Clinical Update: June 2022

INTERACT RX: A LOOK AT CLINICAL UTILITY THROUGH A DISCUSSION OF INTERACTIONS FOUND

InterACT Rx Overview

Since 2016, Aegis Sciences Corporation has offered definitive testing for numerous substances that may contribute to drug-drug interactions (DDIs) with commonly prescribed pain management, behavioral health, and medication-assisted treatment drugs. Polypharmacy is an example of a factor that may deem a patient more suitable for InterACT Rx testing. In a 2018 study by Schrecker et al, polypharmacy patients were four times more likely to have a DDI identified.[1]

Over the years, Aegis has refined and expanded the InterACT Rx test to include an increasing number of relevant prescription and non-prescription substances and provide a broader assessment of potential interactions. While DDIs are known to occur between prescription drugs, it is also possible for interactions to occur with foods and supplements. The abbreviation DDI will be used to include these additional sources as well for the purpose of this discussion. InterACT Rx testing includes commonly prescribed substances within the following drug classes: Antiarrhythmics, Antidepressants, Antipsychotics, Antidiabetics, Antiemetics, Gastric Reflux Medications, Antiepileptics, Antihypertensives, Antimicrobials, Antiretrovirals, Antithrombotics, Bronchodilators, Chemotherapeutic Agents, Foods & Supplements, Skeletal Muscle Relaxants, Steroids, Hormones, and several other miscellaneous drugs. When InterACT Rx is ordered, all the substances within the InterACT Rx testing profile are tested, and any substances identified as present are checked against each other and substances identified as present in medication adherence testing. Interacting pairs are reported to the clinician, along with the interaction severity and a clinical description of the interaction.

Objective Insight Through Definitive Testing

DDIs can lead to adverse drug events (ADEs) which may be mild, moderate, life-threatening, or fatal. It has been estimated that approximately 50% of ADEs are preventable.[2] There are multiple methods used for identifying and preventing DDIs, including medication reconciliation practices, pharmacy-based drug utilization review, reviewing prescription drug monitoring program data, and use of automated DDI software in electronic medical record systems. Unfortunately, none of these tools are infallible, and all are subject to incomplete data, which is a major limitation to their accuracy. InterACT Rx analyzes biological fluids to identify recently-ingested substances that may not have been reported by the patient and reports clinically actionable data to clinicians, allowing them to resolve drug interactions safely.

Actionable Results

The percentage of samples with reported interactions is a testament to the clinical value of this testing. In samples for which InterACT Rx testing was ordered by a clinician between January 2021 and April 2022, at least one pair of interacting substances was found in 55% of samples. Some samples had two or more pairs of interacting substances found. DDIs may be pharmacokinetic and/or pharmacodynamic, with impact to cytochrome P450 enzymatic activity and potentially reduced or enhanced clinical effects. The interaction description provided by Aegis explains the clinical effects of a DDI which allows for better understanding of the severity of the interaction.

Most Identified Interacting Substances

Buprenorphine has been the medication most often identified in DDIs through InterACT Rx testing. Buprenorphine is metabolized primarily by n-dealkylation via cytochrome enzymes CYP3A4, as well as glucuronide conjugation.[3] If CYP3A4 function is induced by another medication, this can lead to decreased plasma concentrations of buprenorphine and decreased efficacy or onset of withdrawal syndrome.[4] An example of this type of interaction is buprenorphine with carbamazepine. See below for an example of how this interaction is reported.

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Buprenorphine	Consistent	1,510 ng/mL	Test result is consistent and expected with prescribed drug.
Cotinine	PRESENT	6,590 ng/mL	Test result indicates active use of tobacco product.

Drug-Drug Interaction (DDI)

Potential Interaction Detected		Interaction Severity	Interaction Description
Buprenorphine	Carbamazepine	MODERATE	Concurrent use of strong CYP3A4 inducer may result in decreased levels of alfentanil, buprenorphine, fentanyl, hydrocodone, methadone, morphine, and oxycodone which may result in decreased effectiveness and may precipitate withdrawal symptoms.(1-8)

Citations in interaction descriptions can be provided as needed. DDI disclaimers can be found at https://www.aegislabs.com/about-ddi. Please contact Clinical Scientists at 1-877-552-3232 for more information.

BioDetect™

Result	Comment
EXPECTED	Test result is consistent with routinely analyzed human urine.

Test(s) Requested Contents

Tested For	Result	Laboratory Result
Buprenorphine		
Buprenorphine	**POSITIVE**	308 ng/mL
Norbuprenorphine	**POSITIVE**	1200 ng/mL
Alcohol Metabolites		
Ethyl Glucuronide	NONE DETECTED	
Ethyl Sulfate	NONE DETECTED	
Amphetamines	NONE DETECTED	
Benzodiazepines	NONE DETECTED	
Gabapentin/Pregabalin	NONE DETECTED	
Cocaine Metabolite Opiates	NONE DETECTED	
6-Monoacetylmorphine	NONE DETECTED	
Methadone	NONE DETECTED	
Fentanyl	NONE DETECTED	
Carisoprodol/Meprobamate	NONE DETECTED	
Tramadol	NONE DETECTED	
Bupropion	NONE DETECTED	
Methylphenidate	NONE DETECTED	
Naloxone	NONE DETECTED	
Naltrexone	NONE DETECTED	
Cotinine	NONE DETECTED	
Cotinine	**POSITIVE**	708 ng/mL
3-hydroxycotinine	**POSITIVE**	5880 ng/mL
Drug-Drug Interactions		
Carbamazepine Epoxide	**POSITIVE**	

Specimen Validity Testing

Tested For	Comment	Result	Normal Range
Creatinine	NORMAL	227.9 mg/dL	20 – 370 mg/dL
pH	NORMAL	5.36	4.5 - 9.0

These tests were developed and their performance characteristics determined by Aegis Sciences Corporation. They have not been cleared or approved by the US Food and Drug Administration.
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If CYP3A4 function is inhibited by another medication, this can lead to increased plasma concentrations of buprenorphine and increased or prolonged opioid effects. The most commonly identified buprenorphine-involved DDIs (with over 100 occurrences of each interaction) are as follows:

Buprenorphine	**Gabapentin**
Buprenorphine	**Methamphetamine**
Buprenorphine	**Clonazepam**
Buprenorphine	**Alcohol**
Buprenorphine	**Fentanyl**
Buprenorphine	**Quetiapine**
Buprenorphine	**Cyclobenzaprine**
Buprenorphine	**Oxycodone**
Buprenorphine	**Promethazine**
Buprenorphine	**Olanzapine**
Buprenorphine	**Hydrocodone**
Buprenorphine	**Pregabalin**
Buprenorphine	**Tizanidine**
Buprenorphine	**Lorazepam**
Buprenorphine	**Morphine**
Buprenorphine	**Tramadol**
Buprenorphine	**Methocarbamol**
Buprenorphine	**Methylphenidate**
Buprenorphine	**Zolpidem**
Buprenorphine	**Risperidone/Paliperidone**
Buprenorphine	**Oxymorphone**
Buprenorphine	**Carisoprodol / Meprobamate**
Buprenorphine	**Methadone**
Buprenorphine	**Carbamazepine**
Buprenorphine	**Haloperidol**
Buprenorphine	**Codeine**
Buprenorphine	**Lurasidone**
Buprenorphine	**Dextromethorphan/Levorphanol**
Buprenorphine	**Phenobarbital**
Buprenorphine	**Primidone**

The second most identified drug involved in DDIs by InterACT Rx testing is oxycodone. Oxycodone is metabolized by CYP3A4 to noroxycodone and by CYP2D6 to oxymorphone. Noroxycodone does not produce analgesia, so DDIs with oxycodone that cause CYP3A4 induction or CYP2D6 inhibition can lead to decreased pain relief for the patient. Patients who express inadequate pain control may be falsely labeled as drug-seeking when a DDI may be reducing the efficacy of their medication. Identification of drug interactions with pain medications is important, not only for resolution of the interaction and improved medication safety and efficacy, but also to ensure that the prescribed dose of the pain medication continues to be appropriate. If a dose increase was prescribed to overcome reduced efficacy, and a DDI impacting oxycodone metabolism is resolved, the patient may experience supratherapeutic effects. Careful monitoring, especially around medication changes to resolve DDIs, is important to ensure safe and appropriate dosing.

Even with medication reconciliation efforts and other measures of evaluating for DDIs, it is very easy for short-term medications to cause DDIs as well. Here is an example showing clarithromycin and inhibition of oxycodone metabolism via CYP3A4. Patients may visit urgent care centers and use alternate pharmacies for acute illnesses due to convenience or because their regular provider or pharmacy is not open. These medications may not be able to be fully vetted for drug interactions since the acute care provider may not have access to the patient's full medical records and the dispensing pharmacy may not be aware of all the patient's medications.

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Pregabalin (Lyrica)	NOT PRESENT	<5 mcg/mL	Test result indicates patient may not be taking drug prescribed.
Morphine	PRESENT	18,800 ng/mL	Test result is consistent and expected with prescribed drug.
Oxycodone	PRESENT	25,500 ng/mL	Test result is consistent and expected with prescribed drug.

Drug-Drug Interaction (DDI)

Potential Interaction Detected		Interaction Severity	Interaction Description
Clarithromycin (Biaxin)	Oxycodone	SEVERE	The concurrent administration of a CYP3A4 inhibitor may result in elevated levels of and toxicity from alfentanil, fentanyl,(1,2) hydrocodone,(3) and oxycodone(4), including profound sedation, respiratory depression, coma, and/or death.

Citations in interaction descriptions can be provided as needed. DDI disclaimers can be found at https://www.aegislabs.com/about-ddi. Please contact Clinical Scientists at 1-877-552-3232 for more information.

BioDetect™	Result	Comment
	EXPECTED	Test result is consistent with routinely analyzed human urine.

Test(s) Requested Contents

Tested For	Result	Laboratory Result
Buprenorphine	NONE DETECTED	
Tapentadol	NONE DETECTED	
Amphetamines	NONE DETECTED	
Barbiturates	NONE DETECTED	
Benzodiazepines	NONE DETECTED	
Gabapentin/Pregabalin	NONE DETECTED	
Cocaine Metabolite	NONE DETECTED	
Opiates		
Morphine	**POSITIVE**	18600 ng/mL
Hydromorphone	**POSITIVE**	274 ng/mL
Oxycodone	**POSITIVE**	11000 ng/mL
Oxymorphone	**POSITIVE**	6530 ng/mL
Noroxycodone	**POSITIVE**	7970 ng/mL
6-Monoacetylmorphine	NONE DETECTED	
Methadone	NONE DETECTED	
Meperidine	NONE DETECTED	
Fentanyl	NONE DETECTED	
Carisoprodol/Meprobamate	NONE DETECTED	
Tramadol	NONE DETECTED	
Drug-Drug Interactions		
Amitriptyline (Elavil)	**POSITIVE**	
Clarithromycin (Biaxin)	**POSITIVE**	
Nortriptyline (Pamelor)	**POSITIVE**	

Specimen Validity Testing

Tested For	Comment	Result	Normal Range
Creatinine	NORMAL	260 mg/dL	20 – 370 mg/dL
pH	NORMAL	6.23	4.5 - 9.0

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The most commonly identified oxycodone-involved DDIs (with over 100 occurrences of each interaction) are as follows:

Oxycodone Alcohol
Oxycodone Pregabalin
Oxycodone Tizanidine
Oxycodone Promethazine
Oxycodone Quetiapine
Oxycodone Zolpidem
Oxycodone Furanocoumarin (Grapefruit Marker)
Oxycodone Paroxetine
Oxycodone Verapamil
Oxycodone Primidone

Also in the top 10 most identified interacting drugs is citalopram/escitalopram. Testing for citalopram/escitalopram at Aegis does not differentiate the isomers of this drug, so some results may be caused by taking citalopram, while others may be caused by patients taking escitalopram. The most common DDI identified with citalopram/escitalopram is with esomeprazole/omeprazole. Esomeprazole/omeprazole is an inhibitor of CYP2C19 which is one of the major enzymes responsible for citalopram/escitalopram metabolism.[5] Inhibition of citalopram/escitalopram metabolism can result in elevated levels of the drug and increase the risk of QTc prolongation and life-threatening arrhythmias, including torsades de pointes. Since citalopram/escitalopram is frequently prescribed in both primary care and behavioral health settings, and esomeprazole/omeprazole is available over the counter without a prescription, this is an especially important interaction for clinicians to review. Patients often fail to report over the counter medication use due to a perception of safety and assumption of minimal impact to their overall medication regimen.

The most commonly identified citalopram/escitalopram-involved DDIs (with over 100 occurrences of each interaction) are as follows:

Citalopram / Escitalopram Esomeprazole/Omeprazole
Citalopram / Escitalopram Metoprolol
Citalopram / Escitalopram Trazodone
Citalopram / Escitalopram Cyclobenzaprine
Citalopram / Escitalopram Quetiapine
Citalopram / Escitalopram Hydroxyzine
Citalopram / Escitalopram Tramadol
Citalopram / Escitalopram Promethazine
Citalopram / Escitalopram Ondansetron
Citalopram / Escitalopram Methamphetamine
Citalopram / Escitalopram Tizanidine
Citalopram / Escitalopram Clopidogrel
Citalopram / Escitalopram Fentanyl
Citalopram / Escitalopram Methadone
Citalopram / Escitalopram Phentermine
Citalopram / Escitalopram Fluconazole
Citalopram / Escitalopram Mirtazapine
Citalopram / Escitalopram Venlafaxine
Citalopram / Escitalopram Sumatriptan
Citalopram / Escitalopram Quinine
Citalopram / Escitalopram Donepezil
Citalopram / Escitalopram Warfarin
Citalopram / Escitalopram Fluoxetine
Citalopram / Escitalopram Rivaroxaban
Citalopram / Escitalopram Haloperidol
Citalopram / Escitalopram Nortriptyline
Citalopram / Escitalopram Risperidone/Paliperidone

There are many commonly-prescribed medications in pain management, addiction recovery, behavioral health, primary care, and other clinical specialties that can contribute to clinically significant DDIs. Overall, the most commonly identified drugs involved in DDIs (with over 10,000 occurrences of DDIs involving each drug) are:

Buprenorphine
Oxycodone
Gabapentin
Hydrocodone
Cyclobenzaprine
Tramadol
Citalopram / Escitalopram
Amphetamine
Quetiapine
Methamphetamine
Alcohol
Bupropion
Fentanyl
Alprazolam
Trazodone
Clonazepam
Duloxetine
Promethazine
Tizanidine
Fluoxetine
Metoprolol
Benzodiazepine Metabolites
Morphine

Determining Medical Necessity for InterACT Rx Testing

As with any type of laboratory testing, the decision to order InterACT Rx testing is at the clinical discretion of the ordering provider, with consideration of the patient's medical history, current presentation, and medication regimen complexity. It is not a test that should be ordered for every patient or on every urine or oral fluid sample provided by a patient, and it is not intended as a screening tool simply as broader testing tool to see what substances a patient has recently ingested. The following are proposed criteria for considering InterACT Rx testing:

- Polypharmacy (patients taking ≥5 medications)
- Patient experiencing intolerance to prescribed therapy
- Patient experiencing reduced response or lack of medication efficacy
- Dose escalation requirements for effective treatment
- Risk of incomplete medication profile due to complexity of past medical history
- Patient at risk of morbidity from drug interaction
- Patient presenting with or reporting signs of an ADE
- Recent hospitalization or other care transition

InterACT Rx has been shown in multiple studies to improve the rate of DDI detection, diagnosis, and treatment.[6-8] When utilized appropriately, objective results of definitive testing can help clinicians improve medication management and outcomes and reduce overall health system costs.

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.

References:

1. Schrecker J, Puet B, Hild C, Schwope DM. Characterization of drug-drug interactions in patients whose substance intake was objectively identified by detection in urine. *Expert Opin Drug Metab Toxicol*. 2018;14(9):973-978. doi:10.1080/17425255.2018.1509953
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4. Reckitt Benckiser Pharmaceuticals, Inc. Suboxone prescribing information. Richmond, VA. August 2012
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7. Peabody J, Tran M, Paculdo D, Schrecker J, Valdenor C, Jeter E. Clinical Utility of Definitive Drug¯Drug Interaction Testing in Primary Care. *J Clin Med*. 2018;7(11):384. Published 2018 Oct 25. doi:10.3390/jcm7110384
8. Peabody J, Schrecker J, Heltsley R, et al. Randomized Trial to Improve Primary Care Patient Management and Patient Outcomes Using a Drug-Drug Interaction Test: Confirmation of the DECART Simulated Patient Clinical Utility Trial Results. *Diagnostics (Basel)*. 2021;11(7):1266. Published 2021 Jul 15. doi:10.3390/diagnostics11071266