

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

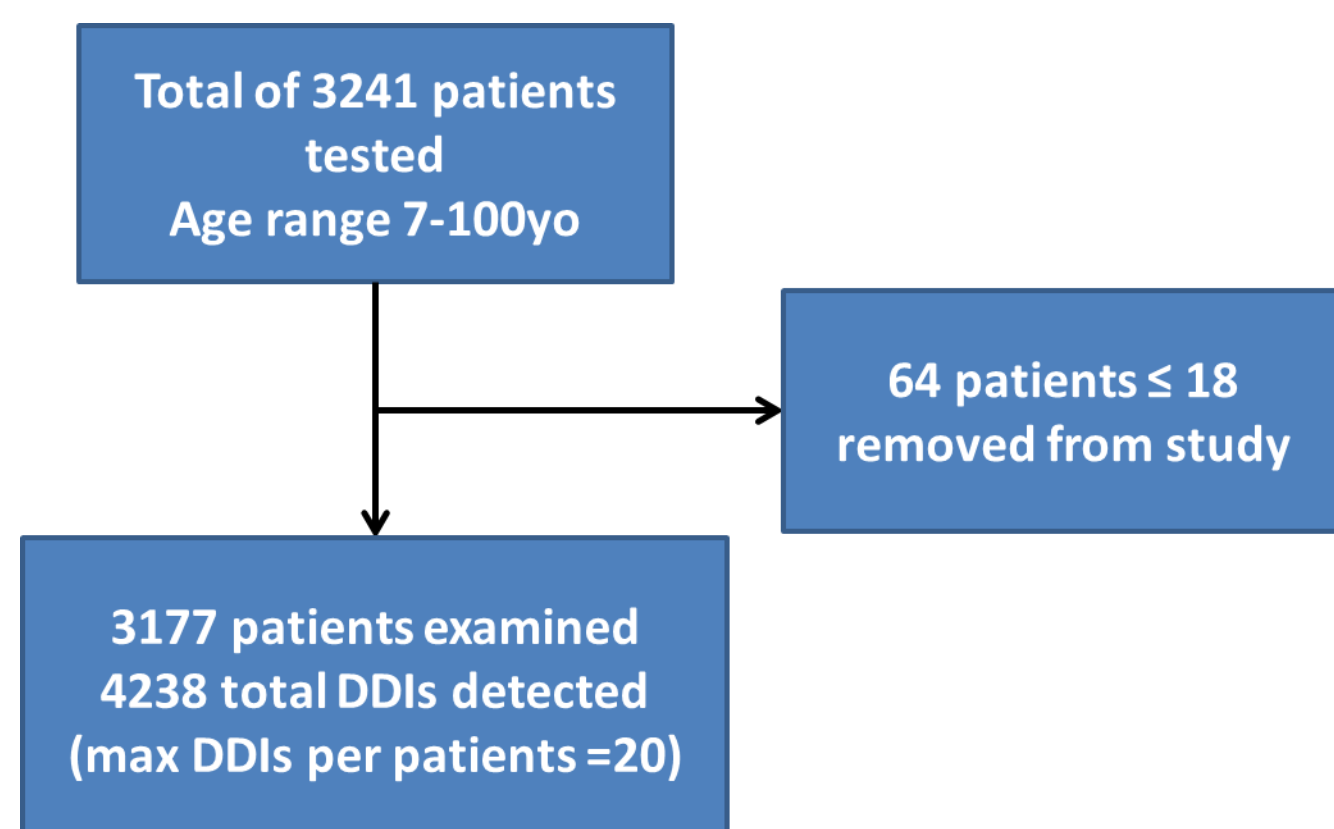
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## Introduction

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; 352(11):1112-20.
  3. Valdivia Pharmaceuticals, LLC March, 2013.
  4. Toprol-XL (metoprolol succinate) US prescribing information. AstraZeneca LP March, 2011.
  5. Woosley RL, Romero KA. www.CredibleMeds.org, QDRUGS 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. KenPharm, Inc. October, 2019.
  10. Zohydro ER (hydrocodone bitartrate) US prescribing information. Zogenix Inc. August, 2014. OxyContin (oxycodone hydrochloride) US prescribing information. Purdue Pharma L.P. September, 2018.
  11. Duvia (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 (oxycodone hydrochloride) US prescribing information. Endo Pharmaceuticals, Inc. September, 2018.
  14. Nucynta ER (tapentadol) US prescribing information. Janssen Pharmaceuticals December, 2016.
  15. Zohydro ER (hydrocodone bitartrate) US prescribing information. Zogenix Inc. August, 2014.

## Results

### Region Demographics

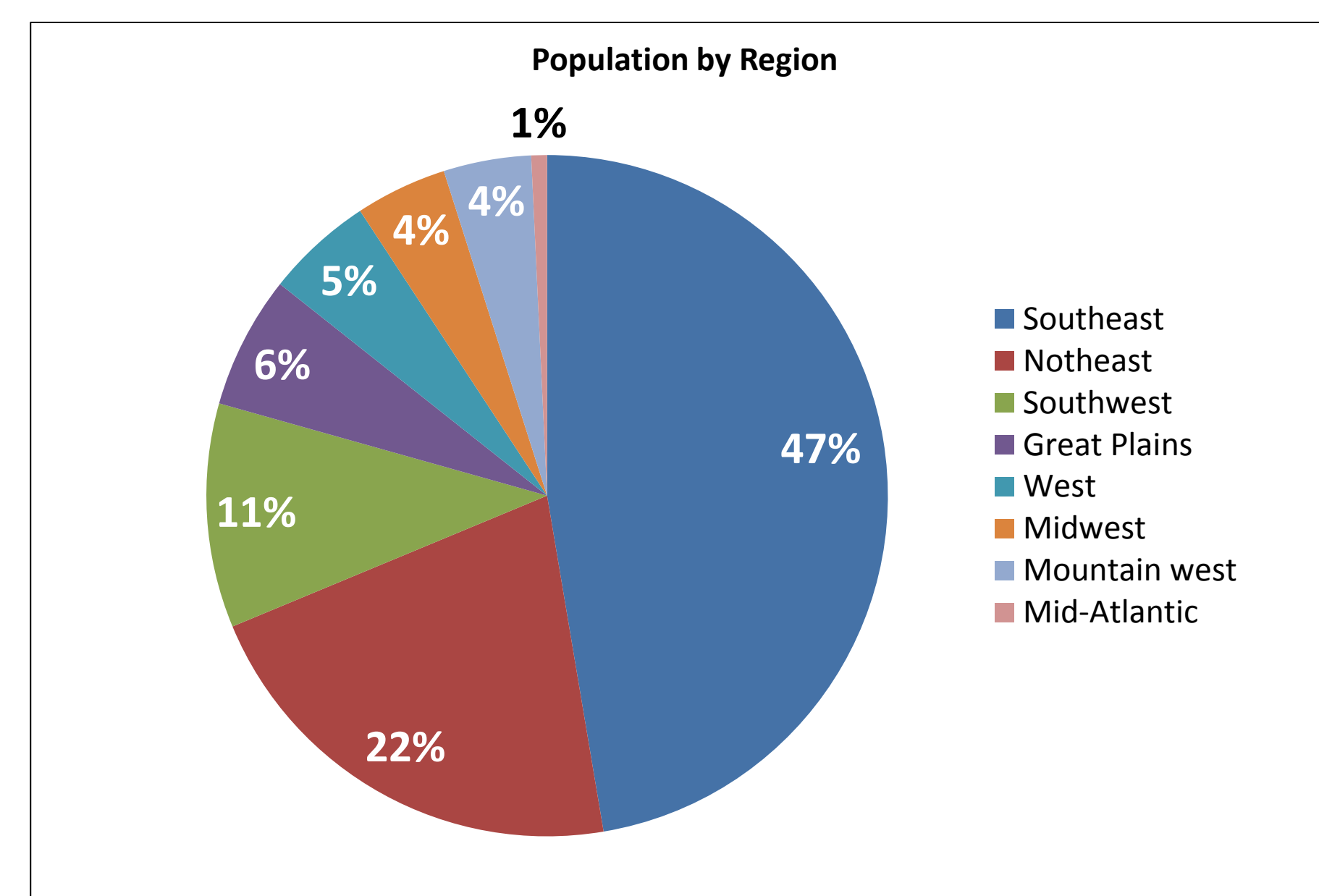


Figure 1: Oral fluid samples were obtained from regions across the country. The majority of samples came from the Southeast region with the fewest coming from the Mid-Atlantic. A total of 3177 samples were analyzed in the study from the first quarter of 2021.

### Age Range

| Age range, y | N           | ≥ 5 Substances Present (% <sup>a</sup> ) |
|--------------|-------------|--|
| 18-44        | 1139        | 244 (21.4)                               |
| 45-64        | 1313        | 350 (26.7)                               |
| ≥ 65         | 725         | 179 (24.7)                               |
| <b>Total</b> | <b>3177</b> | <b>773 (24.3)</b>                        |

<sup>a</sup>Number of patients in age group with 5 or 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.

### Number of Potential DDIs Present

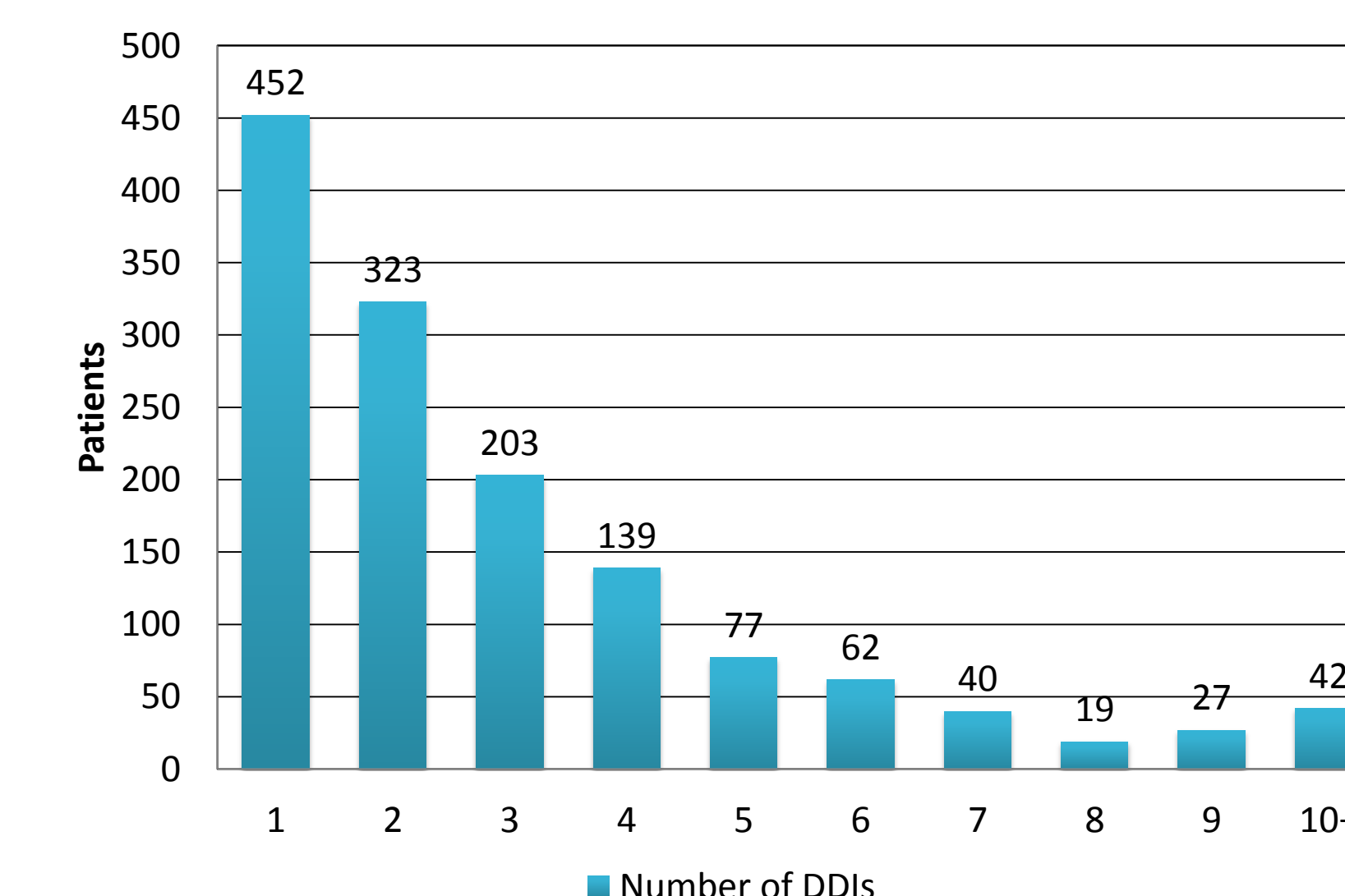


Figure 4: The total number of potential interactions detected in oral fluid for tested patients. Most patients tested in oral fluid exhibited 1-2 potential interactions; however, several patients tested exhibited more than 10 potential interactions. These data illustrate the usefulness and utility of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

### Polypharmacy in Patients

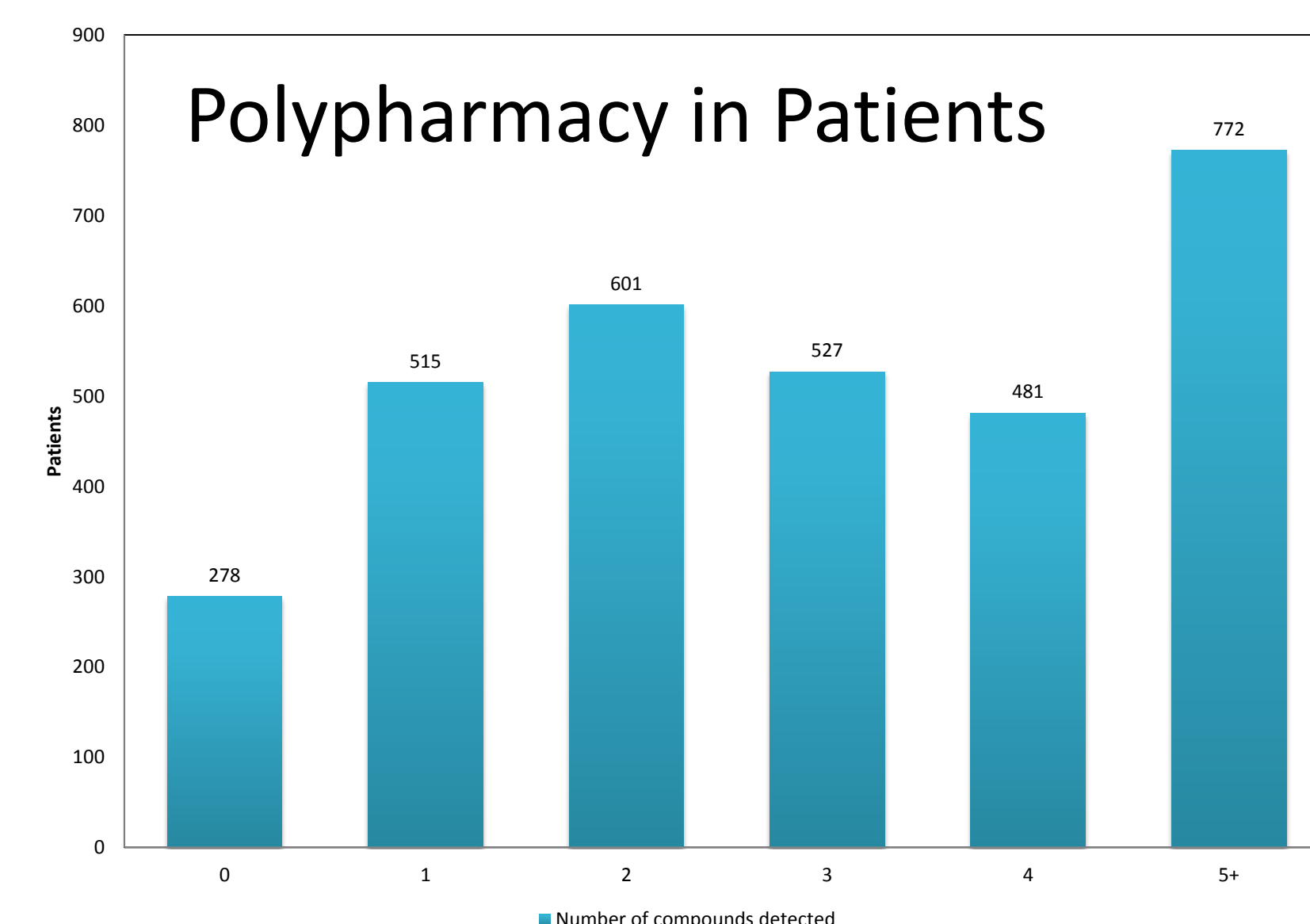


Figure 2: The number of compounds detected in each oral fluid sample through all testing performed. These data show that a large number of samples exhibit polypharmacy (5+ substances) and that, similar to urine, multiple substances can be detected in this method.

### Severity of Potential Interactions

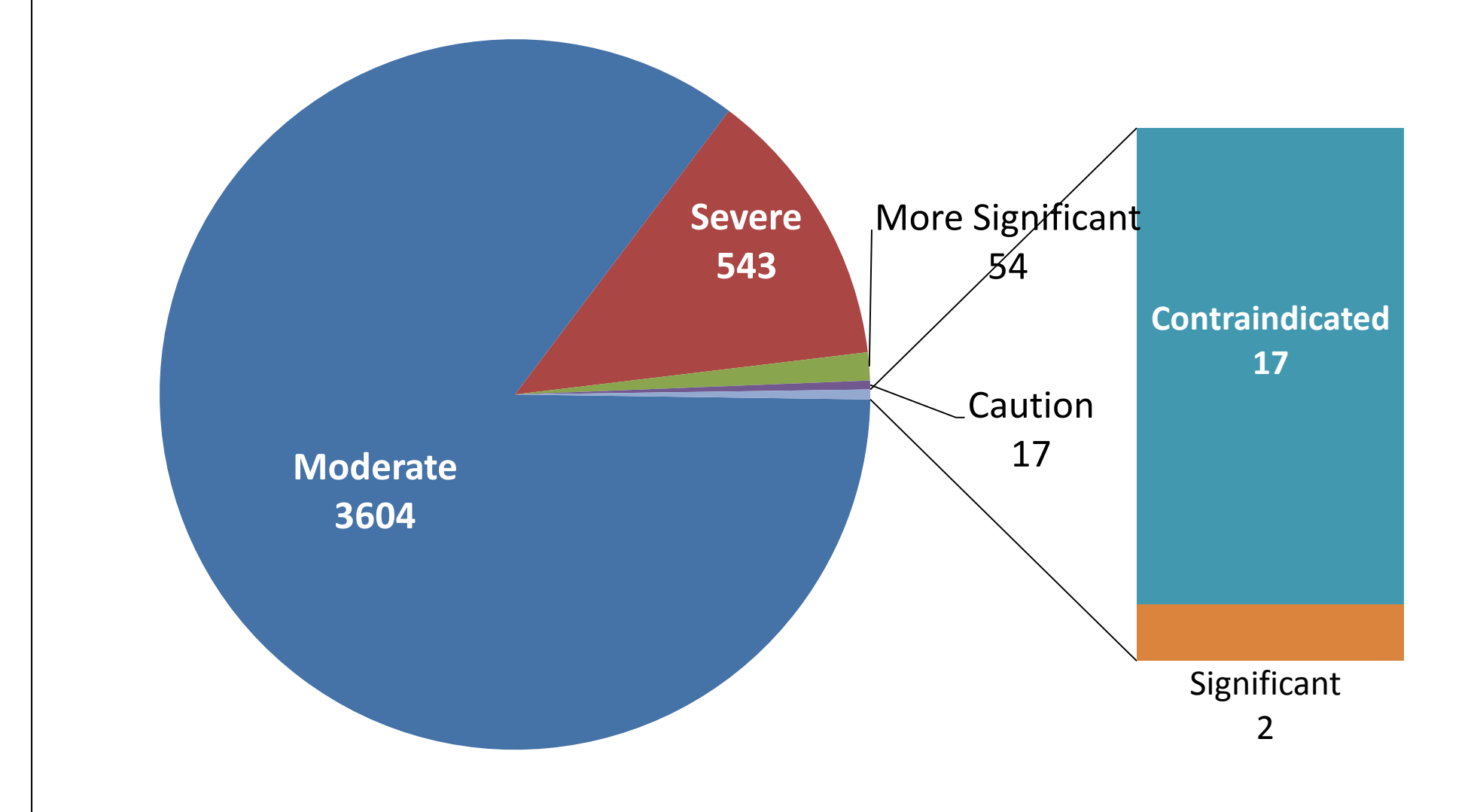


Figure 3: Chart illustrating the degree of severity of the interaction detected. The majority of the potential interactions were moderate. However, over 13% of the total interactions detected were either severe or contraindicated. These data are similar to what has been observed in urine testing for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

| DDI Testing Profile      |                        |                        |                           | Oral Fluid Comprehensive Testing Profile |                     |                        |                          |                       |
|--------------------------|------------------------|------------------------|---------------------------|--|---------------------|------------------------|--------------------------|-----------------------|
| 2-Hydroxyitraconazole    | Carbidopa Metabolite   | Famotidine             | N-Desmethyl Azithromycin  | Primidone                                | Morphine            | MDA                    | Clozapine N-oxide        | Fluvoxamine           |
| 2-Hydroxyflinavir        | Fluconazole            | Carvedilol             | N-Desmethyl Terbinafine   | Promethazine Sulfoxide                   | Oxymorphone         | Methamphetamine        | Desmethylclozapine       | Desmethylclomipramine |
| 3-Hydroxyguanfacine      | Chloroquine            | Fluoxetine             | N-Desmethylcitalopram     | Propranolol                              | Hydromorphone       | Phentermine            | Clozapine                | Clomipramine          |
| 4-OH Onasepazole 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-Hydroxymethorexate     | Ciprofloxacin          | Fluvoxamine            | Nebivolol                 | Quinine                                  | Codine              | Carisoprodol           | 7-Hydroxy Quetiapine     | Trimipramine          |
| 7-Hydroxywarfarin        | Citalopram             | Formoterol             | Nefazodone                | Ranitidine                               | Noroxycodone        | Nortapentadol          | Norquetiapine            | Mirtazapine           |
| 8-Hydroxyefavirenz       | Clarithromycin         | Fosamprenavir          | Nefinavir                 | Ranolazine                               | Oxycodone           | Tapentadol             | Quetiapine               | Proprityline          |
| 9-Hydroxyrisperidone     | Clobazam               | Guanfacine             | Nevirapine                | Rifabutin                                | Norhydrocodone      | Gabapentin             | Clonidine                | Nortriptyline         |
| Albuterol                | Clomipramine           | Haloperidol            | Nifedipine Carboxylate    | Rifampin                                 | Hydrocodone         | Pragalin               | Lofexidine               | Amiripiline           |
| alpha-Hydroxymetoprolol  | Clonidine              | Hydroxypropion         | Nifedipine                | Risperidone                              | Flurazepam          | Norketamine            | Promethazine Sulfoxide   | Norcytobenzaprine     |
| Amiodarone               | Cobicistat             | Hydroxypropion         | Nitroglycerin             | Risperidone                              | Oxazepam            | Ketamine               | Oxcarbazepine Metabolite | Cyclobenzaprine       |
| Amiripiline              | Cyclobenzaprine        | Hydroxypropion         | Norethindrone             | Ritonavir                                | Alprazolam          | Hydroxypropion         | Oxcarbazepine            | Desmethyldoxepin      |
| Amisulpride              | Dantrolene             | Hydroxypropion         | Norlophedrine             | Rivaroxaban                              | Lorazepam           | Bupropion              | Carbamazepine Epoxide    | Doxepin               |
| Amphetamine              | Desmethylamitriptyline | Ketocozazole           | O-Desmethylvenlafaxine    | Sumatriptan Metabolite                   | 6-MAM               | Hydroxypropion         | Carbamazepine            | Methocarbamol         |
| Amphetamine              | Desmethylamitriptyline | Levetiracetam          | O-Desmethylvenlafaxine    | Sumatriptan Metabolite                   | 6-MAM               | Hydroxypropion         | Carbamazepine            | Metaxalone            |
| Amphetamine              | Desmethylamitriptyline | Levetiracetam          | O-Desmethylvenlafaxine    | Sumatriptan Metabolite                   | 6-MAM               | Hydroxypropion         | Carbamazepine            | Metaxalone            |
| Atazanavir               | Desmethylamitriptyline | Lansoprazole N-Oxide   | Ondansetron               | Tipranavir                               | N-Desmethyltramadol | Ibuprofen              | Atomoxetine              | Dextropropriphan      |
| Atomoxetine              | Dexamethasone          | Levodopa Metabolite    | Ondansetron               | Tipranavir                               | N-Desmethyltramadol | Ibuprofen              | Atomoxetine              | Dextropropriphan      |
| Atorvastatin             | Dihydrokavain          | Levofloxacin Orboxacin | Ondansetron               | Tipranavir                               | N-Desmethyltramadol | Ibuprofen              | Atomoxetine              | Dextropropriphan      |
| Atorvastatin Lactone     | Dihydrokavain          | Levofloxacin Orboxacin | Ondansetron               | Tipranavir                               | N-Desmethyltramadol | Ibuprofen              | Atomoxetine              | Dextropropriphan      |
| Avanafil                 | Diltiazem              | Locacerein             | Paroxetine Metabolite III | Verapamil                                | Norbutenpropine     | Buprenorphine          | Haloperidol              | Loperamide            |
| Azithromycin             | Diltiazem              | Locacerein             | Paroxetine Metabolite III | Verapamil                                | Norbutenpropine     | Buprenorphine          | Haloperidol              | Loperamide            |
| Baclofen                 | Doxepin                | Methocarbamol          | Paroxetine Metabolite III | Verapamil                                | Norbutenpropine     | Buprenorphine          | Haloperidol              | Loperamide            |
| Bergapton                | Doxorubicin            | Methotrexate           | Perphenazine              | Voriconazole N-Oxide                     | Naloxone            | Levetiracetam          | Fluoxetine               | 7-hydroxymirtazapine  |
| Bupropion                | Duloxetine             | Methylprednisolone     | Phenobarbital             | Warfarin                                 | EDDP                | Dehydroepiandrosterone | Paroxetine MTB III       | Mirtazapine           |
| Butalbital               | Enflurane              | Metoprolol             | Pioglitazone              | Nersertraline                            | Methadone           | Aripiprazole           | Paroxetine               | Oral fluid ethanol    |
| Canagliflozin            | Enflurane              | Metoprolol             | Pioglitazone              | Nersertraline                            | Benzoyllecgonine    | Brexipiprazole         | Nersertraline            |                       |
| Carbamazepine            | Erythromycin           | Metronidazole          | Poconazole                | Prednisone                               | Cocaine             | Hydroxyzine            | Sertraline               |                       |
| Carbamazepine Epoxide    | Etravirine             | Mirabegron             |                           |  | Amphetamine         | Asenapine              | Fluvoxamine Acid         |                       |

## Conclusions

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.

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