Clinical Update: June 2023

SPOTLIGHT ON POTENTIAL INTERACTIONS INVOLVING BEHAVIORAL HEALTH & SUBSTANCE USE DISORDER MEDICATIONS

Drug-drug and drug-food interactions (DDIs) contribute to adverse drug events (ADEs) which can range in severity from mild effects to life-threatening. DDIs may be more likely to occur or more problematic in some individuals, depending on the number of medications they take, recent events in their medical care, and the complexity of their medical history. DDIs can easily go undiagnosed which contributes to the estimated $30.1 billion cost to the collective healthcare system.[1-4] Other research has noted that the risk of an ADE or DDI increases with polypharmacy, and the number of patients taking five or more prescription drugs (which is the definition of polypharmacy) has more than doubled between 1988 and 2018.[5-6] Patients with multiple diagnoses or receiving care from multiple healthcare providers may be at increased risk of DDIs and related ADEs.

While multiple tools exist for identifying DDIs, each can have limitations. Individuals may fail to report all prescription drugs, over the counter (OTC) medications, and herbal supplements. Pharmacy-based drug utilization review may be incomplete if the patient uses multiple pharmacies, and OTC medications may not be included in the pharmacy software for evaluation. Prescription Drug Monitoring Programs (PDMPs) are informative regarding controlled substances only and automated DDI identification software is only able to analyze the data that has been entered; omissions can result in an incomplete DDI analysis.

The task of understanding and mitigating DDIs can be quite complex and is best supported by the right tools to help clinicians have clarity regarding recently ingested substances and the risk for interactions between those substances. Aegis Sciences Corporation offers a laboratory-developed and validated test on urine and saliva samples which utilizes a liquid chromatography-tandem mass spectrometry-based (LC/MS/MS) confirmatory method to detect many commonly-prescribed substances capable of impacting prescription medication pharmacokinetics (such as drug absorption or metabolism) or pharmacodynamics.

Aegis DDI testing (for substances outlined in Table 1) can be added with medication adherence monitoring to provide a broad evaluation of potential DDI and adverse event risk. (For more information about InterACT Rx testing, go to https://www.aegislabs.com/about-ddi.)

Table 1. Substances Detected in Aegis DDI Testing

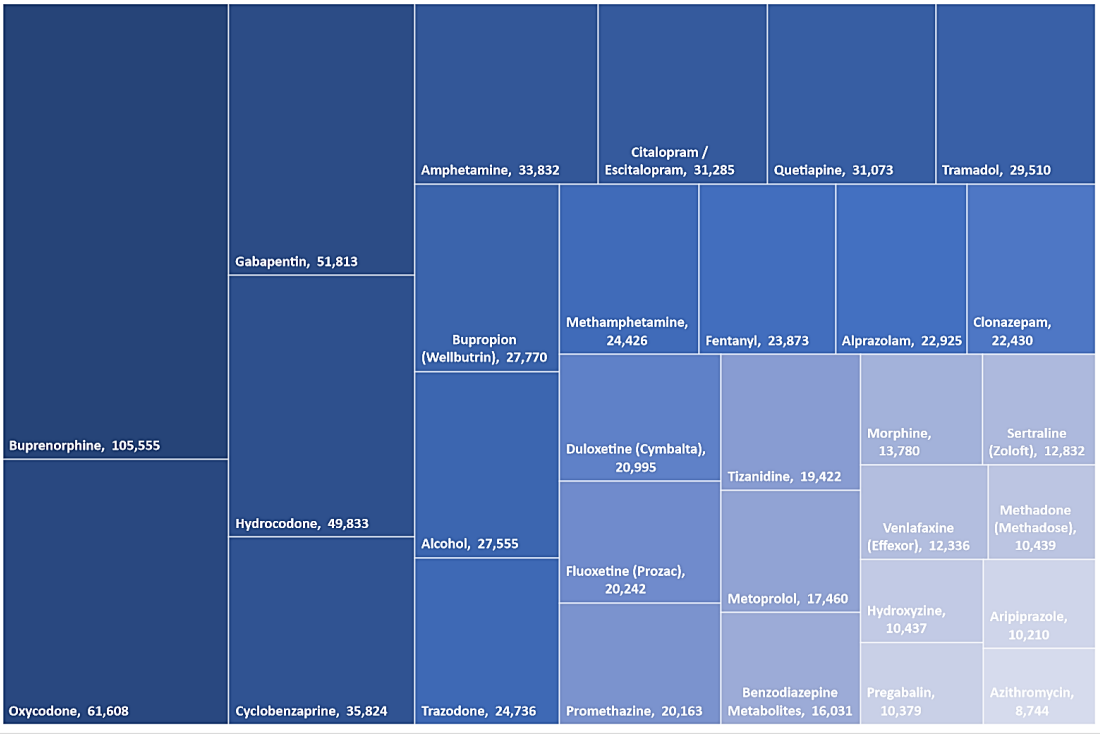
ANTIARRHYTHMICS	Amiodarone	Quinidine	Ranolazine
ANTIDEPRESSANTS & ANTIPSYCHOTICS	Amitriptyline Aripiprazole Asenapine Bupropion Chlorpromazine Citalopram/Escitalopram Clomipramine Desipramine Desvenlafaxine Doxepin	Duloxetine Fluoxetine Fluphenazine Fluvoxamine Haloperidol Iloperidone Nefazodone Nortriptyline Olanzapine Paliperidone	Paroxetine Perphenazine Quetiapine Risperidone Sertraline Thioridazine Trazodone Venlafaxine
ANTIEMETICS & GASTRIC REFLUX	Cimetidine Esomeprazole/Omeprazole Famotidine	Lansoprazole Metoclopramide Ondansetron	Promethazine Ranitidine
ANTIEPILEPTICS	Carbamazepine Clobazam Lamotrigine	Oxcarbazepine Phenobarbital Phenytoin	Primidone
ANTIHYPERTENSIVES	Amlodipine	Labetalol	Propranolol

	Atenolol Carvedilol Diltiazem	Metoprolol Nebivolol Nifedipine	Timolol Verapamil
ANTIMICROBIALS & ANTIRETROVIRALS	Acyclovir (Urine only) Atazanavir Azithromycin Chloroquine Ciprofloxacin Clarithromycin Cobicistat Darunavir Delavirdine Fluconazole Fosamprenavir	Indinavir Itraconazole Efavirenz Erythromycin Etravirine Ketoconazole Levofloxacin/Ofloxacin Metronidazole Nelfinavir Nevirapine Posaconazole	Quinine Rifabutin Rifampin Rifapentine Ritonavir Saquinavir Terbinafine Tipranavir Valacyclovir (Urine only) Voriconazole
ANTI-PARKINSON AGENTS	Carbidopa/Levodopa	Ropinirole	
ANTITHROMBOTICS	Apixaban Clopidogrel	Rivaroxaban Warfarin	
CHEMOTHERAPEUTIC AGENTS	Abiraterone Anastrozole	Doxorubicin Enzalutamide	Nilotinib Pazopanib
COGNITIVE ENHANCEMENT	Atomoxetine Donepezil	Guanfacine Memantine	
FOODS & SUPPLEMENTS	Grapefruit Furanocoumarins	Kava	St. John's Wort
INHALED CORTICOSTEROIDS & BETA AGONISTS	Albuterol	Formoterol	Salmeterol
STEROIDS & HORMONES	Dexamethasone	Methylprednisolone	Prednisone
MISCELLANEOUS	Atorvastatin Avanafil Baclofen Butalbital Canagliflozin Cyclobenzaprine	Hydroxyzine Linagliptin Lorcaserin Methadone Methocarbamol Methotrexate	Mirabegron Pioglitazone Sumatriptan Tizanidine Zileuton (Urine only)

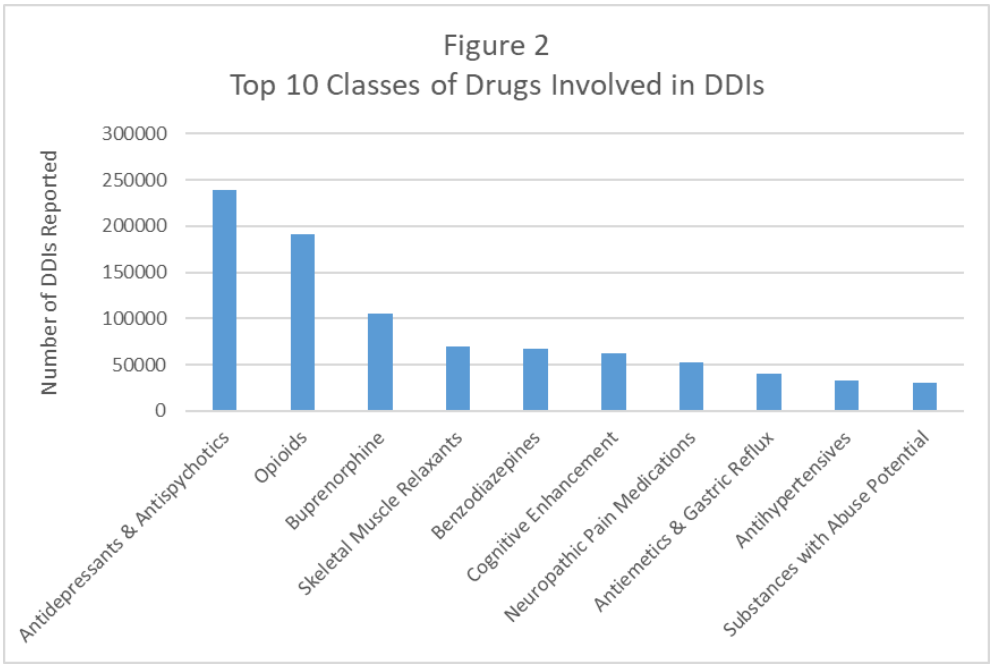
A data analysis was performed on the reported DDIs from samples collected 1/1/2021 thru 3/16/2023. This data is not inclusive of *all* samples reported during the time frame as DDI testing is only performed based on clinician order and is not ordered on every sample. DDIs were examined for the frequency of interactions by drug class involved. Interacting pairs of substances have been selected for special focus for this discussion due to their relevancy to the behavioral health and substance use disorder (SUD) space.

The data analysis included 501,478 potential DDIs reported from 169,357 samples. A total of 2,136 unique pairs of interacting substances were identified (with some drugs interacting with multiple other substances). Buprenorphine was the most frequently involved drug in a reported DDI with 105,555 (21%) of the interactions involving buprenorphine. Other drugs frequently involved in potential DDIs include Amphetamine (33,832), Citalopram/Escitalopram (31,285), Quetiapine (31,037), Bupropion (27,770), Duloxetine (20,995), Fluoxetine (20,242), and Methadone (10,439). The 30 most-frequently involved drugs in DDIs reported are shown in Figure 1.

FIGURE 1 - PROPORTION OF INTERACTING DRUGS AMONG TOP 30 DETECTED



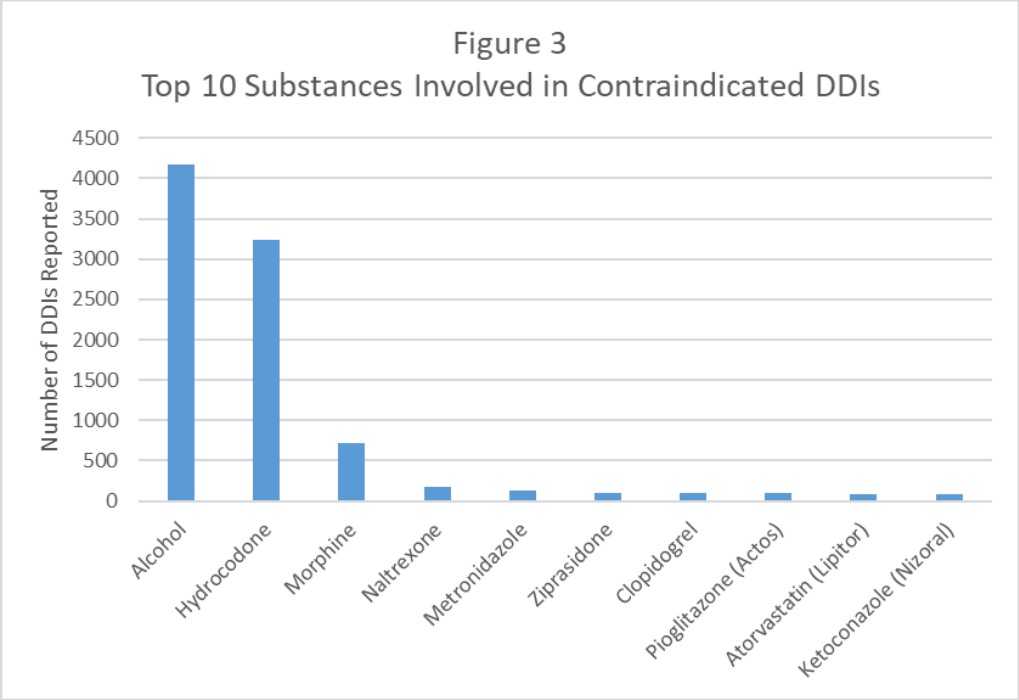
Antidepressants & Antipsychotics were involved in 238,403 (48%) of the DDIs reported. Benzodiazepines contributed to 66,782 (13%). Figure 2 shows the top 10 classes of drugs involved in DDIs.



Buprenorphine, Methadone, and Naltrexone – all drugs commonly used in medication assisted treatment (MAT) for SUD – comprise 23% of all interactions reported during this time frame (116,202 DDIs). Antimicrobials &

Antiretrovirals were involved in 25,902 DDIs. Antihistamines, Antiemetics, & Gastric Reflux medications together totaled 50,673 DDIs.

Interactions were also reported by levels of severity including Contraindicated, Severe, Moderate, Most Significant, More Significant, and Significant. There were 9,896 Contraindicated interactions reported with 4,167 involving Alcohol (42%). The top 10 substances involved in Contraindicated DDIs are shown in Figure 3.



From a drug class perspective, Antidepressants & Antipsychotics were involved in 282 Contraindicated DDIs. MAT drugs (including buprenorphine, methadone, and naltrexone) contributed to 234 Contraindicated DDIs. There were 119,782 Severe DDIs reported, and of those 34,901 (29%) involved Antidepressants & Antipsychotics. Buprenorphine contributed to 11,705 Severe DDIs.

DDIs pose a real threat to the treatment success of individuals in behavioral health and SUD treatment. The result of this analysis indicates that over 1 in 5 DDIs reported involved buprenorphine, and almost 1 out of every 2 interactions involved an Antidepressant or an Antipsychotic medication. Some individuals in behavioral health or SUD care also live with human immunodeficiency virus (HIV) which could be impacted by DDIs involving Antiretrovirals. Besides the independent risks of use of alcohol, its identification as contributing to a DDI is a reminder of the central nervous system depression that alcohol can also add to prescription and substance use.

MAT drugs can be subject to pharmacokinetic and pharmacodynamic DDIs that can impact treatment success. The inducement or inhibition of CYP3A4 can affect buprenorphine levels in the body which may require dose adjustments for optimal therapeutic response.[7] Methadone can cause a life-threatening arrhythmia known as torsades de pointes, and the risk of this can be exacerbated by DDIs.[8] Additional DDIs are possible with methadone that can lead to reduced efficacy, increased toxicity, or precipitated withdrawal symptoms.

This data is not inclusive of all samples received during the time frame as DDI testing is only performed as ordered based on assessment of medical necessity by the clinician with consideration of the complexity of the patient's medication regimen, past medical history, and potential risk for morbidity associated with DDIs. Thus, although more frequent utilization of this testing is not necessarily indicated based on available data, the data presented

here could be an underrepresentation of the true frequency of DDIs occurring. Furthermore, medication adherence testing is performed according to clinician order, so there could be additional substances present in the specimens that could contribute to additional DDIs that were not reported in the results. An additional element of data that is not included in this analysis are the substances that were identified in DDI testing but were not found to contribute to DDIs. The information that results from the DDI test can also be helpful in preventing DDIs as prescribers can reference this in making prescribing decisions.

DDIs have the potential to lead to ADEs and affect treatment outcomes for individuals taking multiple prescription drugs, OTC medications, and/or herbal supplements. Objective data regarding recently ingested substances is a powerful tool for the identification DDIs and potential harm reduction. DDI analysis in urine or oral fluid may be considered for individuals who may be at increased risk for morbidity from drug interactions, those who take multiple prescription drugs, those who may not provide a complete medication history, and those who see multiple providers or manage multiple chronic medical conditions. This type of testing provides additional clarity and transparency regarding an individual's substance use to help clinicians make more informed prescribing decisions.

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct. (Calibri 10pt)

References:

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