# **Oral Fluid as a Viable Matrix for Detecting Drug-Drug Interactions**

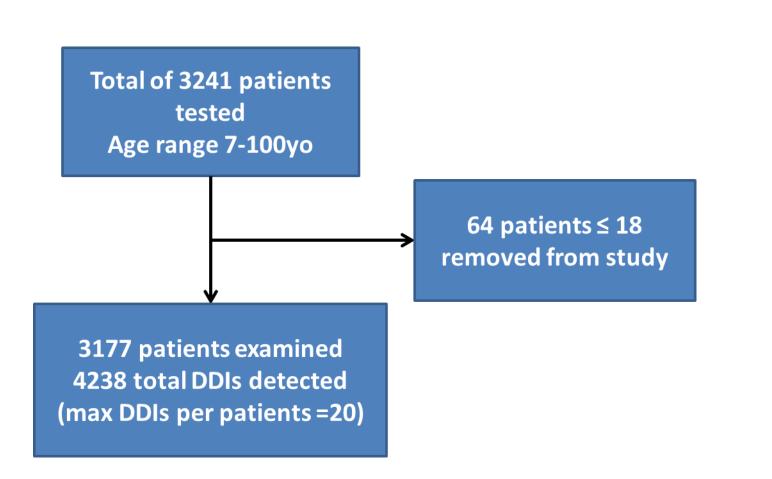
**Aegis Sciences Corporation, Nashville, TN** 

## Introduction

Drug-drug interactions (DDIs) are a substantial concern for many patients and monitoring for DDIs is critical to preventing adverse drug events (ADEs) and potential hospitalization, particularly for those under treatment for multiple conditions and/or under the care of multiple providers. Detection of drugs and other interacting substances (e.g. foods and/or supplements) in biological fluids provides a direct means to assess what patients have ingested, providing an objective detection of potential DDIs that may be missed by traditional drug reconciliation programs or pharmacy staff. Typically, urine is used to assess ingested drugs; however, oral fluid (OF) has been increasingly evaluated as a useful alternative matrix in clinical and forensic toxicology, drug monitoring programs and telehealth settings. We recently began offering an OF test for detection of common interactants in a pain management, addiction treatment and behavioral health population. Given the lack of prevalence data for many of these interacting substances in OF, we conducted a post-release evaluation of the ability to detect these substances and identify potential DDIs in this matrix.

# Methods

Over 180 drugs in oral fluid were monitored through LC-MS/MS testing. Briefly, OF samples collected with a commercial collection device were processed via automated SPE and extracts were diluted without drying and injected onto an LC-MS/MS system. A modified C18 column was used to chromatograph compounds and qualitative detection was via scheduled multiple reaction monitoring using electrospray with polarity switching. Several categories of drug were monitored including behavioral health, antibiotic, and cardiovascular compounds as well as food/supplement ingestion markers. These samples were tested either through our DDI testing profile and, if ordered, our oral fluid testing profile. Over 3100 patient samples were processed to determine potential DDIs (including severity) and category of analytes involved. Patients under the age of 18 were removed from the study (n=64).



**References:** 1. FDA (US Food and Drug Administration). FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm518473.htm August 31, 2016. 2. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005 Mar 17; 352(11):1112-20.

- 3. Validus Pharmaceuticals. LLC March, 2013. 4. Toprol-XL (metoprolol succinate) US prescribing information. AstraZeneca LP March, 2011
- 5. Woosley RL, Romero KA. www.Crediblemeds.org, QTdrugs List, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755. November 17, 2015.
- 6. Preskorn SH, Beber JH, Faul JC, Hirschfeld RM. Serious adverse effects of combining fluoxetine and tricyclic antidepressants. Am J Psychiatry 1990 Apr;147(4):532
- 7. Actiq (fentanyl citrate) Australian prescribing information. Orphan Australia Pty Ltd. November 2, 2002. 8. Duragesic (fentanyl) US prescribing information. Janssen Pharmaceuticals, Inc. August, 2014.
- 9. Apadaz (benzhydrocodone and acetaminophen) US prescribing information. KemPharm, Inc.. October, 2019. 10. Zohydro ER (hydrocodone bitarate) US prescribing information. Zogenix Inc. August, 2014. OxyContin (oxycodone hydrochloride) US prescribing information. Perdue Pharma L.P. September, 2018.
- 11. Dsuvia (sufentanil) sublingual tablet US prescribing information. AcelRx Pharmaceuticals, Inc. November, 2018. 12. Avinza (morphine extended-release capsules) US prescribing information. Ligand Pharmaceuticals Incorporated April, 2014.
- 13. Opana ER (oxymorphone hydrochloride) US prescribing information. Endo Pharmaceuticals, Inc. September, 2018. 14. Nucynta ER (tapentadol) US prescribing information. Janssen Pharmaceuticals December, 2016.
- 15. Zohydro ER (hydrocodone bitarate) US prescribing information. Zogenix Inc. August, 2014.

200 method. 2-Hydroxyitra 2-Hydroxyne 3-Hydroxygu 4-OH Omepraz 7-Hydroxy ( 7-Hydroxyme 7-Hydroxyv 8-Hydroxye 9-Hydroxyris Abirate Albute alpha-Hydroxyı Amioda Amitripty Amlodi Amlodipine Ampren

# Brian E Cox PhD, David M Schwope, PhD, Paul D'Aloise, MS, Josh Schrecker, Pharm D and Rebecca Heltsley, PhD

#### **Region Demographics**

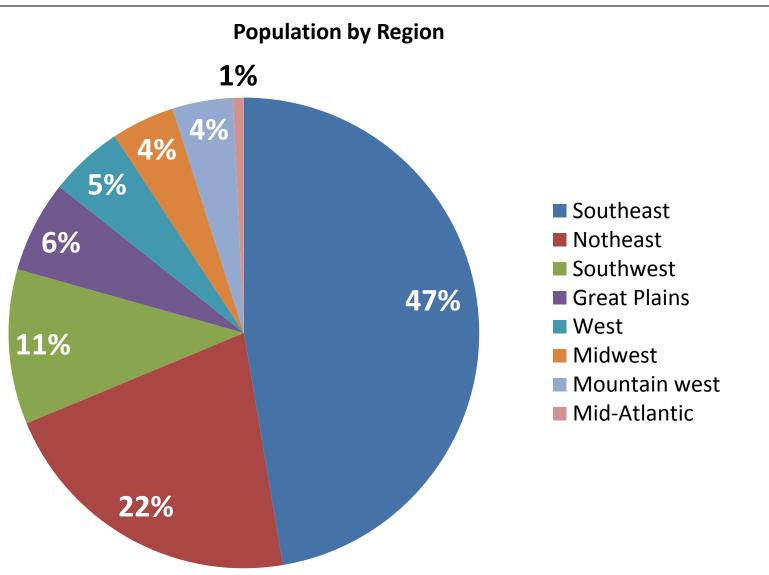


Figure 1: Oral fluid samples were obtained from regions across the country. The majority of samples came from the Southeast region with the fewest coming from the Mid-Atlantic. A total of 3177 samples were analyzed in the study from the first quarter of 2021.

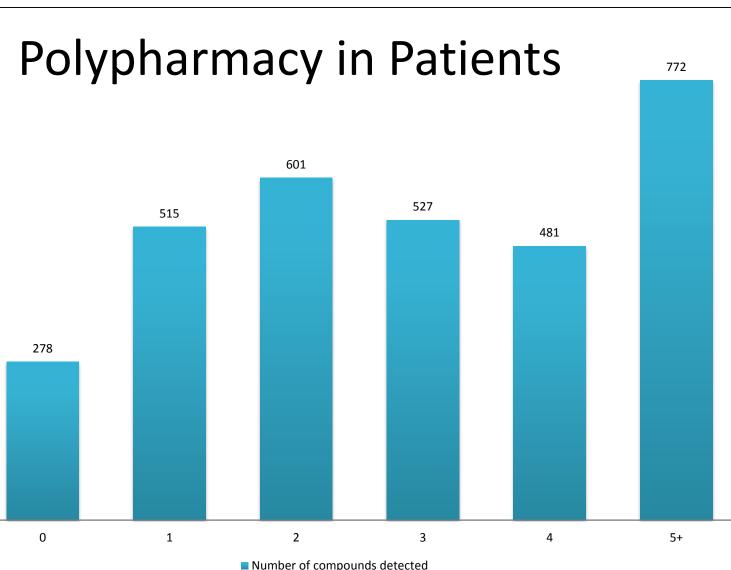


Figure 2: The number of compounds detected in each oral fluid sample through all testing performed. These data show that a large number of samples exhibit polypharmacy (5+ substances) and that, similar to urine, multiple substances can be detected in this

		≥5 Substances				
Age range, y	N	Present (% <sup>a</sup> )				
18-44	1139	244 (21.4)				
45-64	1313	350 (26.7)				
≥65	725	179 (24.7)				
Total	3177	773 (24.3)				
Total3177773 (24.3) <sup>a</sup> Number of patients in age group with 5 or more						

number of patients in age group with 5 of more substances detected in the oral fluid divided by N for the age group then multiplied by 100

Table 1: All age groups were represented in the study. As in urine, observed polypharmacy was not related to age, demonstrating the utility of DDI testing across all ages.

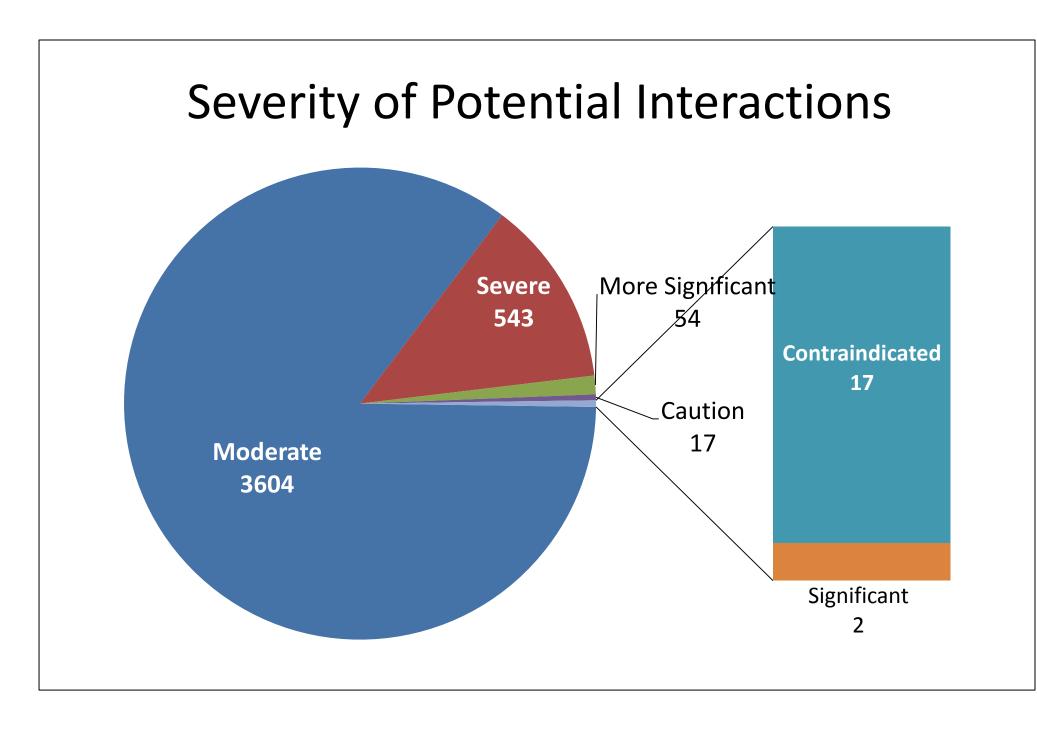


Figure 3: Chart illustrating the degree of severity of the interaction detected. The majority of the potential interactions were moderate. However, over 13% of the total interactions detected were either severe or contraindicated. These data are similar to what has been observed in urine testing for potential DDIs.

<b></b>								
DDI Testing Profile				Oral Fluid Comprehensive Testing Profile				
2-Hydroxyitraconazole	Carbidopa Metabolite	Famotidine	N-Desmethyl Azithromycin	Primidone	Morphine	MDA	Clozapine N-oxide	Fluvoxamine
2-Hydroxynelfinavir	Carvedilol	Fluconazole	N-Desmethyl Terbinafine	Promethazine Sulfoxide	Oxymorphone	Methamphetamine	Desmethylclozapine	Desmethylclomipramine
3-Hydroxyguanfacine	Chloroquine	Fluoxetine	N-Desmethylcitalopram	Propranolol	Hydromorphone	Phentermine	Clozapine	Clomipramine
4-OH Omeprazole Sulfide	Chlorpromazine	Fluphenazine	N-Despropyl Ropinirole	Quetiapine	Dihydrocodeine	MDMA	N-Desmethylolanzapine	Desipramine
7-Hydroxy Quetiapine	Cimetidine	Fluvoxamine Acid	NDM-Carboxy Terbinafine	Quinidine	Norcodeine	Meprobamate	Olanzapine	Imipramine
7-Hydroxymethotrexate	Ciprofloxacin	Fluvoxamine	Nebivolol	Quinine	Codeine	Carisoprodol	7-Hydroxy Quetiapine	Trimipramine
7-Hydroxywarfarin	Citalopram	Formoterol	Nefazodone	Ranitidine	Noroxycodone	Nortapentadol	Norquetiapine	Mirtazepine
8-Hydroxyefavirenz	Clarithromycin	Fosamprenavir	Nelfinavir	Ranolazine	Oxycodone	Tapentadol	Quetiapine	Protriptyline
9-Hydroxyrisperidone	Clobazam	Guanfacine	Nevirapine	Rifabutin	Norhydrocodone	Gabapentin	Clonidine	Nortripyline
Abiraterone	Clomipramine	Haloperidol	Nifedipine Carboxylate	Rifampin	Hydrocodone	Pregabalin	Lofexidine	Amitriptyline
Albuterol	Clopidogrel COOH	Hydroxybupropion	Nifedipine	Rifapentine	Flurazepam	Norketamine	Promethazine Sulfoxide	Norcyclobenzaprine
alpha-Hydroxymetoprolol	Clopidogrel	Hydroxymetronidazole	Nilotinib	Risperidone	Oxazepam	Ketamine	Oxcarbazepine Metabolite	Cyclobenzaprine
Amiodarone	Cobicistat	Hydroxypioglitazone	Norcyclobenzaprine	Ritonavir	Alprazolam	Hydroxybupropion	Oxcarbazepine	Desmethyldoxepin
Amitriptyline	Cyclobenzaprine	Hydroxyritonavir	Nordoxepin	Rivaroxaban	Lorazepam	Bupropion	Carbamazepine Epoxide	Doxepin
Amlodipine	Darunavir	Hydroxyzine	Norfluoxetine	Ropinirole	7-Aminoclonazepam	6-Hydroxybuspirone	Carbamazepine	Methocarbamol
Amlodipine Metabolite	Deacetyl Diltiazem N-O	Hyperforin	Norquetiapine	Salmeterol	Clonazepam	Buspirone	Cariprazine	Metaxalone
Amprenavir	Dehydroaripiprazole	Iloperidone	Norsertraline	Saquinavir	Temazepam	9-Hydroxyrisperidone	Chlorpromazine	Baclofen
Anastrozole	Dehydrotizanidine	Indanivir	Nortriptyline	Sertraline	Diazepam	Risperidone	Perphenazine	Suvorexant
Apixaban	Delavirdine	Itraconazole	Norverapamil	Sumatriptan	Nordiazepam	Ziprasidone	Fluphenazine	Eszopiclone
Aripiprazole	Desethylamiodarone	Ketoconazole	O-Desmethylvenlafaxine	Sumatriptan Metabolite	6-MAM	Hydroxylurasidone	Vortioxetine	Zaleplon
Asenapine	Desipramine	Labetalol	OH-Lansoprazole Sulfide	Terbinafine	Heroin	Lurasidone	Topiramate	Zolpidem-COOH
Atazanavir	Desmethylclobazam	Lamotrigine	Olanzapine	Thioridazine	6-Acetylcodeine	m-CPP	Duloxetine	Zolpidem
Atenolol	Desmethylranitidine	Lansoprazole N-Oxide	Omeprazole Sulfone	Timolol	O-desmethyltramadol	Trazodone	O-desmethylvenlafaxine	Ritalinic Acid
Atomoxetine	Dexamethasone	Levodopa Metabolite	Ondansetron	Tipranavir	Tramadol	Vilazodone	Venlafaxine	Methylphenidate
Atorvastatin	Dihydrokavain	Levofloxacin/Ofloxacin	Oxcarbazepine	Tizanidine	N-desmethyltramadol	Iloperidone	Atomoxetine	Dextrorphan
Atorvastatin Lactone	Dihydroxybergamottin	Linagliptin	Oxcarbazepine Metabolite	Trazodone	Norfentanyl	3-Hydroxy Guanfacine	Milnacipran	Dextromethorphan
Avanafil	Diltiazem	Lorcaserin	Paroxetine	Venlafaxine	Fentanyl	Guanfacine	N-desmethylcitalopram	Diphenhydramine
Azithromycin	Donepezil	Memantine	Paroxetine Metabolite III	Verapamil	Norbuprenorphine	Haloperidol	Citalopram	Loperamide
Baclofen	Doxepin	Methocarbamol	Pazopanib	Voriconazole	Buprenorphine	Lamotrigine	Norfluoxetine	Lorcaserin
Bergaptol	Doxorubicin	Methotrexate	Perphenazine	Voriconazole N-Oxide	Naloxone	Levetiracetam	Fluoxetine	7-hydroxymitragynine
Bupropion	Duloxetine	Methylprednisolone	Phenobarbital	Warfarin	EDDP	Dehydroaripiprazole	Paroxetine MTB III	Mitragynine
Butalbital	Efavirenz	Metoclopramide	Phenytoin		Methadone	Aripiprazole	Paroxetine	Oral fluid ethanol
Canagliflozin	Enzalutamide	Metoprolol	Pioglitazone		Benzoylecgonine	Brexpiprazole	Norsertraline	
Carbamazepine	Erythromycin	Metronidazole	Posaconazole		Cocaine	Hydroxyzine	Sertraline	
Carbamazepine Epoxide	Etravirine	Mirabegron	Prednisone		Amphetamine	Asenapine	Fluvoxamine Acid	

#### **Copyright © 2021 Aegis Sciences Corporation All Rights Reserved**

# Results

#### Age Range

Analytes tested in oral fluid that can be used for determining potential DDIs.



#### Number of Potential DDIs Present

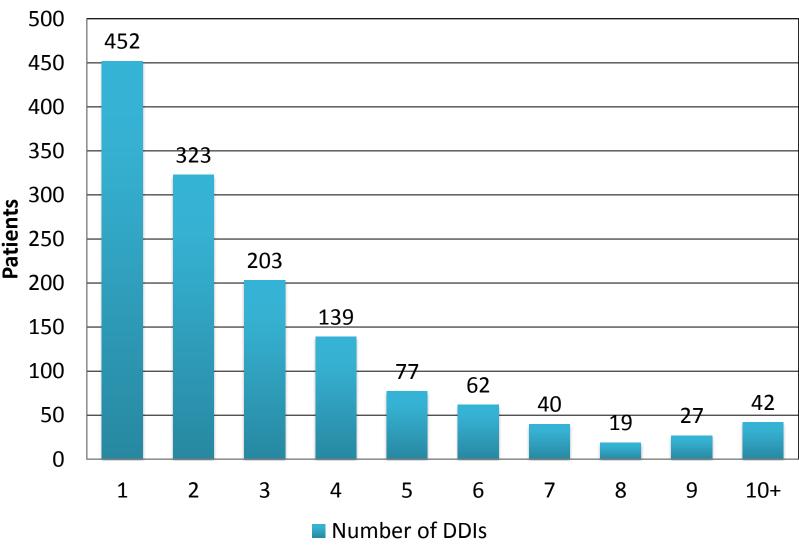


Figure 4: The total number of potential interactions detected in oral fluid for tested patients. Most patients tested in oral fluid exhibited 1-2 potential interactions; however, several patients tested exhibited more than 10 potential interactions. These data illustrate the usefulness and utility of testing patients for potential DDIs using oral fluid.

Moderate	Concurrent use of op profound sedation, re				
Moderate	Concurrent use of opi				
Moderate	derivatives, may result				
	Concurrent use of am				
	syndrome. Symptom				
	hyperreflexia, clonus,				
Moderate	amphetamines or phe				
	hypertension more di				
	desvenlafaxine, dulox				
	paroxetine, sertraline,				
Moderate	Concurrent use of CY				
Wiouerate	metoprolol.(3,4)				
	Concurrent administra				
	metabolized by CYP2				
	for seizures, severe an				
Severe	Clomipramine, desipi				
Severe	CredibleMeds(5) as p				
	may increase the risk				
	with clomipramine, a				
	serotonin syndrome.				
	Concurrent use of buy				
Severe	withdrawal symptoms				
	decreased opioid side				
	The concurrent admir				
Severe	from alfentanil,(6,7) l				
	sufentanil,(11) includ				
	Use of alcohol may re				
Contraindicated	release capsules,(12)				
	extended-release tabl				



Detection of potential DDIs in OF via LC-MS/MS provides valuable information to clinicians, particularly when treating patients not able or willing to disclose all medications taken, patients being treated for multiple conditions or patients seeing multiple providers. Many of the potential ADEs observed in this cohort were for drugs not routinely monitored in OF compliance testing; testing for these other classes of drugs is important for pain and/or behavioral health specialists to help prevent ADEs in their patients. These findings further expand the applicability of OF testing and when combined with the ease of collection and sample handling, provide further justification for the use of this matrix in the clinical toxicology, drug monitoring and telehealth settings.

#### **Top DDIs by class**

bioids and other CNS depressants, such as muscle relaxants, may result in espiratory depression, coma, and/or death.(1)

pioids and other CNS depressants, such as antipsychotics, including phenothiazine ult in profound sedation, respiratory depression, coma, and/or death.(1) nphetamines with agents that affect serotonin may increase the risk of serotonin ns of serotonin syndrome may include tremor, agitation, diaphoresis, s, tachycardia, hyperthermia, and muscle rigidity.(2) Concurrent use of entermine and a SNRI may increase the risk for high blood pressure or make lifficult to control. SSRIs and SNRIs linked to this monograph are: citalopram, oxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, e, venlafaxine, vilazodone and vortioxetine. CYP2D6 inhibitors may result in elevated levels of and toxicity from

ration of fluoxetine or paroxetine with selected cyclic agents which are 2D6 or CYP2C19 may result in an increase in serum levels, toxicities (e.g. risk anticholinergic effect), and/or clinical effects of the tricyclic agent or trazodone. bramine, imipramine, nortriptyline, and trimipramine are classified by possible QT prolonging agents. Increased serum levels of these tricyclic agents for torsades de pointes. Concurrent administration of fluoxetine or paroxetine and perhaps with imipramine or high dose amitriptyline may increase the risk for

prenorphine with other opioids in opioid dependent patients may result in ns. Concurrent use in other patients may result in additive or decreased analgesia, effects, and/or renarcotization.

inistration of a CYP3A4 inhibitor may result in elevated levels of and toxicity benzhydrocodone,(8) fentanyl,(6,7) hydrocodone,(9) oxycodone(10), and ding profound sedation, respiratory depression, coma, and/or death. result in an acceleration of opioid release from Avinza (morphine) extended-Opana (oxymorphone) extended-release tablets,(13) Nucynta (tapentadol) lets,(14) and Zohydro (hydrocodone) extended-release capsules.(15)

### Conclusions