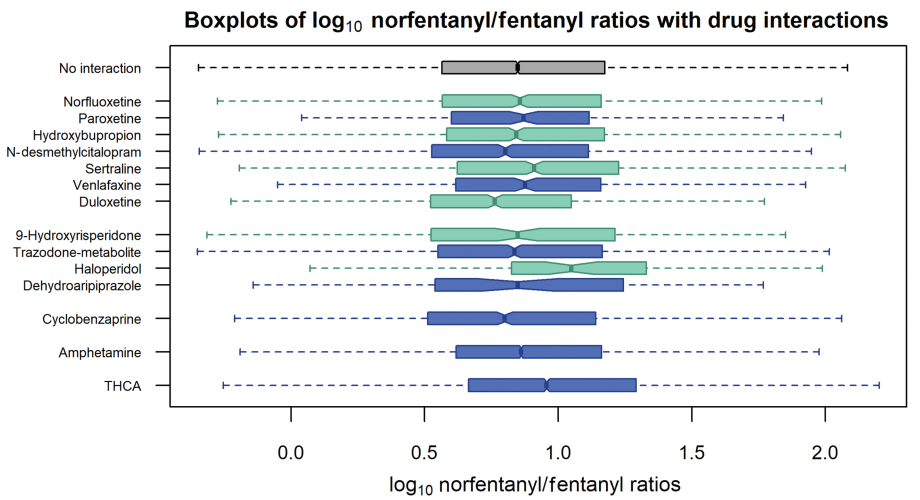
DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	0.41	0.34	0.52	(0.17, 0.62)	37,793	184,537	NA	NA
Norfluoxetine	0.41	0.39	0.36	(0.19, 0.63)	2,432	8,866	<0.001	0.10
Paroxetine	0.41	0.38	0.38	(0.18, 0.62)	658	2,630	<0.001	0.08
Hydroxybupropion	0.41	0.39	0.37	(0.16, 0.64)	3,979	14,399	<0.001	0.09
N-desmethylcitalopram	0.41	0.39	0.37	(0.2, 0.62)	3,760	13,653	<0.001	0.09
Sertraline	0.44	0.41	0.38	(0.21, 0.65)	2,717	10,726	<0.001	0.14
Venlafaxine	0.48	0.45	0.42	(0.24, 0.7)	1,263	4,600	<0.001	0.21
Duloxetine	0.42	0.40	0.36	(0.19, 0.63)	1,838	5,573	<0.001	0.11
9-Hydroxyrisperidone	0.45	0.43	0.38	(0.22, 0.67)	544	1,605	<0.001	0.17
Trazodone-metabolite	0.47	0.45	0.33	(0.26, 0.67)	4,164	10,944	<0.001	0.21
Haloperidol	0.43	0.42	0.42	(0.22, 0.66)	194	305	<0.001	0.15
Dehydroaripiprazole	0.48	0.46	0.34	(0.26, 0.67)	400	1,038	<0.001	0.23
Cyclobenzaprine	0.45	0.42	0.44	(0.22, 0.67)	2,450	5,320	<0.001	0.15
Amphetamine	0.40	0.35	0.47	(0.15, 0.62)	9,811	29,676	0.31	0.01
THCA	0.39	0.36	0.42	(0.16, 0.62)	14,510	60,575	<0.001	0.04

(b)

Figure 6. Boxplots and table of statistics for norbuprenorphine/buprenorphine log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of norbuprenorphine/buprenorphine log-ratios, filtered for DDIs. (b) Table of statistics for norbuprenorphine/buprenorphine log-ratios, filtered for DDIs.

potent inhibitors of CYP2D6.[4,5,7,22] The MR of hydromorphone/morphine was slightly decreased by fluoxetine, paroxetine, and bupropion, indicating weak inhibition and minor involvement of CYP2D6 in its metabolism. We also observed that coadministration of fluoxetine, paroxetine, or bupropion resulted in a small increase in the MR of norhydrocodone/hydrocodone, and noroxycodone/oxycodone, indicating a weak enhanced metabolism. It is possible that inhibition of the CYP2D6 pathway leads to enhanced metabolism of the alternate CYP3A4 pathway. This produces greater amounts of the norhydrocodone and noroxycodone resulting in higher MRs.

We noted the effect of fluoxetine, paroxetine, and bupropion on the MR of desipramine/imipramine. The MR of desipramine/imipramine largely increased in the presence of these DDIs. However, the differences between fluoxetine and paroxetine with the control were not statistically significant, probably due to the small sample sizes. Imipramine is metabolized to desipramine mainly by CYP2C19, with minor contributions from CYP1A2 and CYP3A4.[44,75] Desipramine subsequently undergoes further hydroxylation by CYP2D6. The higher MR of desipramine/imipramine indicates inhibition by fluoxetine, paroxetine, and bupropion of the CYP2D6-mediated hydroxylation of desipramine.



(a)

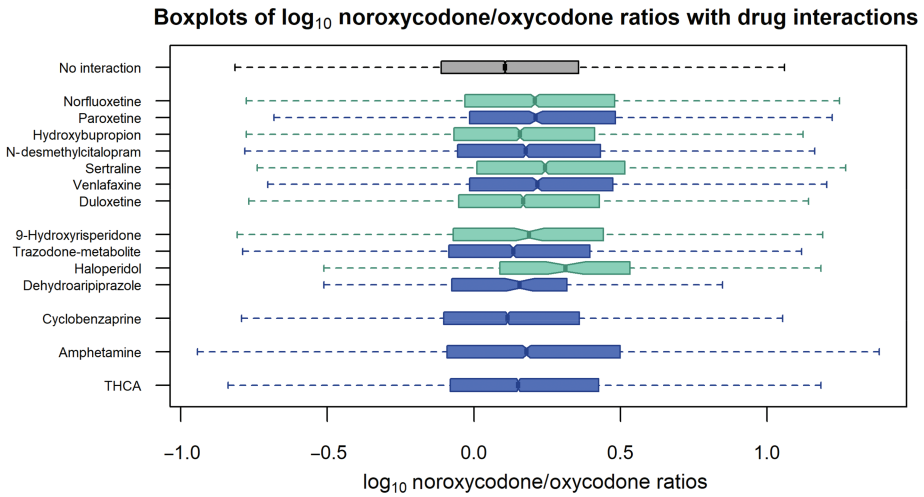
DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	0.85	0.87	0.47	(0.57, 1.17)	11,861	22,085	NA	NA
Norfluoxetine	0.86	0.86	0.43	(0.57, 1.16)	594	1,007	0.50	–0.02
Paroxetine	0.87	0.88	0.40	(0.6, 1.12)	146	247	0.50	0.04
Hydroxybupropion	0.84	0.88	0.44	(0.58, 1.17)	710	1,173	0.30	0.03
N-desmethylcitalopram	0.80	0.83	0.44	(0.53, 1.11)	821	1,408	0.002	–0.08
Sertraline	0.91	0.94	0.44	(0.62, 1.23)	575	911	<0.001	0.16
Venlafaxine	0.88	0.88	0.48	(0.62, 1.16)	266	476	0.61	0.03
Duloxetine	0.76	0.80	0.39	(0.52, 1.05)	609	991	<0.001	–0.15
9-Hydroxyrisperidone	0.85	0.86	0.47	(0.53, 1.21)	131	188	0.88	–0.01
Trazodone-metabolite	0.84	0.86	0.43	(0.55, 1.17)	1,248	1,687	0.67	–0.01
Haloperidol	1.05	1.06	0.44	(0.83, 1.33)	68	73	<0.001	0.41
Dehydroaripiprazole	0.85	0.88	0.43	(0.54, 1.24)	48	59	0.84	0.02
Cyclobenzaprine	0.80	0.84	0.43	(0.51, 1.14)	869	1,207	0.02	–0.06
Amphetamine	0.86	0.90	0.40	(0.62, 1.16)	9,652	18,171	<0.001	0.07
THCA	0.96	0.97	0.44	(0.66, 1.29)	5,498	9,735	<0.001	0.24

(b)

Figure 7. Boxplots and table of statistics for norfentanyl/fentanyl log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of norfentanyl/fentanyl log-ratios, filtered for DDIs. (b) Table of statistics for norfentanyl/fentanyl log-ratios, filtered for DDIs.

This reduces clearance of desipramine that results in increased desipramine concentration, which in turn increases the ratio of desipramine to imipramine. Pharmacokinetic interactions between fluoxetine or paroxetine and desipramine are well known. Previous studies had shown that coadministration of fluoxetine or paroxetine resulted in a 2- to 5-fold increase in plasma concentration of desipramine, along with signs of toxicity (sedation, dry mouth, urinary retention). This was attributed to inhibition of desipramine 2-hydroxylation by CYP2D6.[76-81] Study also showed 5-fold increase in AUC of desipramine in the presence of bupropion, indicating marked inhibition of desipramine metabolism.[82] Metabolism of amitriptyline was similarly affected as in imipramine—however, with smaller effect size. As tricyclic antidepressants, both imipramine and amitriptyline follow similar metabolic pathways. Our study showed coadministration of paroxetine and bupropion resulted in a slightly higher MR of nortriptyline/amitriptyline. This effect can also be attributed to inhibition of the CYP2D6-mediated hydroxylation of nortriptyline. Some case reports have described nortriptyline toxicity following bupropion cotreatment.[83] Fluoxetine did not affect the metabolism of amitriptyline.

We could not explain our metabolite/parent drug ratios for alprazolam. Alprazolam is extensively



(a)

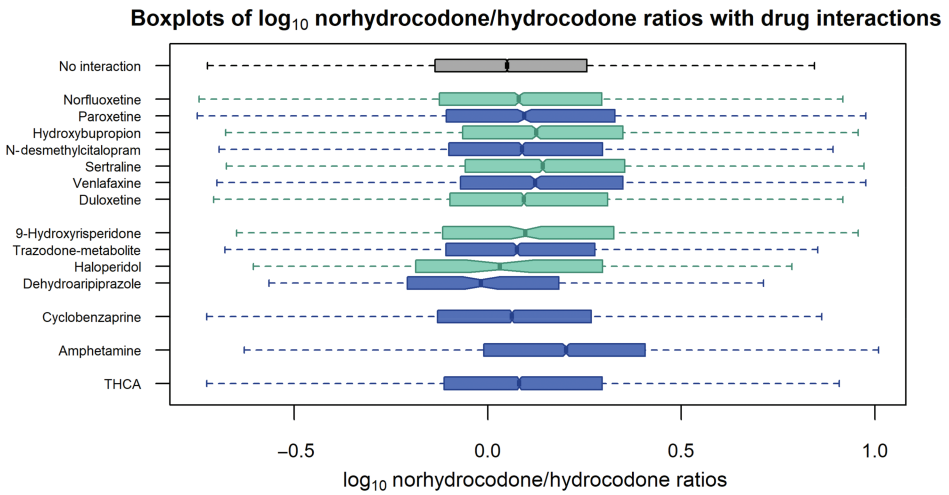
DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	0.11	0.10	0.53	(–0.11, 0.36)	41,198	94,405	NA	NA
Norfluoxetine	0.21	0.24	0.46	(–0.03, 0.48)	1,811	3,416	<0.001	0.26
Paroxetine	0.21	0.25	0.41	(–0.01, 0.48)	658	1,295	<0.001	0.29
Hydroxybupropion	0.16	0.19	0.41	(–0.07, 0.41)	1,793	3,320	<0.001	0.18
N-desmethylcitalopram	0.18	0.21	0.41	(–0.06, 0.43)	3,471	6,418	<0.001	0.21
Sertraline	0.24	0.27	0.47	(0.01, 0.51)	2,344	4,308	<0.001	0.32
Venlafaxine	0.22	0.26	0.41	(–0.01, 0.47)	1,302	2,508	<0.001	0.30
Duloxetine	0.17	0.21	0.41	(–0.05, 0.43)	4,380	8,195	<0.001	0.21
9-Hydroxyrisperidone	0.19	0.20	0.36	(–0.07, 0.44)	151	276	<0.001	0.19
Trazodone-metabolite	0.14	0.17	0.41	(–0.08, 0.4)	2,788	5,195	<0.001	0.14
Haloperidol	0.31	0.27	0.49	(0.09, 0.52)	77	116	<0.001	0.33
Dehydroaripiprazole	0.16	0.15	0.30	(–0.08, 0.32)	106	161	0.030	0.10
Cyclobenzaprine	0.12	0.14	0.43	(–0.1, 0.36)	7,506	13,669	<0.001	0.08
Amphetamine	0.18	0.19	0.56	(–0.09, 0.5)	2,728	4,392	<0.001	0.18
THCA	0.15	0.17	0.48	(–0.08, 0.43)	10,041	20,682	<0.001	0.14

(b)

Figure 8. Boxplots and table of statistics for noroxycodone/oxycodone log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of noroxycodone/oxycodone log-ratios, filtered for DDIs. (b) Table of statistics for noroxycodone/oxycodone log-ratios, filtered for DDIs.

metabolized in humans, primarily by CYP 3A4, to two major metabolites in the plasma: 4-hydroxyalprazolam and α-hydroxyalprazolam.[37,84,85] However, we observed that fluoxetine and bupropion reduced the MR of α-hydroxyalprazolam/alprazolam, implying CYP2D6 might be involved in its metabolism. Some studies have reported that fluoxetine may decrease the metabolism of alprazolam through inhibition of CYP3A4.[86] The metabolism of alprazolam was also negatively affected by citalopram, sertraline, and duloxetine; however, the effect size was very small.

Our data show that citalopram, sertraline, venlafaxine, duloxetine, trazodone, and aripiprazole are weak inhibitors of CYP2D6, based on their mild inhibition of the metabolism of dextromethorphan, oxycodone, hydrocodone, tramadol, and morphine. In this case, the MRs of dextrorphan/dextromethorphan, oxymorphone/oxycodone, hydromorphone/hydrocodone, O-desmethyltramadol/tramadol, and hydromorphone/morphine slightly decreased in the presence of these DDIs. Results are consistent with previous studies that showed these drugs are weak inhibitors of CYP2D6.[4-6,10-12,14,22] Venlafaxine further moderately decreased the MR of norketamine/ketamine. Metabolism of ketamine to norketamine is mediated mainly by CYP3A4, with minor contributions from CYP2B6 and CYP2C9.[45,87] Venlafaxine



(a)

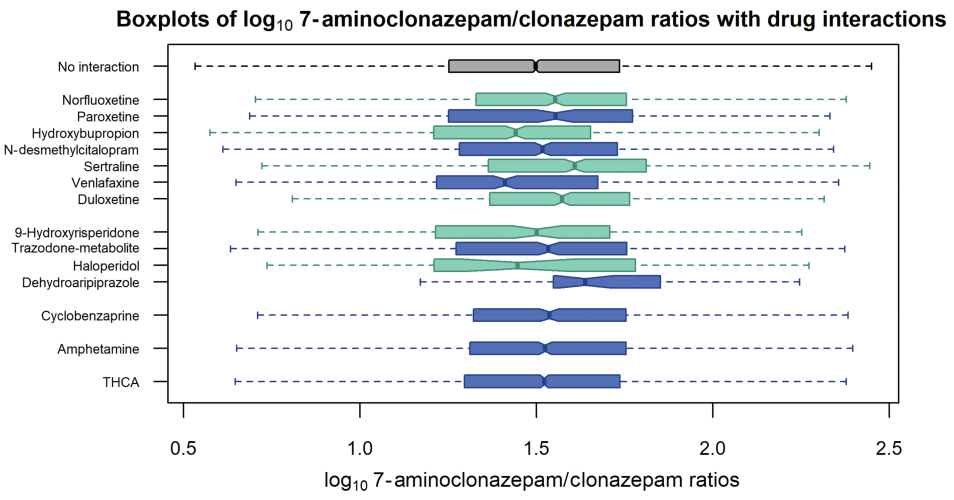
DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	0.05	0.07	0.33	(–0.14, 0.26)	45,705	93,567	NA	NA
Norfluoxetine	0.08	0.10	0.33	(–0.12, 0.29)	2,205	3,766	<0.001	0.11
Paroxetine	0.10	0.12	0.33	(–0.11, 0.33)	911	1,604	<0.001	0.16
Hydroxybupropion	0.13	0.15	0.31	(–0.06, 0.35)	2,090	3,551	<0.001	0.25
N-desmethylcitalopram	0.09	0.11	0.32	(–0.1, 0.3)	4,592	8,247	<0.001	0.14
Sertraline	0.14	0.16	0.32	(–0.06, 0.35)	3,081	5,384	<0.001	0.29
Venlafaxine	0.12	0.15	0.34	(–0.07, 0.35)	1,648	2,835	<0.001	0.27
Duloxetine	0.09	0.12	0.32	(–0.1, 0.31)	5,163	9,240	<0.001	0.16
9-Hydroxyrisperidone	0.10	0.11	0.35	(–0.12, 0.32)	181	316	0.01	0.15
Trazodone-metabolite	0.08	0.10	0.31	(–0.11, 0.28)	2,961	4,833	<0.001	0.09
Haloperidol	0.03	0.05	0.37	(–0.19, 0.3)	67	83	0.77	–0.04
Dehydroaripiprazole	–0.02	0.01	0.29	(–0.21, 0.18)	110	183	0.01	–0.17
Cyclobenzaprine	0.06	0.08	0.32	(–0.13, 0.27)	8,264	13,849	<0.001	0.04
Amphetamine	0.20	0.20	0.33	(–0.01, 0.41)	3,297	5,396	<0.001	0.41
THCA	0.08	0.10	0.34	(–0.11, 0.3)	8,967	15,745	<0.001	0.10

(b)

Figure 9. Boxplots and table of statistics for norhydrocodone/hydrocodone log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of norhydrocodone/hydrocodone log-ratios, filtered for DDIs. (b) Table of statistics for norhydrocodone/hydrocodone log-ratios, filtered for DDIs.

is a minor CYP3A4 substrate, but previous studies reported that venlafaxine had very minimal to nonsignificant inhibitory effect on CYP3A4 activity.[11,88-90] Our data, however, indicate that venlafaxine could potentially inhibit CYP3A4. Furthermore, aripiprazole moderately increased the MR of 7-aminoclonazepam/clonazepam, indicating enhanced metabolism. The metabolism of both clonazepam and aripiprazole is mediated by CYP3A4 and may explain the interaction.

Risperidone did not significantly affect the metabolism of dextromethorphan, oxycodone, hydrocodone, tramadol, and morphine. Results are consistent with study indicating risperidone is a relatively weak CYP2D6 inhibitor and not expected to significantly affect the clearance of drugs metabolized by the CYP2D6 pathway.[91] However, risperidone significantly enhanced the metabolism of ketamine, indicated by the large increase in the MR of norketamine/ketamine in its presence (Hedges' g = 1.30). There is evidence of interaction between ketamine and risperidone.[92] Neuroimaging studies showed that treatment with risperidone attenuated ketamine-induced brain perfusion changes in healthy individuals.[93-95] Although this was attributed to the opposing effects of risperidone and ketamine



(a)

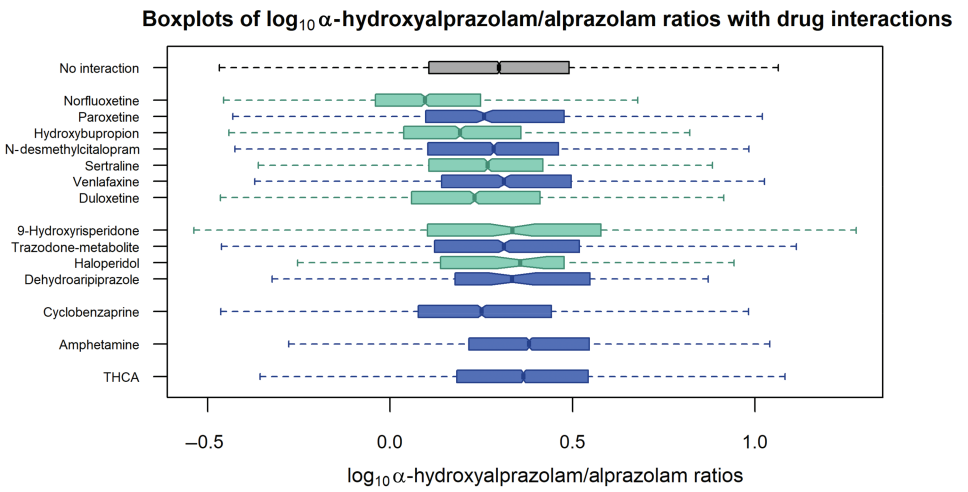
DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	1.50	1.43	0.56	(1.25, 1.74)	3,582	7,721	NA	NA
Norfluoxetine	1.55	1.45	0.60	(1.33, 1.75)	354	652	0.37	0.04
Paroxetine	1.55	1.51	0.37	(1.25, 1.77)	136	253	<0.001	0.15
Hydroxybupropion	1.44	1.42	0.39	(1.21, 1.65)	374	672	0.58	–0.02
N-desmethylcitalopram	1.52	1.50	0.36	(1.28, 1.73)	593	1,075	<0.001	0.14
Sertraline	1.61	1.52	0.53	(1.36, 1.81)	366	662	<0.001	0.17
Venlafaxine	1.41	1.44	0.37	(1.22, 1.67)	292	518	0.55	0.02
Duloxetine	1.57	1.55	0.35	(1.37, 1.76)	409	741	<0.001	0.23
9-Hydroxyrisperidone	1.50	1.42	0.45	(1.21, 1.71)	74	141	0.89	–0.01
Trazodone-metabolite	1.53	1.51	0.35	(1.27, 1.76)	391	654	<0.001	0.16
Haloperidol	1.45	1.50	0.45	(1.23, 1.77)	26	34	0.36	0.13
Dehydroaripiprazole	1.64	1.67	0.26	(1.55, 1.84)	27	38	<0.001	0.43
Cyclobenzaprine	1.54	1.50	0.43	(1.32, 1.75)	438	684	<0.001	0.13
Amphetamine	1.53	1.49	0.49	(1.31, 1.75)	829	1,468	<0.001	0.11
THCA	1.52	1.50	0.38	(1.3, 1.74)	1,526	3,758	<0.001	0.15

(b)

Figure 10. Boxplots and table of statistics for 7-aminoclonazepam/clonazepam log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of 7-aminoclonazepam/clonazepam log-ratios, filtered for DDIs. (b) Table of statistics for 7-aminoclonazepam/clonazepam log-ratios, filtered for DDIs.

at the D_2 receptor, Doyle et al.[93] also noted significantly lower plasma levels of ketamine in the risperidone arm than in the placebo arm (without risperidone). Doyle et al.[93] suggested the possibility that the attenuated ketamine effect was due to risperidone-induced increase in CYP3A4 metabolizing enzymatic activity, resulting in a lowered dose of ketamine. Our results are consistent with findings from Doyle et al.[93]

Haloperidol moderately inhibited metabolism of dextromethorphan, indicated by the moderate decrease in the MR of dextrorphan/dextromethorphan (Hedges' g = 0.58). This result is consistent with previous studies showing strong inhibitory effects of haloperidol on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.[96-98] Haloperidol also moderately increased the MR of norfentanyl/fentanyl (Hedges' g = 0.41). Haloperidol is both a substrate and inhibitor of CYP3A4, and an inhibitor of CYP2D6.[60] Fentanyl is a CYP3A4 substrate, thus one would expect its metabolism to be inhibited by haloperidol. However, we observed a moderately enhanced metabolism of fentanyl by haloperidol. This is in contrast to a previous study that indicated haloperidol has no influence on the pharmacokinetics of fentanyl.[99] Morita et al.,[100] on the other hand, reported development of neuroleptic malignant



(a)

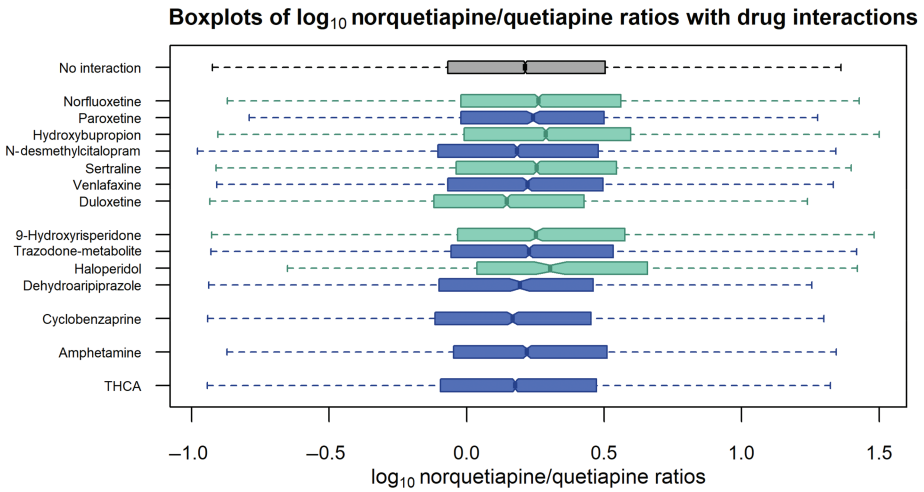
DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	0.30	0.30	0.30	(0.11, 0.49)	13,494	25,898	NA	NA
Norfluoxetine	0.10	0.12	0.25	(–0.04, 0.25)	1,060	1,859	<0.001	–0.63
Paroxetine	0.26	0.30	0.29	(0.1, 0.48)	411	740	0.56	–0.02
Hydroxybupropion	0.19	0.20	0.25	(0.04, 0.36)	941	1,617	<0.001	–0.34
N-desmethylcitalopram	0.28	0.29	0.27	(0.1, 0.46)	2,225	3,795	0.004	–0.05
Sertraline	0.27	0.27	0.25	(0.11, 0.42)	1,311	2,223	<0.001	–0.11
Venlafaxine	0.31	0.32	0.27	(0.14, 0.5)	686	1,258	0.01	0.07
Duloxetine	0.23	0.24	0.27	(0.06, 0.41)	1,324	2,171	<0.001	–0.20
9-Hydroxyrisperidone	0.34	0.35	0.35	(0.1, 0.58)	105	163	0.06	0.18
Trazodone-metabolite	0.31	0.33	0.31	(0.12, 0.52)	980	1,549	<0.001	0.10
Haloperidol	0.36	0.33	0.28	(0.14, 0.47)	45	60	0.51	0.08
Dehydroaripiprazole	0.33	0.36	0.28	(0.18, 0.55)	54	89	0.04	0.21
Cyclobenzaprine	0.25	0.26	0.28	(0.08, 0.44)	1,931	3,067	<0.001	–0.13
Amphetamine	0.38	0.38	0.28	(0.22, 0.55)	2,745	5,157	<0.001	0.27
THCA	0.37	0.37	0.29	(0.18, 0.54)	4,565	8,808	<0.001	0.22

(b)

Figure 11. Boxplots and table of statistics for α-hydroxyalprazolam/alprazolam log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of hydroxyalprazolam/alprazolam log-ratios, filtered for DDIs. (b) Table of statistics for α-hydroxyalprazolam/alprazolam log-ratios, filtered for DDIs.

syndrome in a terminally ill cancer patient after co-administration of fentanyl and haloperidol, although the presence of mineral imbalance could have contributed to the syndrome.

The metabolism of buprenorphine and methadone was not strongly affected by the selective serotonin reuptake inhibitors (SSRI)/SNRI/antipsychotics in this study. CYP3A4 is the main enzyme involved in the metabolism of buprenorphine and methadone.[101-103] However, other CYP enzymes also play a role in their metabolism, including 2B6, 2C19, 2C9, and 2D6 for methadone[104] and 2C8 for buprenorphine.[105] Although we observed a small increase in the MRs of norbuprenorphine/buprenorphine and EDDP/methadone in the presence of these drugs, the measured effects were relatively small (Hedges' g ≤ 0.1-0.2). Previous studies reported no adverse reactions or clinically significant interaction between sertraline, citalopram, or amphetamine with methadone and buprenorphine.[106-108] Fluoxetine was also not associated with clinically important increases in methadone.[109,110] On the other hand, a case report describes a clinically relevant interaction between methadone and duloxetine, wherein coadministration of both drugs resulted in signs of opioid overdose (sweating, drowsiness, fatigability, and pruritus).[111] Authors suggested that this interaction was due to competitive inhibition at the CYP2D6 level, resulting in increased plasma concentration and effects of methadone. We observed a small



(a)

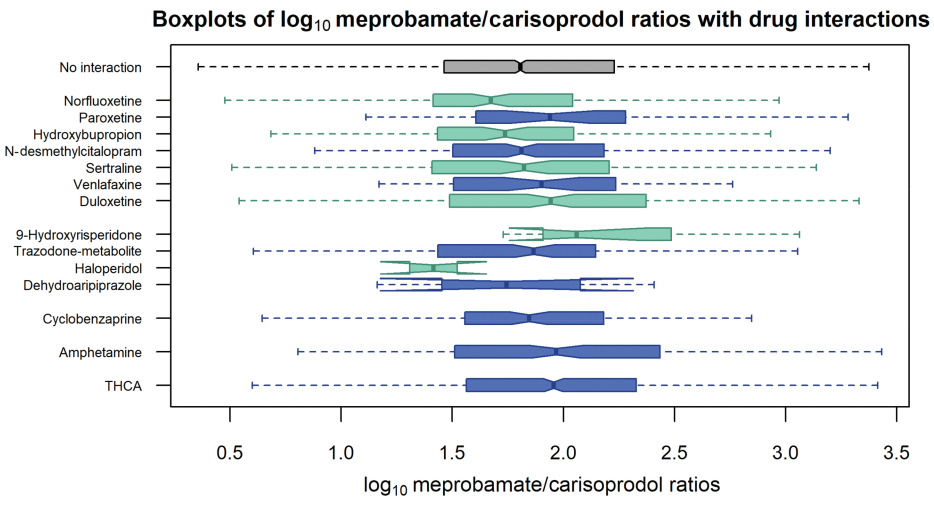
DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	0.21	0.22	0.44	(–0.07, 0.5)	13,497	39,660	NA	NA
Norfluoxetine	0.26	0.28	0.45	(–0.02, 0.56)	1,805	5,349	<0.001	0.13
Paroxetine	0.24	0.24	0.44	(–0.02, 0.5)	492	1,296	0.09	0.05
Hydroxybupropion	0.29	0.30	0.45	(–0.01, 0.6)	2,439	7,483	<0.001	0.17
N-desmethylcitalopram	0.18	0.20	0.45	(–0.1, 0.48)	2,648	7,590	<0.001	–0.05
Sertraline	0.25	0.26	0.45	(–0.04, 0.54)	2,129	5,902	<0.001	0.09
Venlafaxine	0.22	0.22	0.43	(–0.07, 0.5)	1,060	2,993	0.54	–0.01
Duloxetine	0.15	0.16	0.44	(–0.12, 0.43)	1,478	3,922	<0.001	–0.13
9-Hydroxyrisperidone	0.25	0.27	0.47	(–0.03, 0.58)	553	1,697	<0.001	0.12
Trazodone-metabolite	0.23	0.24	0.45	(–0.06, 0.53)	1,846	4,338	0.01	0.04
Haloperidol	0.30	0.34	0.47	(0.04, 0.66)	186	305	<0.001	0.26
Dehydroaripiprazole	0.19	0.21	0.45	(–0.1, 0.46)	270	563	0.49	–0.03
Cyclobenzaprine	0.17	0.17	0.44	(–0.12, 0.45)	1,171	2,214	<0.001	–0.11
Amphetamine	0.22	0.24	0.48	(–0.05, 0.51)	1,853	3,484	0.03	0.04
THCA	0.18	0.20	0.45	(–0.1, 0.47)	3,816	8,526	<0.001	–0.04

(b)

Figure 12. Boxplots and table of statistics for norquetiapine/quetiapine log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of norquetiapine/quetiapine log-ratios, filtered for DDIs. (b) Table of statistics for norquetiapine/quetiapine log-ratios, filtered for DDIs.

decrease in the MR of EDDP/methadone (probably due to increased methadone) in the presence of duloxetine, which supports previous findings.

We also did not observe strong effects of the SSRI/SNRI/antipsychotics on the metabolism of quetiapine, carisoprodol, and tapentadol. Quetiapine is extensively metabolized by CYP3A4, with minor participation of CYP2D6,[38,112,113] while the metabolism of carisoprodol is mediated mainly by CYP2C19.[40] Although we observed slight increase or decrease in the MRs of norquetiapine/quetiapine in the presence of these drugs, the measured effects were relatively small (Hedges' g ≤ 0.1-0.2). For the MR of meprobamate/carisoprodol, the only statistically significant DDI effects were seen in the presence of fluoxetine and duloxetine. For tapentadol, the only significant DDI effect was a moderate increase in the MR of N-desmethyltapentadol/tapentadol by venlafaxine. Tapentadol is extensively metabolized through phase II conjugation (70 percent), while phase I metabolism mediated by CYP2C9, CYP2C19, CYP2B6, and CYP2D6 occurs to a lesser extent (15 percent).[114,115] Previous studies showed that tapentadol has low potential for DDIs involving CYP1A2, CYP2C9, and CYP3A4, and only minimal interaction with CYP2D6.[116-119] The small sample size could have affected some of the DDI results on carisoprodol and tapentadol.



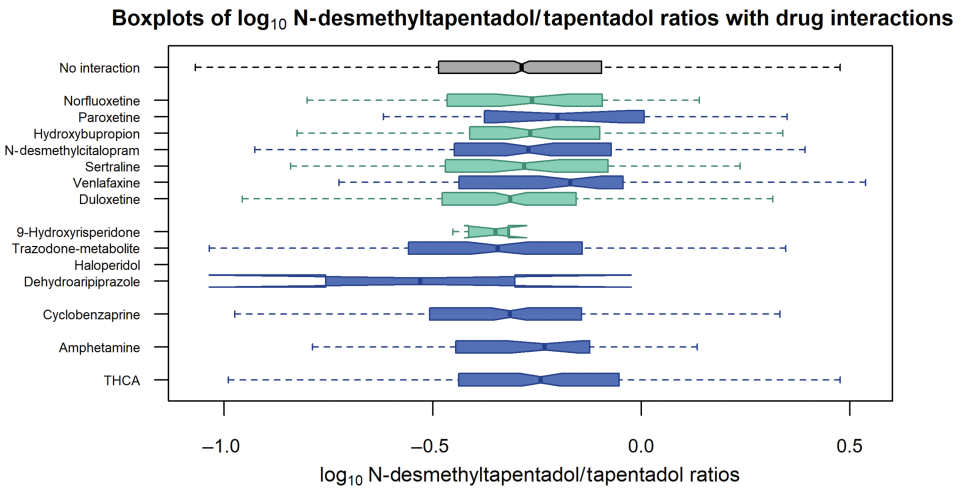
(a)

DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	1.81	1.83	0.66	(1.46, 2.23)	1,497	2,627	NA	NA
Norfluoxetine	1.67	1.74	0.51	(1.42, 2.04)	75	144	0.045	–0.14
Paroxetine	1.94	1.98	0.62	(1.61, 2.28)	20	31	0.17	0.24
Hydroxybupropion	1.74	1.76	0.57	(1.43, 2.03)	68	100	0.24	–0.11
N-desmethylcitalopram	1.81	1.85	0.47	(1.5, 2.18)	127	249	0.48	0.04
Sertraline	1.82	1.79	0.54	(1.41, 2.2)	89	126	0.44	–0.06
Venlafaxine	1.90	1.93	0.42	(1.52, 2.23)	38	50	0.11	0.15
Duloxetine	1.94	1.92	0.56	(1.49, 2.37)	135	196	0.03	0.14
9-Hydroxyrisperidone	2.06	2.12	0.65	(1.91, 2.49)	6	9	0.22	0.44
Trazodone-metabolite	1.87	1.83	0.50	(1.43, 2.15)	107	155	0.93	0.01
Haloperidol	1.42	1.42	0.15	(1.36, 1.47)	2	2	0.16	–0.62
Dehydroaripiprazole	1.75	1.77	0.62	(1.45, 2.08)	3	3	0.90	–0.08
Cyclobenzaprine	1.85	1.84	0.48	(1.56, 2.18)	114	137	0.65	0.03
Amphetamine	1.97	1.91	0.77	(1.51, 2.43)	105	162	0.15	0.13
THCA	1.96	1.92	0.72	(1.56, 2.33)	422	775	<0.001	0.14

(b)

Figure 13. Boxplots and table of statistics for meprobamate/carisoprodol log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of meprobamate/carisoprodol log-ratios, filtered for DDIs. (b) Table of statistics for meprobamate/carisoprodol log-ratios, filtered for DDIs.

We also examined the effects of cyclobenzaprine and amphetamine on the metabolism of the 18 drug pairs. Cyclobenzaprine is metabolized by CYP3A4 and CYP1A2, and to a lesser extent by CYP2D6,[63,64] while amphetamine is metabolized by CYP2D6.[65] Thus, both cyclobenzaprine and amphetamine have the potential for interactions with drugs metabolized by these CYP enzymes. Our data show cyclobenzaprine slightly decreased the MR of norketamine/ketamine, EDDP/methadone, and nortriptyline/amitriptyline, with small, measured effects indicating weak inhibition (Hedges' g ≤ 0.18-0.33). The effects of cyclobenzaprine on the metabolism of the remaining drug pairs were very small (Hedges' g ≤ 0.15). With amphetamine, our data show slight to moderate decrease in the MR of dextrorphan/dextromethorphan (Hedges' g = 0.3), and O-desmethyltramadol/tramadol (Hedges' g = 0.67) in its presence. This suggests amphetamine is a mild to moderate CYP2D6 inhibitor. Amphetamine also increased the MR of noroxycodone/oxycodone, norhydrocodone/hydrocodone, α-hydroxyalprazolam/alprazolam, norketamine/ketamine, and nortriptyline/amitriptyline, indicating enhanced metabolism, with small to moderate measured effects (Hedges' g < 0.18-0.41). It is



(a)

DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	−0.29	−0.29	0.29	(−0.49, −0.1)	620	1,215	NA	NA
Norfluoxetine	−0.26	−0.28	0.24	(−0.46, −0.1)	33	52	0.83	0.03
Paroxetine	−0.20	−0.18	0.28	(−0.37, 0)	9	14	0.18	0.37
Hydroxybupropion	−0.27	−0.26	0.27	(−0.41, −0.1)	36	72	0.36	0.10
N-desmethylcitalopram	−0.27	−0.26	0.29	(−0.45, −0.07)	53	111	0.26	0.11
Sertraline	−0.28	−0.29	0.28	(−0.47, −0.08)	34	58	0.94	0.01
Venlafaxine	−0.17	−0.19	0.28	(−0.44, −0.04)	37	77	0.003	0.35
Duloxetine	−0.31	−0.31	0.27	(−0.48, −0.16)	122	183	0.48	−0.05
9-Hydroxyrisperidone	−0.35	−0.37	0.06	(−0.4, −0.32)	2	4	0.09	−0.26
Trazodone-metabolite	−0.34	−0.34	0.28	(−0.56, −0.14)	59	89	0.12	−0.16
Haloperidol	NA	NA	NA	(NA, NA)	0	0	NA	NA
Dehydroaripiprazole	−0.53	−0.53	0.32	(−0.64, −0.42)	2	2	0.48	−0.82
Cyclobenzaprine	−0.32	−0.33	0.29	(−0.51, −0.14)	112	188	0.09	−0.13
Amphetamine	−0.23	−0.29	0.25	(−0.45, −0.12)	28	35	0.97	0.00
THCA	−0.24	−0.25	0.29	(−0.44, −0.05)	96	163	0.06	0.16

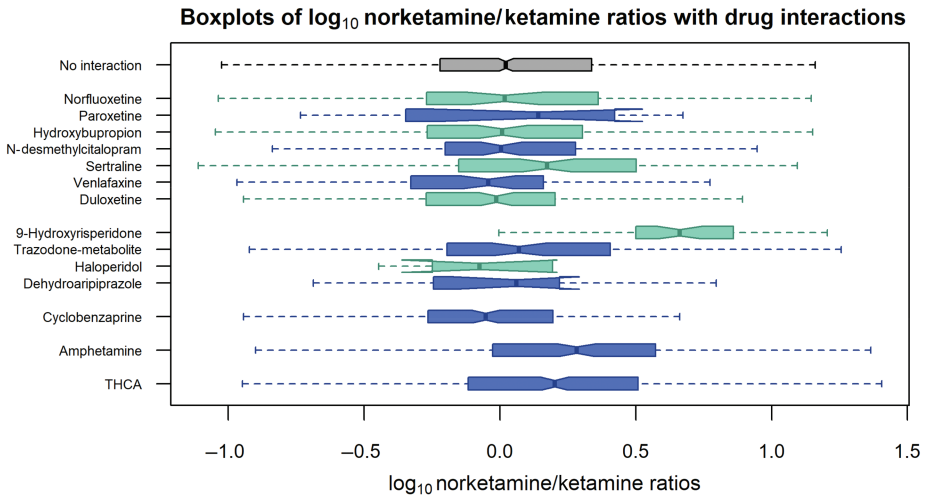
(b)

Figure 14. Boxplots and table of statistics for N-desmethyltapentadol/tapentadol log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of N-desmethyltapentadol/tapentadol log-ratios, filtered for DDIs. (b) Table of statistics for N-desmethyltapentadol/tapentadol log-ratios, filtered for DDIs.

possible that amphetamine inhibits CYP2D6 and causes enhanced metabolism of the alternate CYP pathways in these drug pairs.

We chose to examine cannabinoids as inhibitors, since many physicians or patients use these drugs to treat their pain and other medical conditions.[120,121] THC is metabolized mainly by CYP2C9, CYP2C19, and CYP3A4.[66] In vitro studies by Doohan et al.[122] indicated that cannabinoids such as THC inhibit CYP2C19, while partially inhibiting or not affecting CYP2D6, CYP3A4, and CYP2B6. Our data, however, show increased MRs in most drugs, with small, measured effects (except for the moderate effect on ketamine). We speculate that this implies that for some drugs, metabolism is enhanced by THC, possibly showing the need for increased dosage.

In our studies, many of the SNRI/SSRI drugs were not disclosed. This is a common failing of test requisitions; medication lists are not complete, or the medications are not disclosed to the caregiver. A study by Bordson et al.[123] pointed out this shortcoming of medication lists. A reason this information is important is due to the provider not knowing patients are on these inhibitors, which could reflect on their response to pain and other medications. Coates and Lazarus[20] describe the drug interactions of the opiates hydrocodone, oxycodone, and morphine. However, Coates and Lazarus[20] did not



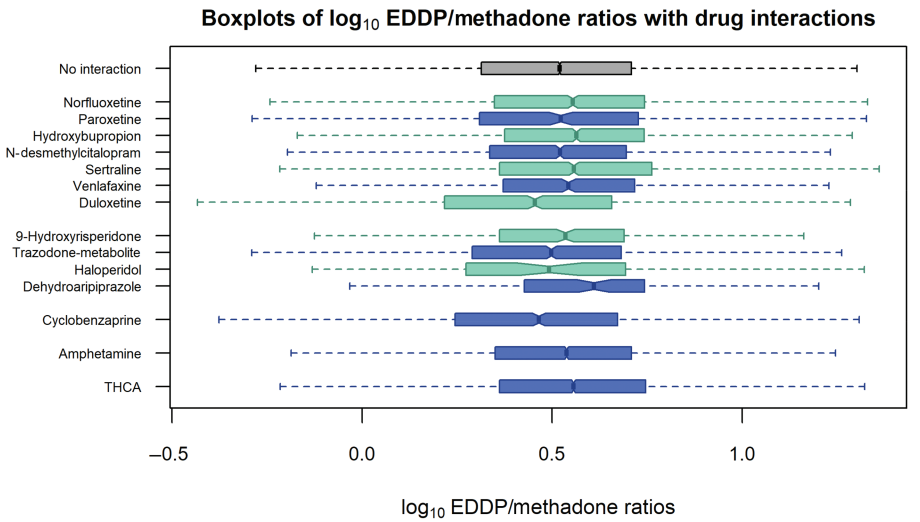
(a)

DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	0.02	0.06	0.44	(–0.22, 0.34)	819	1,077	NA	NA
Norfluoxetine	0.02	0.06	0.46	(–0.27, 0.36)	47	54	0.99	0.00
Paroxetine	0.14	0.07	0.46	(–0.26, 0.36)	10	10	0.95	0.02
Hydroxybupropion	0.01	0.02	0.43	(–0.26, 0.3)	74	104	0.36	–0.09
N-desmethylcitalopram	0.01	0.04	0.41	(–0.2, 0.28)	83	112	0.68	–0.04
Sertraline	0.17	0.16	0.47	(–0.15, 0.5)	59	115	0.04	0.22
Venlafaxine	–0.04	–0.11	0.40	(–0.33, 0.16)	36	63	0.002	–0.38
Duloxetine	–0.01	0.00	0.45	(–0.27, 0.2)	104	154	0.14	–0.13
9-Hydroxyrisperidone	0.66	0.64	0.36	(0.5, 0.86)	22	51	<0.001	1.30
Trazodone-metabolite	0.07	0.08	0.46	(–0.19, 0.41)	77	96	0.61	0.06
Haloperidol	–0.08	0.06	0.51	(–0.24, 0.16)	6	6	0.99	–0.01
Dehydroaripiprazole	0.06	0.04	0.44	(–0.24, 0.2)	7	10	0.90	–0.04
Cyclobenzaprine	–0.05	–0.05	0.40	(–0.26, 0.2)	175	227	<0.001	–0.25
Amphetamine	0.28	0.23	0.45	(–0.03, 0.57)	154	201	<0.001	0.40
THCA	0.20	0.19	0.46	(–0.11, 0.51)	300	406	<0.001	0.29

(b)

Figure 15. Boxplots and table of statistics for norketamine/ketamine log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of norketamine/ketamine log-ratios, filtered for DDIs. (b) Table of statistics for norketamine/ketamine log-ratios, filtered for DDIs.

discuss the drug interactions occurring in the case of metabolic conversion of morphine to hydromorphone. Our observations agree with those of Coates and Lazarus, who noted that hydrocodone was inhibited by paroxetine, resulting in a decrease in hydromorphone AUC with a minimal increase in hydrocodone AUC. They attributed this inhibition to its effect on the CYP2D6 enzyme. They also found that cannabis caused a decrease in hydrocodone plasma levels and an increased absorption rate of hydrocodone. Coates and Lazarus also observed that in the case of oxycodone, paroxetine decreased oxymorphone plasma levels with no significant impact on oxycodone plasma concentration and attributed this effect to the inhibition of CYP2D6. Paroxetine inhibition caused an increase in AUC of oxycodone and noroxycodone; a decrease in oxymorphone plasma levels was considered to be due to the inhibition of CYP2D6. Similarly, fluoxetine and norfluoxetine caused a decrease in oxymorphone formation, and an increase in oxycodone plasma levels as a consequence of the inhibition of CYP2D6 pathway. They also observed that cyclobenzaprine caused a decrease in oxymorphone and noroxycodone formation as an effect of the inhibition of both CYP2D6 and CYP3A4. In their work, they summarized the results of the inhibition by listing inhibiting drugs by CYP450 2D6, which included duloxetine, fluoxetine, paroxetine, and sertraline. We noted similar inhibition of



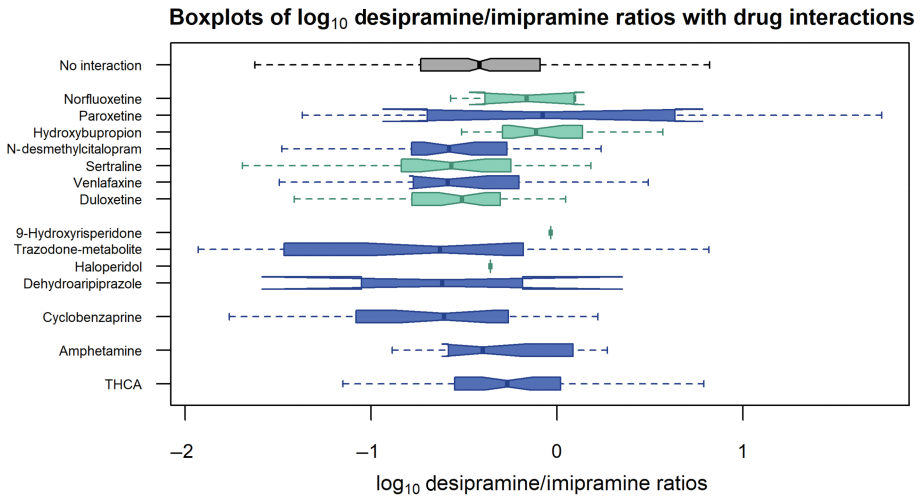
(a)

DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	0.52	0.52	0.33	(0.31, 0.71)	10,554	49,698	NA	NA
Norfluoxetine	0.56	0.55	0.32	(0.35, 0.74)	580	2,099	<0.001	0.11
Paroxetine	0.52	0.51	0.33	(0.31, 0.73)	154	492	0.79	–0.01
Hydroxybupropion	0.56	0.57	0.32	(0.38, 0.74)	756	2,869	<0.001	0.15
N-desmethylcitalopram	0.52	0.52	0.31	(0.34, 0.7)	810	2,526	0.44	0.02
Sertraline	0.56	0.57	0.31	(0.36, 0.76)	681	2,349	<0.001	0.15
Venlafaxine	0.54	0.56	0.30	(0.37, 0.72)	280	937	<0.001	0.14
Duloxetine	0.46	0.44	0.34	(0.22, 0.66)	494	1,306	<0.001	–0.22
9-Hydroxyrisperidone	0.54	0.52	0.26	(0.36, 0.69)	127	494	0.97	0.00
Trazodone-metabolite	0.50	0.49	0.31	(0.29, 0.68)	857	2,057	<0.001	–0.08
Haloperidol	0.49	0.53	0.34	(0.27, 0.69)	53	64	0.66	0.06
Dehydroaripiprazole	0.61	0.59	0.28	(0.43, 0.74)	75	135	0.003	0.22
Cyclobenzaprine	0.47	0.46	0.33	(0.24, 0.67)	768	1,686	<0.001	–0.18
Amphetamine	0.54	0.54	0.30	(0.35, 0.71)	4,228	14,675	<0.001	0.06
THCA	0.56	0.56	0.32	(0.36, 0.75)	4,136	18,103	<0.001	0.15

(b)

Figure 16. Boxplots and table of statistics for 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)/methadone log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of EDDP/methadone log-ratios, filtered for DDIs. (b) Table of statistics for EDDP/methadone log-ratios, filtered for DDIs.

the MR by these drugs. None of the drugs in our study were listed as CYP3A4 inhibitors. Coates and Lazarus made the following clinical suggestions to minimize the effects of these potential inhibitions. Hydrocodone inhibition of CYP3A4 pathway could result in decreased norhydrocodone formation with increases in hydrocodone plasma concentrations. This effect may lead to increases in pharmacodynamic effects, eg, analgesia or respiratory depression. They recommended a decrease in the dosage or frequency of hydrocodone intake and, if possible, removal of CYP3A4 inhibitor from the regimen. In this case, CYP2D6 inhibition of hydrocodone to hydromorphone formation could lead to decreases in pharmacodynamic effect (analgesia). The provider should review patients' genotypes for CYP2D6 and alterations in dosing may be necessary for ultra metabolizing individuals. In summary, using urinary excretion data, the presence of SNRI/SSRI and other drugs that can inhibit or enhance metabolism matches data from other studies. For example, these and other studies clearly show inhibition of the metabolism of some opiate drugs. These inhibiting or enhancing drugs are often not disclosed on medication lists presented to the laboratory. As shown in Table 6, fluoxetine and paroxetine are disclosed as medications 52 and 37 percent of the time, respectively.



(a)

DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	–0.42	–0.43	0.46	(–0.73, –0.09)	147	298	NA	NA
Norfluoxetine	–0.17	–0.18	0.27	(–0.35, 0.04)	6	6	0.08	0.53
Paroxetine	–0.08	0.03	1.09	(–0.6, 0.51)	4	6	0.36	0.95
Hydroxybupropion	–0.11	–0.06	0.41	(–0.29, 0.14)	15	25	<0.001	0.81
N-desmethylcitalopram	–0.58	–0.58	0.43	(–0.78, –0.27)	22	39	0.05	–0.32
Sertraline	–0.57	–0.58	0.44	(–0.83, –0.25)	13	28	0.09	–0.33
Venlafaxine	–0.59	–0.48	0.46	(–0.77, –0.21)	9	19	0.65	–0.11
Duloxetine	–0.51	–0.57	0.47	(–0.78, –0.31)	26	39	0.08	–0.30
9-Hydroxyrisperidone	–0.04	–0.04	NA	(–0.03, –0.03)	1	1	NA	NA
Trazodone-metabolite	–0.63	–0.72	0.82	(–1.46, –0.2)	15	28	0.08	–0.57
Haloperidol	–0.36	–0.36	NA	(–0.36, –0.36)	1	1	NA	NA
Dehydroaripiprazole	–0.62	–0.62	0.61	(–0.84, –0.4)	2	2	0.74	–0.41
Cyclobenzaprine	–0.61	–0.62	0.60	(–1.07, –0.28)	16	26	0.13	–0.40
Amphetamine	–0.40	–0.31	0.39	(–0.58, 0.09)	14	23	0.17	0.26
THCA	–0.27	–0.24	0.48	(–0.54, 0.02)	27	48	0.02	0.40

(b)

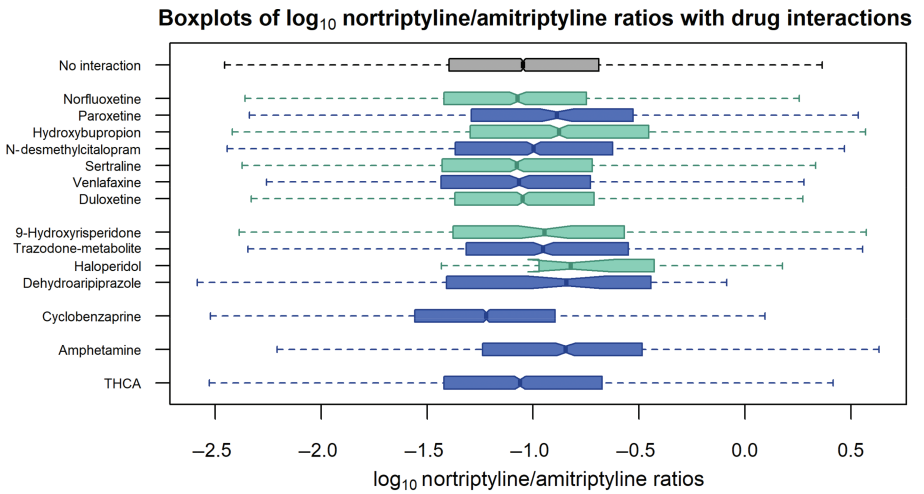
Figure 17. Boxplots and table of statistics for desipramine/imipramine log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of desipramine/imipramine log-ratios, filtered for DDIs. (b) Table of statistics for desipramine/imipramine log-ratios, filtered for DDIs.

In this study, we used our test results from what we term definitive drug tests which quantitatively measure the parent drug and its metabolite. One other use of definitive testing is to discern many of the drugs not disclosed on the drug test requisition. Table 7 shows the incidence of the interfering drugs in our patient population (representing 4+ year period, from January 2020 to September 2024). For SSRI drugs, this incidence was about 2.85 percent.

There are other limitations of the study that may have affected the findings of the DDIs. CYP genotyping was not done or provided, thus the extent of its contribution on the MRs is unknown. In addition, drug specific factors, such as route of administration, doses, timing of administration, and patient factors, such as hepatic function, renal function, past medical history/disease conditions, were also not known and may have impacted the MRs and DDI study results. A small sample size generally leads to a higher p-value and could have limited statistical power in some cases.

CONCLUSION

The pattern of inhibition or enhancement observed in this study reinforces our concept that urinary excretion of metabolite and parent drug can



(a)

DDI	Median (log)	Mean (log)	Std. dev.	IQR	No. patients	No. obs.	p-Value	Hedges' *g*
No interaction	–1.05	–1.01	0.59	(–1.4, –0.69)	5,500	10,911	NA	NA
Norfluoxetine	–1.07	–1.01	0.70	(–1.42, –0.75)	390	856	0.92	0.00
Paroxetine	–0.89	–0.86	0.73	(–1.29, –0.53)	131	254	0.002	0.24
Hydroxybupropion	–0.88	–0.85	0.68	(–1.3, –0.45)	479	1,077	<0.001	0.27
N-desmethylcitalopram	–1.00	–0.95	0.66	(–1.37, –0.62)	750	1,439	0.002	0.10
Sertraline	–1.08	–1.02	0.63	(–1.43, –0.72)	515	1,188	0.63	–0.02
Venlafaxine	–1.07	–1.02	0.65	(–1.43, –0.73)	289	646	0.59	–0.02
Duloxetine	–1.05	–1.00	0.62	(–1.37, –0.71)	923	1,651	0.56	0.02
9-Hydroxyrisperidone	–0.95	–0.95	0.61	(–1.38, –0.57)	64	112	0.29	0.11
Trazodone-metabolite	–0.95	–0.90	0.66	(–1.31, –0.55)	420	693	<0.001	0.18
Haloperidol	–0.82	–0.74	0.57	(–0.97, –0.46)	17	18	0.06	0.46
Dehydroaripiprazole	–0.84	–0.92	0.65	(–1.41, –0.44)	43	75	0.24	0.15
Cyclobenzaprine	–1.22	–1.20	0.57	(–1.56, –0.9)	2,579	4,791	<0.001	–0.33
Amphetamine	–0.85	–0.85	0.55	(–1.24, –0.49)	416	728	<0.001	0.27
THCA	–1.06	–1.00	0.62	(–1.42, –0.67)	1,173	2,236	0.65	0.01

(b)

Figure 18. Boxplots and table of statistics for nortriptyline/amitriptyline log-ratios, filtered for drug–drug interactions (DDIs). (a) Boxplots of nortriptyline/amitriptyline log-ratios, filtered for DDIs. (b) Table of statistics for nortriptyline/amitriptyline log-ratios, filtered for DDIs.

be used to estimate the DDIs of pain management and substance abuse treatment medications with other coadministered drugs. We have identified MRs of metabolite/parent drug that are expected and out of range for 18 drugs in an earlier study. From these analyses of drug metabolism, MRs that are outside of the expected range should trigger the provider to consider pharmacogenomic testing, DDIs, or deception. In the case of possible DDIs affecting drug metabolism, we and others have observed that the medication lists given with the test requisition are incomplete. For example, our data indicate that Prozac was listed only half the time. Definitive testing for the presence of more drugs makes the drug ingestion data more accurate. From this information, one can use our current DDI system or use our MR information to alert the provider about a possible deleterious DDI. On this last point, we know that providers have some patients that have undesirable side effects from their medications. If more extensive testing is performed, it might identify the cause, or at the very least point out that the patient's metabolism of the drug is unusual, giving them some reason to alter the medication dosage or switch to a different drug. The discussions the laboratory has with the providers should help them do better prescribing, or check the

Table 5. Summary of estimated drug–drug interaction effects. "0" denotes no effect on metabolism, "–" denotes a possible inhibitory effect, and "+" denotes a possible enhancing effect

Drug pairs	MR (95 percent CI)	Fluoxetine	Paroxetine	Bupropion	Citalopram	Sertraline	Venlafaxine	Duloxetine	Risperidone	Trazodone	Haloperidol	Aripiprazole	Cyclobenzaprine	Amphetamine	THC
Dextrorphan/dextromethorphan	0.157-245.14	–	–	–	–	–	–	–	0	–	–	–	0	–	–
Oxymorphone/oxycodone	0.016-7.216	–	–	–	–	–	–	–	0	–	0	–	+	0	+
Hydromorphone/hydrocodone	0.024-2.354	–	–	–	–	–	–	–	0	–	0	–	0	0	+
O-desmethyltramadol/tramadol	0.406-6.787	–	–	–	–	–	–	–	0	–	0	+	0	–	0
Hydromorphone/morphine	0.0018-0.185	–	–	–	–	–	–	0	0	0	0	0	0	0	0
Norbuprenorphine/buprenorphine	0.268-10.125	+	+	+	+	+	+	+	+	+	+	+	+	0	+
Norfentanyl/fentanyl	1.109-55.488	0	0	0	–	+	0	–	0	0	+	0	–	+	+
Noroxycodone/oxycodone	0.152-9.874	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Norhydrocodone/hydrocodone	0.313-5.518	+	+	+	+	+	+	+	+	+	0	–	+	+	+
7-Aminoclonazepam/clonazepam	0.496-147.77	0	+	0	+	+	0	+	0	+	0	+	+	+	+
α-Hydroxyalprazolam/alprazolam	0.565-7.797	–	0	–	–	–	+	–	0	+	0	+	–	+	+
Norquetiapine/quetiapine	0.235-12.996	+	0	+	–	+	0	–	+	+	+	0	–	+	–
Meprobamate/carisoprodol	5.483-942.04	–	0	0	0	0	0	+	0	0	0	0	0	0	+
N-desmethyltapentadol/tapentadol	0.152-1.929	0	0	0	0	0	+	0	0	0	0	0	0	0	0

Table 5. Summary of estimated drug–drug interaction effects. "0" denotes no effect on metabolism, "–" denotes a possible inhibitory effect, and "+" denotes a possible enhancing effect (continued)

Drug pairs	MR (95 percent CI)	Fluoxetine	Paroxetine	Bupropion	Citalopram	Sertraline	Venlafaxine	Duloxetine	Risperidone	Trazodone	Haloperidol	Aripiprazole	Cyclobenzaprine	Amphetamine	THC
Norketamine/ketamine	0.163-9.307	0	0	0	0	+	–	0	+	0	0	0	–	+	+
EDDP/methadone	0.763-15.752	+	0	+	0	+	+	–	0	–	0	+	–	+	+
Desipramine/imipramine	0.055-2.584	(+)	(+)	+	0	0	0	0	0	0	0	0	0	0	+
Nortriptyline/amitriptyline	0.010-1.593	0	+	+	+	0	0	0	0	+	0	0	–	+	0

THC: tetrahydrocannabinol; EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.

Table 6. Summary of SSRI medication disclosure

Drug	No. detected	No. medications disclosed (percent of detection)
Fluoxetine	6,272	3,287 (52 percent)
Paroxetine	2,822	1,054 (37 percent)

SSRI: selective serotonin reuptake inhibitors.

Table 7. Frequency of potential drug–drug interactions

Drug	No. detected
(Nor)Fluoxetine (SSRI)	25,683
Paroxetine (SSRI)	5,506
N-desmethylcitalopram (SSRI)	32,088
Sertraline (SSRI)	26,830
Venlafaxine (SNRI)	19,322
Duloxetine (SNRI)	21,944
Hydroxybupropion (NDRI)	75,594
9-Hydroxyrisperidone	18,978
Trazodone-metabolite	62,719
Haloperidol	3,876
Dehydroaripiprazole	8,168
Cyclobenzaprine	77,440
Amphetamine	331,948
THCA	464,925
Total interactions	1,175,021
Total specimens	3,152,723

SNRI: serotonin-norepinephrine reuptake inhibitors; THC: tetrahydrocannabinol; SSRI: selective serotonin reuptake inhibitors; NDRI: norepinephrine-dopamine reuptake inhibitors.

patient for genetic variances, or review more closely all the medications and nutritional supplements the patient is taking and thus identify potential or real medication adverse reactions.

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