

## Severe Drug-Drug Interactions: Reported and Missed

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### Abstract

Drug-drug interactions are well known to have major adverse reactions. Many physicians are not aware of all the drugs their patients are taking so these interactions are not known to them. We tested more than 300,000 urine and oral fluid specimens from patients in pain treatment and substance abuse rehabilitation programs for 79 drugs and their metabolites. We used software developed by Elsevier to calculate if there was a severe drug-drug interaction for those specimens which tested positive for two potentially interacting drugs. The severe category was defined as “the use of these medications together is contraindicated, or the medications are not usually taken concurrently because the interaction may be life-threatening or may cause serious harm” We observed 1989 severe interactions. Many were not revealed to the patient’s care giver. We argue such drug-drug interactions are potentially misclassified as “opioid” deaths.

**Keywords:** Drug-drug interactions; Opioid; Benzodiazepines

### Background

In 2016, there were more than 63,600 drug overdose deaths reported in the US [1]. Approximately 66% of these overdoses involved an opioid, including prescription opioids and illicit opioids like heroin and illicitly manufactured fentanyl. This number is 5 times higher than the number reported in 1999 [1]. In many cases, these deaths are not due solely to opiates, but rather due to drug- drug interactions (DDI) involving opiates used or mixed with other drugs such as benzodiazepines [2]. To help offset such potential deaths, the 2012 CDC advisory on prescribing indicated that opioids and benzodiazepines should not be co-prescribed [1].

In addition to the dangerous interactions possible between benzodiazepines and opiates, several other drug-drug interactions have been identified and are responsible for a significant number of deaths. These deaths can be attributed in most cases to patients not always adhering to their prescribed drug regimens either intentionally or unintentionally [3,4] as well as treating physicians not informed of all drugs their patients are taking [5]. Use of prescription drug monitoring

programs [6] and drug testing can further assist providers in obtaining a more complete clinical picture of their patients.

As a reference laboratory monitoring patients drug compliance, we had the unique opportunity to take a retrospective look at a defined data set to establish the extent of these drug-drug interactions in our patient population.

### Methods

From January 1, 2018 to October 31, 2018, we performed drug testing on 384,478 samples received from clients, mainly pain clinics and rehabilitation centres. The sample population was a mix of urine and oral fluid samples. The method of analysis has been described by Krock et al. [7]. Once tested, positive results were automatically entered into the Elsevier, Inc./Gold Standard Drug Database (GSDD); this software program identifies drug-drug interactions. A severe drug-drug interaction is defined as “the use of these medications together is contraindicated, or the medications are not usually taken concurrently because the interaction may be life-threatening or may cause serious harm” [8]. A list of the tested drugs and/or their metabolites is presented in Table 1.

7-hydroxymitragynine	Fluoxetine/norfluoxetine	Naltrexone metabolite (6-beta naltrexol)
Alprazolam/alphahydroxyalprazolam	Gabapentin	Oxazepam
Amitriptyline/nortriptyline	Haloperidol	Oxycodone/noroxycodone
Amphetamine	Heroin metabolite (6-MAM)	Oxymorphone
Aripiprazole or metabolite	Hydrocodone/norhydrocodone	Paroxetine
Buprenorphine/norbuprenorphine	Hydromorphone	PCP (Phencyclidine)
Bupropion metabolite	Imipramine/desipramine	Phentermine
Carisoprodol/meprobamate	ketamine/norketamine	Pregabalin
Citalopram or metabolite	Lorazepam	Propoxyphene

Clonazepam/7-aminoclonazepam	MDA, MDEA, MDMA	Quetiapine/norquetiapine
Cocaine metabolite (Benzoyllecgonine)	MDPV	Risperidone metabolite
Codeine	Meperidine	Sertraline
Cotinine	Methadone/EDDP	Tapentadol/N-desmethyltapentadol
Cyclobenzaprine	Methamphetamine	Temazepam
Dextromethorphan/dextrorphan	Methylone	THCA (Marijuana metabolite)
Diazepam/nordiazepam	Methylphenidate	Tramadol/O-desmethyltramadol
Duloxetine	Mitragynine	Trazodone or metabolite
Fentanyl/norfentanyl	Morphine	Venlafaxine
	Naloxone	Zolpidem/carboxyzolpidem

**Table 1:** Test panel containing list of the tested drugs and/or their metabolites.

For each patient sample, we divided the data into two categories of severe drug-drug interactions- those from drugs tested and reported to the requesting provider and those from drugs tested but not reported

to providers since they did not request testing; these are referred to as missed DDIs. This data is presented in Table 2. The study was approved by ASPIRE IRB Santee California.

Drug-drug interaction (DDI)	Ordered and identified DDI	Missed (Non-ordered) and identified DDI
Phentermine+amphetamine	240	324
Methylphenidate+amphetamine	218	296
Phentermine+methamphetamine	111	142
Methylphenidate+methamphetamine	70	98
Venlafaxine+duloxetine	36	108
Fluoxetine+sertraline	36	202
Paroxetine+fluoxetine	8	79
Paroxetine+setraline	1	20
Total	720	1269

**Table 2:** Severe drug-drug interactions identified. The severe interactions are defined by the Elsevier database. The frequency of each observed drug was obtained from our LC-MS/MS data.

## Results

Of the 384,478 patient samples tested from January 01, 2018 to October 31, 2018, there were a total of 1,989 severe DDIs identified. For those drug tests ordered by healthcare providers, we observed a total of 720 severe DDIs. In many cases the ordering physician did not request testing for many drugs responsible for severe DDIs. These accounted for 1,269 severe DDIs. Table 2 lists only the severe interactions as defined by the Elsevier database and our comparative program.

The 384,478 patient samples represent 149,766 individual patients. Of the missed severe DDIs, there were 1060 samples with one or more severe DDIs from 785 patients.

## Discussion

Laboratory data can reveal unique trends that other data sources cannot. We used urine and oral fluid results to establish that the patients had taken the test drugs. This is a more accurate method than prescription drug monitoring which does not track whether the patient truly ingested the prescribed drug or drugs and may be incomplete.

This study is limited by the tests we performed, the patient population from which samples were derived and the drug-drug interactions available in the Elsevier/GSSD database. We further limited the study to only severe DDIs. We also do not have any data to show that these severe interactions did occur.

We reviewed two categories of positive tests resulting in severe DDIs. The first was based on positive drug results where the tests were ordered by providers. The second category was based on positive drug results where tests were not ordered by providers, also known as

missed DDIs. The data clearly show that by ordering minimal testing, the provider can miss one or more severe drug-drug interactions.

We argue that drug-drug interactions can be a major cause of morbidity and mortality. Our results are in agreement with other studies pointing to the prevalence of non-adherence of patients to their prescribed regimens as well as prescribers not having the full list of what drugs their patients are truly ingesting [9].

## Conclusion

“Out of the 384,478 patient samples tested and severe 1,989 DDI's identified; the majority were found to be missed (non-ordered), about 1,269 cases. This illustrates that non-reported drug-drug interactions are possibly the major causes of morbidity and mortality in reported drug overdoses. The lack of proper awareness among the prescribers and patients of all the ingested drugs could be the main reason for hundreds of deaths every year, which are misclassified as 'opioid' deaths.

The true extent of severe drug-drug interactions can be provided with more complete drug test panels and data base analysis of the test results, possibly resulting in fewer cases of DDI deaths.”

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