Helping Clinicians
Make Better Decisions

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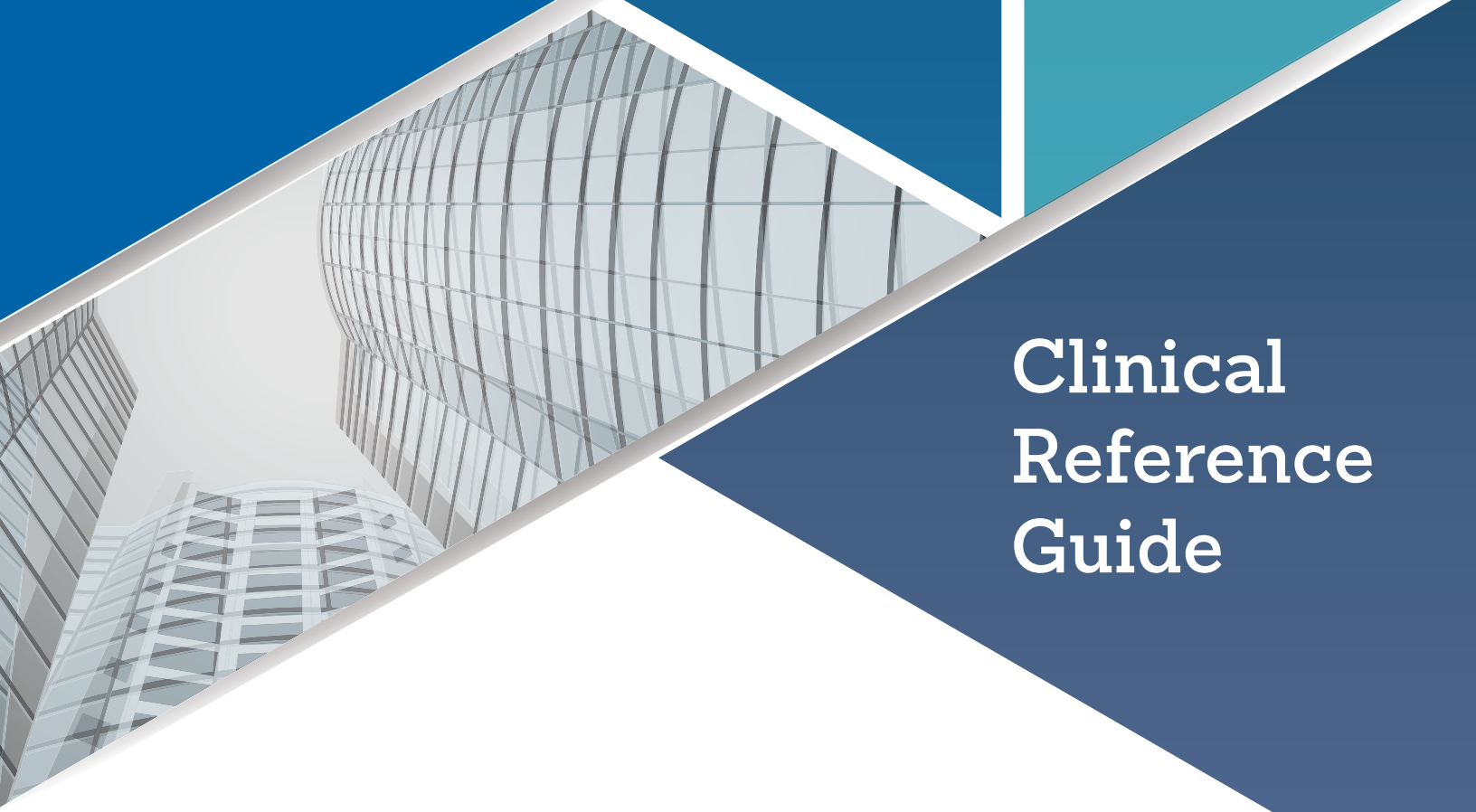


Clinical Reference Guide

Definitive Testing – Interpreting Unexpected Results

Definitive Testing – Interpreting Unexpected Results

Testing results may be unexpected for various reasons. Misinterpretation of results can lead to poor patient outcomes. Consultation with a toxicologist, clinical pharmacist, or other expert with knowledge of toxicology, pharmacology, and result interpretation is strongly encouraged, especially when results are unexpected.

Clinicians must use professional judgment to decide when definitive analytical techniques, such as gas chromatography/mass spectrometry (GC/MS) or liquid chromatography/tandem mass spectrometry (LC/MS/MS), are needed in the clinical setting. Testing with more specific methods assists the clinician by:

- Identifying which specific drugs are present within the drug class.
- Ruling out false positives due to cross-reactivity in presumptive immunoassay tests.
- Preventing false negatives due to poor cross-reactivity in presumptive immunoassay methods.
- Testing using lower thresholds.
- Identifying additional drugs and metabolites missed in presumptive immunoassay tests.

A. Interpretation Considerations with Definitive Testing

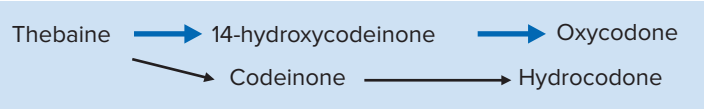
Unanticipated outcomes from definitive testing may be either correct, due to a number of well understood phenomena, or, much more rarely, incorrect and a result of testing process failures that can arise from a variety of causes. Incorrect results are often attributable to pre-analytical factors. Samples can be misidentified or mixed-up during the collection process. Contamination during collection may also be a concern since testing is in the parts-per-billion concentration range for many drugs. Specimen collection procedures must be carefully crafted and rigorously adhered to in order to prevent errors. Once specimens are received in the laboratory, risks for error may be managed through a variety of strategies. An aggressive Quality Management System is critical to obtaining accurate test results. Starting with a rigorous method validation program, including open and blind quality control specimens in every analytical batch, and frequent proficiency testing is the basis for quality testing outcomes. Analysis of medication monitoring samples presents a variety of challenges to a toxicology laboratory that may require unique solutions.

Unexpected Positive Results

Unexpected false positives arising from immunoassay presumptive testing are readily resolved by definitive mass spectrometry analyses. Additionally, true unexpected positives may be detected when definitive testing is applied to negative presumptive immunoassay specimens. Such findings are attributable to cross-reactivity limitations that are characteristic of this presumptive methodology in contrast to the molecular level specificity of mass spectrometry techniques. When interpreting unexpected positive results by mass spectrometry, it is important to note that patient under-reporting and denial of nonprescribed or illicit drug use are common; 46% of patients with positive toxicology test results denied illicit drug use during research interviews, despite guaranteed anonymity.[1] In addition, there are a variety of common excuses given by patients once confronted by a positive drug test (e.g., passive exposure). These are often promulgated on online message boards, but typically there is no basis in scientific fact. Those caveats aside, there are instances when an unexpected positive result has a rational explanation that does not involve extracurricular drug use, and it is important to explore these before taking action.

Unexpected true positives with mass spectrometry testing may occur when minor metabolism routes for one opiate result in small amounts of another opiate present in a urine or oral fluid specimen. Additionally, manufacturers allow the presence of "process impurities" in their pharmaceutical products, thus unexpected positives may result from the presence of these pharmaceutical impurities. Some common medications, such as morphine, oxycodone, and oxymorphone, all contain small amounts of other opiate drugs. These impurities may be formed during the manufacturing process and be present in the final formulation (see Figure 9.1). The allowed percentages are very small, usually 0.1-0.5%, and do not have a clinically significant pharmacologic effect. Known pharmaceutical impurities found in

Figure 9.1: Hydrocodone Formed During Oxycodone Manufacturing Process



opiate pain medications are listed in Table 9.1. Some researchers have proposed that methamphetamine may be present in pharmaceutical preparations of amphetamine (including Adderall® and Vyvanse®), with methamphetamine being present in urine at 0.5% or less of the amphetamine concentration.[3,4]

Table 9.1: *Pharmaceutical Impurities in Commercial Opiate Pain Relievers*[2]

PRESCRIPTION DRUG	PHARMACEUTICAL IMPURITIES	ALLOWABLE LIMIT (%)	TYPICAL OBSERVED (%)
Codeine	Morphine	0.15	0.01-0.1
Hydrocodone	Codeine	0.15	0-0.1
Hydromorphone	Morphine Hydrocodone	0.15 0.1	0-0.025 0-0.025
Morphine	Codeine	0.5	0.01-0.05
Oxycodone	Hydrocodone	1.0	0.02-0.12
Oxymorphone	Hydromorphone Oxycodone	0.15 0.5	0.03-0.1 0.05-0.4

Traditionally, it has been thought that pharmaceutical impurities do not affect urine drug test results. However, if the urine concentration of a prescribed medication is high, then impurities may be detectable. Dr. Haddox and colleagues reported this possibility in a poster at the American Academy of Pain Medicine annual meeting in 2010.[2] Additional reports have surfaced regarding patients taking oxycodone testing positive for small amounts of hydrocodone, and patients receiving hydromorphone testing positive for small amounts of morphine.[5,6] Small amounts of hydrocodone in patients taking oxycodone have been reported in 72% of patients with urine oxycodone concentrations greater than 100,000 ng/mL.[6] Codeine is a known impurity in morphine preparations.[7,8] Unexpected positive results due to pharmaceutical impurities may occur in oral fluid as well.

Although a pharmaceutical impurity percentage may not translate to the same percentage ratio in urine or oral fluid, until more information is published on this subject, caution should be exercised whenever interpreting unexpected opiate results for a known impurity. Detection of an impurity and subsequent misinterpretation of results could cause significant patient harm, especially when assessing for treatment adherence. Following review of published literature and internal data, Aegis has adopted reporting rules to address the potential presence of pharmaceutical impurities in urine and oral fluid specimens. If non-prescribed opiates (which are known pharmaceutical impurities) are detected in conjunction with their active pharmaceutical ingredient, and if the relative concentration meets known pharmaceutical impurity limits, Aegis suppresses the result for the potential pharmaceutical impurity. In such cases, the potential impurity will be classified as a negative result, limiting undue concern regarding potential use of non-prescribed drugs.

For a list of possible reasons for drug presence with definitive results, please refer to Table 9.2.

Unexpected Negative Results

With appropriate testing methods in place, false negatives should be considerably less of a concern with definitive testing as opposed to presumptive immunoassay. Performing testing by mass spectrometry methods will reduce the incidence of false negatives from lack of cross-reactivity on the immunoassay test. Any unexpected result should be discussed with the patient and a toxicology or pharmacology expert, if necessary.[12]

If a prescribed medication is truly negative by definitive testing methods, there are a number of clinical scenarios that may contribute to this unexpected result:

- The patient may be diverting the medication.
- The patient may not be adhering to the prescribed medication regimen due to adverse effects, fear of becoming addicted, fear of running out, or a decreased need for pain relief.
- The patient may have run out of the medication early due to “bingeing” or increasing use to relieve suboptimally treated pain (pseudoaddiction).
- The medication is taken on an as-needed (PRN) basis. PRN use may shorten the period of detection, especially for blood or oral fluid.
- The concentration of parent drug and/or

metabolite(s) fell below reporting thresholds at the time of specimen collection. This may occur when the patient has not taken the drug within the time frame of the drug's period of detection.

- The ingested drug did not have time to appear in urine (e.g., initial dose of medication was ingested an hour before a urine test).
- The patient may not be absorbing the medication (e.g., sustained-release drugs given to a patient with short bowel syndrome). Absorption issues may also occur with transdermal formulations in cases involving higher amounts of adipose tissue, patches falling off, or non-adherence to a prescribed schedule.
- The patient is prescribed a transdermal formulation; some transdermal formulations (e.g. Butrans®) may not be detectable in blood or oral fluid.
- The patient receives intrathecally-administered medications, which may not be consistently detectable in urine and are extremely unlikely to be detected in blood or oral fluid.
- The patient may be rapidly metabolizing the drug, either due to genetic factors or enzyme induction by drug-drug interactions. This may contribute to negative results, particularly if appropriate metabolites are not included in laboratory testing.
- The patient may be undergoing dialysis, which can remove certain drugs from the blood.

To minimize the risk of unexpected false negatives, a laboratory providing mass spectrometry testing should implement a testing program which includes the following precautionary measures:

- Test for a broad range of prescription drugs and their major metabolites. Many laboratories do not have testing options adequate for the detection of the many prescription drugs used in pain management and behavioral health.
- Implement testing methods with appropriately low thresholds. Testing thresholds for medication adherence should be lower than thresholds used in workplace testing. It should be noted that thresholds can also be set too low, which may increase the rate of false positives from contamination or incidental exposure from pharmaceutical impurities and other sources. In addition, extremely low reporting thresholds confound the definition of adherence to a dosing regimen.

Table 9.2: *Possible Sources of Drugs (After Definitive Testing)*

DRUG IDENTIFIED	POTENTIAL SOURCES	COMMENTS
Alprazolam	• Alprazolam (Xanax®) • Designer benzodiazepines	Designer benzodiazepines, such as adinazolam, produced in clandestine laboratories, available as research chemicals, or prescribed in other countries, may be abused in the U.S. and lead to an unexpected alprazolam positive result.[9]
Amphetamine	• Amphetamine (Adderall®, Adzenys®, Dyanavel®, Evekeo®, Mydayis®) • Dextroamphetamine (Dexedrine®) • Lisdexamfetamine (Vyvanse®) • Metabolite of methamphetamine	Amphetamine concentrations are typically less than methamphetamine concentrations when amphetamine is present as a metabolite of methamphetamine.[10]
Benzodiazepine Metabolites	• Chlordiazepoxide (Librax®, Librium®) • Clorazepate (Gen-XENE®, Tranxene®) • Diazepam (Valium®) • Oxazepam • Temazepam (Restoril®) • Designer benzodiazepines	Designer benzodiazepines produced in clandestine laboratories, available as research chemicals, or prescribed in other countries, may be abused in the U.S. and lead to unexpected benzodiazepine metabolite positives. Examples include: camazepam,halazepam,ketazolam, medazepam, nordazepam, pinazepam and prazepam.[10]
Buprenorphine	Buprenorphine (Belbuca®, Bunavail®, Buprenex®, Butrans®, Cassipa®, Probuphine®, Sublocade®, Suboxone®, Zubsolv®)	
Butalbital	Butalbital (Allzital®, Butapap®, Fioricet®, Fiorinal®, Lanorinal®)	
Carisoprodol	Carisoprodol (Soma®)	

DRUG IDENTIFIED	POTENTIAL SOURCES	COMMENTS
Clonazepam	• Clonazepam (Klonopin®) • Designer benzodiazepines	Designer benzodiazepines, such as cloniprazepam, produced in clandestine laboratories, available as research chemicals, or prescribed in other countries, may be abused in the U.S. and lead to an unexpected clonazepam positive result.[11]
Cocaine	• Cocaine (illicit) • Topical cocaine solution (Goprelto®) • Imported coca teas	• Topical cocaine is used as an anesthetic in some ear, nose, and throat procedures.[12] • Cocaine is not related to other anesthetics such as lidocaine and procaine; these “caine” drugs will not cause a positive result for cocaine.[12] • Passive exposure (such as a sexual partner) is not an acceptable explanation for a positive cocaine test.[13] • Coca teas imported from South America are illegal in the U.S. (but readily available through avenues such as the internet) and may contain 2-5 mg of cocaine.[14-19]
Codeine	• Codeine (Tylenol #3®, #4®, Fioricet with Codeine®) • Camphorated Tincture of Opium (Paregoric®) • Tincture of Opium • Belladonna & Opium (B&O) suppositories • Codeine-containing cough suppressants (e.g. Robitussin AC®) • Pharmaceutical impurity in morphine and hydrocodone • Heroin • Poppy seeds	• Pharmaceutical impurity in morphine (up to 0.5%).[2] • Pharmaceutical impurity in hydrocodone (up to 0.15%).[2] • Codeine may be present after use of heroin.[20] • Codeine may be present in urine for several days after ingestion of poppy seeds, typically at lower concentrations than morphine.[12,21] • Following consumption of poppy seeds, codeine may be detected in blood or oral fluid for a few hours.[21,22] • Products containing opium may result in positive findings primarily for morphine, with codeine at lesser concentrations.
Cotinine	• Metabolite of nicotine • Tobacco smoking (cigarette, cigar) • Smokeless tobacco (chewing tobacco, snuff) • Nicotine replacement therapy (Nico-Derm CQ®, Nicorette®) • Electronic cigarette smoking	
Dihydrocodeine	• Dihydrocodeine (Trezix®) • Dihydrocodeine-containing prescription cough suppressants • Metabolite of hydrocodone	
Ethyl Glucuronide (EtG)/ Ethyl Sulfate	• Metabolites of alcohol • Autobrewery syndrome • Electronic cigarette use • Ethanol containing medications • Excessive hand sanitizer use • Ingestion of baker's yeast with sugar • Ingestion of large amounts of grape juice • Ingestion of large amounts of nonalcoholic beer or wine • Kombucha • Post-collection fermentation (hyperglycemia/diabetes)	• Post-collection fermentation may occur in diabetic patients when specimens are contaminated with microorganisms (EtG-only). • See "Testing for Alcohol Use" for more information.
Fentanyl	• Fentanyl (Abstral®, Actiq®, Duragesic®, Fentora®, Lazanda®, Subsys®) • Illicit fentanyl	Clandestinely-produced fentanyl is common and often combined with or sold as heroin or formed into counterfeit pills to look like drugs such as oxycodone, unbeknownst to the user.[23]
Gabapentin	Gabapentin (Gralise®, Horizant®, Neurontin®)	

DRUG IDENTIFIED	POTENTIAL SOURCES	COMMENTS
Heroin	Heroin (illicit)	• Heroin-specific markers include parent heroin, 6-acetylmorphine (6AM), and 6-acetylcodeine (6AC). • Other metabolites which may be present include codeine, morphine, and sometimes hydromorphone.
Hydrocodone	• Hydrocodone (Anexsia®, Hysingla®, Norco®, Reprexain®, Zohydro®) • Major metabolite of Benzhydrocodone (Apadaz®)[25] • MINOR metabolite of codeine • Pharmaceutical impurity in oxycodone and hydromorphone • Hydrocodone-containing cough suppressants (Obredon®, Rezira®, Tussicaps®, Tussigon®, Vituz®)	• Minor metabolite of codeine: hydrocodone concentrations in urine should typically be under 5% of the codeine concentration.[24] • Pharmaceutical impurity in hydromorphone (up to 0.1%).[2] • Pharmaceutical impurity in oxycodone (most notably OxyContin®, up to 1%).[2]
Hydromorphone	• Hydromorphone (Dilaudid®, Exalgo®) • Metabolite of hydrocodone • MINOR metabolite of morphine • Pharmaceutical impurity in oxymorphone	• Minor metabolite of morphine: hydromorphone concentrations in urine are usually under 6% of the morphine concentration.[7,26-29] • Hydromorphone sometimes appears as a metabolite of morphine after heroin ingestion. • Pharmaceutical impurity in oxymorphone (up to 0.15%).[2]
Lorazepam	Lorazepam (Ativan®)	Designer benzodiazepines produced in clandestine laboratories, available as research chemicals, or prescribed in other countries, may be abused in the U.S. and lead to unexpected lorazepam positives. Examples include: cloxazolam, delorazepam and diclazepam.[10]
Ketamine	• Ketamine (Ketalar®) • Esketamine (Spravato®)	Esketamine is the S- isomer of ketamine; Ingestion of esketamine will result in a positive for ketamine with Aegis testing.
Marijuana	• Marijuana • Dronabinol (Marinol®) • Hemp products • Cannabidiol products	• Positive marijuana tests from passive exposure are extremely unlikely. Chances of a positive result increase with heavy smoke exposure, long duration of exposure, lack of ventilation, and if exposure occurs same day as the sample is collected.[30] • Sativex® oromucosal spray may also cause a positive test; Sativex® is not available in the U.S., but is available in Canada. • THC content varies among unregulated hemp and cannabidiol products; the ability of these products to cause a positive marijuana result will depend on the amount of THC present in the product, the amount and frequency of the ingestion, and individual patient pharmacokinetics.[31,32] • Positives in oral fluid from use of dronabinol (Marinol®) are unlikely.[33] • "Highly purified" cannabidiol (Epidiolex®) was developed to contain negligible amounts of THC;[34] thus, it is unlikely to result in a marijuana positive.
MDMA (Ecstasy)	MDMA	
Meperidine	Meperidine (Demerol®)	
Meprobamate	• Meprobamate • Metabolite of carisoprodol (Soma®)	

DRUG IDENTIFIED	POTENTIAL SOURCES	COMMENTS

Methamphetamine	• Methamphetamine (Desoxyn®)
	• Metabolite of benzphetamine
	• Metabolite of selegiline (EMSAM®, Zelapar®)
	• Over-the-counter levmetamfetamine nasal vapoinhaler
	• Illicit methamphetamine
	• Potential pharmaceutical impurity in amphetamine products (e.g. Adderall®, Vyvanse®)
		• Sources of d-isomer:
		  • Methamphetamine (Desoxyn®)
		  • Benzphetamine
		  • Illicit methamphetamine
		• Sources of l-isomer:
		  • Selegiline
		  • Over-the-counter nasal levmetamfetamine vapoinhaler
		  • Illicit methamphetamine
		• Some researchers have proposed that methamphetamine may be present in pharmaceutical preparations of amphetamine (including Adderall® and Vyvanse®), with methamphetamine being present in urine at 0.5% or less of the amphetamine concentration.[3,4]

Methylphenidate	• Methylphenidate/Dexmethylphenidate (Aptensio®, Concerta®, Cotempla®, Daytrana®, Focalin®, Jornay PM®, Metadate®, Methylin®, Quillichew®, Quillivant®, Ritalin®) • Ethylphenidate	Ethylphenidate is a stimulant drug of abuse that shares a metabolite (ritalinic acid) with methylphenidate.[10]
Morphine	• Morphine (Embeda®, Kadian®, MS Contin®, Morphabond™) • Camphorated Tincture of Opium (Paregoric®) • Tincture of Opium • Belladonna & Opium (B&O) suppositories • Metabolite of codeine • Metabolite of heroin • Pharmaceutical impurity in hydromorphone • Poppy seeds	• Poppy seeds in food products (bagels, salad dressings, etc) may result in morphine concentrations in urine up to 2,000 ng/mL.[1] In rare instances, poppy seeds have resulted in higher morphine concentrations, but these occurrences are considered exceptions.[35-40] • Codeine concentrations are typically less than half the morphine concentration (or lower) after poppy seed ingestion.[40,41] • Poppy seeds may result in detectable morphine concentrations in oral fluid for a few hours after typical poppy seed ingestion.[21,42] • Ingestion of poppy seeds may result in positive morphine results in blood for up to 24 hours.[43] • Pharmaceutical impurity in hydromorphone (up to 0.15%).[2] • Products containing opium may result in positive findings primarily for morphine, with codeine at lesser concentrations.
Naloxone	• Naloxone (Narcan®, Evzio®) • Buprenorphine/naloxone combination products (Bunavil®, Suboxone®, Zubsolv®) • Naloxegol (Movantik®)	Naloxone has been found in patients ingesting naloxegol and is thought to be an end-metabolite of naloxegol.[44]
Oxycodone	• Oxycodone (Oxaydo®, Oxycet®, OxyContin®, Percocet®, Percodan®, Roxicet®, Roxicodone®, Roxybond®, Xtampza®) • Pharmaceutical impurity in oxymorphone	Pharmaceutical impurity in oxymorphone (up to 0.5%).[2]
Oxymorphone	• Oxymorphone (Opana®) • Metabolite of oxycodone	
Phenobarbital	• Phenobarbital • Metabolite of primidone (Mysoline®) • Component of some atropine-hyoscyamine combination products (e.g. Donnatal®, Phenohytro™)	
Phentermine	Phentermine (Adipex-P®, Lomaira®, Qsymia®)	
Pregabalin	Pregabalin (Lyrica®)	
Tapentadol	Tapentadol (Nucynta®)	
Tramadol	Tramadol (Conzip®, Ultracet®, Ultram®)	O-desmethyl-tramadol only results may indicate ingestion of a street product called Krypton. Tramadol use may also be a possibility.

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