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Investigating the incidence of false positive outcomes in drug detection assays

Kamil Możdżeń[1], Konrad Kaleta[1], Agnieszka Murawska[1], Edward Pędziwiatr[1], Julia Hypnar[1], Ilie Lastovetskyi[1], Mateusz Kęska[1], Barbara Lorkowska-Zawicka[2], Beata Bujak-Giżycka[2]

[1] Student Scientific Group of Clinical Pharmacology, Jagiellonian University Medical College, Kraków, Poland
[2] Department of Clinical Pharmacology, Jagiellonian University Medical College, Kraków, Poland

Corresponding author: Beata Bujak-Giżycka, Ph.D.
Department of Clinical Pharmacology, Chair of Pharmacology, Jagiellonian University Medical College
ul. Grzegórzecka 16, 31-531 Kraków, Poland
Phone: +48 12 421 11 68; E-mail: beata.bujak-gizycka@uj.edu.pl

Abstract: Immunoassays are widely utilized in urine drug screens due to their simplicity, ease of automation, and rapid results, making them the standard for clinical and workplace drug testing, as well as in rehabilitation programs and legal systems. However, the potential for cross-reactivity with both structurally related and unrelated compounds increases the risk of false-positive results. This poses significant challenges for healthcare professionals, especially in populations undergoing routine drug testing, such as those in recovery or court-ordered monitoring programs. The ongoing opioid epidemic in the United States, which has resulted in countless deaths from both prescription and illicit opioids, underscores the critical importance of accurate drug detection methods. This review evaluates specialized drug assays, highlighting their effectiveness and limitations. While immunoassays are highly sensitive, they often lack specificity, increasing the risk of false positives, which can affect clinical and legal decisions. This research also details substances prone to causing false positives, aiding clinicians in making informed diagnostic and therapeutic decisions.

Keywords: urine drug test, false positive, opioids, tricyclic antidepressants, cocaine.

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Introduction

Immunoassays (IAs) are widely used in urine drug screening (UDS) due to their simplicity, automation capabilities, and quick results, making them a common tool in clinical settings, workplaces, rehabilitation programs, and legal systems. These assays play a crucial role in documenting

drug exposure across various medical fields, including emergency medicine, psychiatry, addiction treatment, and organ transplantation. However, a limitation of IAs is their potential for cross-reactivity with structurally similar unrelated compounds or their metabolites, which can lead to false-positive (F/P) results [1, 2]. This is particularly problematic for populations undergoing routine drug testing, such as individuals in recovery or those under court-ordered monitoring.

Although IAs are highly sensitive, they are susceptible to F/Ps. A positive result from an IA is thus frequently considered preliminary and requires confirmation through more specific testing methods, such as gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS). This two-step process — initial screening followed by confirmatory testing — is crucial for distinguishing true drug use from other causes of drug presence [1]. Clinical interpretation must account for legitimate reasons for the detected drug, such as prescribed medications, making additional testing or a comprehensive medical review essential to avoid wrongly labeling individuals as illicit drug users.

This study aims to discuss the reliability of drug testing on F/Ps related to opioids, tricyclic antidepressants, and cocaine. By analyzing data from scientific literature and case reports, we seek to improve the understanding of dosage thresholds and testing methods most susceptible to F/Ps, thereby improving the accuracy of drug testing in both clinical and forensic contexts.

Opioids test cross-reactivity

Opiates and opioids

Opioids are compounds known for their specific interaction with opioid receptors. Screening for opioid misuse is essential especially in outpatient care, to identify abnormal behavior and prevent negative outcomes. Among the various methods available, urine drug screening is the preferred approach due to its high specificity, sensitivity, ease of use, and cost-effectiveness, despite potential F/Ps from non-illicit substances [1]. Table 1 lists substances and concentrations that may cause F/Ps. Several challenges arise in the interpretation of opioid testing:

Drug transformation and metabolites: CYP450 metabolism of opioids complicates urine test interpretation e.g., codeine's likewise heroin's conversion to morphine via CYP2D6 varies with genetic and environmental factors. Additionally, heroin's morphine conversion—along with impurities like codeine and 6-acetylcodeine can further confound results [2]. Opiate screens detect morphine and codeine (with cross-reactivity to hydrocodone/hydromorphone) and identify heroin via 6-monoacetylmorphine but can't differentiate drugs or detect all opioids—risking false negatives and necessitating confirmatory tests and clinical context [3].

Naloxone and buprenorphine: Semi-synthetic opiates (structurally similar to morphine), are detected in a similar manner, while synthetic opioids require different immunoassays. A notable issue is that naloxone, commonly used to treat suspected overdoses, can cause false positives in opiate immunoassays [4]. Additionally, buprenorphine cross-react with opiates due to structural similarities. Although monitoring tests for opioid therapy typically cover both prescribed buprenorphine and illicit opioids, the potential for cross-reactivity should be considered. Interestingly, elevated morphine levels due to heroin use might be misinterpreted as buprenorphine misuse [4].

Variability in drug interferences: Drug interactions can vary significantly across different assays, leading to inconsistent results for the same drug. Even drugs within the same class can react differently. While laboratory evidence highlights these variations, real-world data remains limited, and

the underlying mechanisms are not fully understood. For instance, false positives for opiates have been strongly associated with certain quinolone antibiotics. Research shows that levofloxacin and ofloxacin can cause F/Ps, with detectable opiate levels persisting for up to 20–25 hours using the EMIT II system [5]. Poppy seed consumption has also been linked to F/Ps, especially in patients treated with low doses of ofloxacin. In contrast, no F/Ps have been reported with ciprofloxacin or norfloxacin. In one instance involving gatifloxacin, a F/P was corrected using GC-MS [5]. The interferences between fluoroquinolones and urine opiate screens is not well understood, with levofloxacin and ofloxacin being common culprits [6].

Fentanyl

The misuse of fentanyl and related compounds has become a significant concern due to their high potential for fatal outcomes. Unlike traditional immunoassays targeting opioids like morphine, most current commercial assays cannot detect fully synthetic opioids e.g., fentanyl, resulting in a critical detection gap. Several automated immunoassay kits have been developed for rapid screening of fentanyl in urine. Kits were primarily designed to detect parent fentanyl and show limited cross-reactivity with metabolites and analogues, e.g., despropionylfentanyl [7, 8].

Research has demonstrated varying degrees of cross-reactivity with fentanyl analogues, such as up to 80% cross-reactivity with acetylfentanyl in specific assays [9]. The accuracy of these assays can also be affected by interference from substances like risperidone and its metabolite 9-hydroxyrisperidone [8]. Notably, both share a chemical moiety like that in fentanyl and were found to cross-react with the fentanyl immunoassay, while norfentanyl, the synthetic opioid, does not.

Rapid-response fentanyl test strips support harm reduction by detecting fentanyl but can give false results when samples contain high levels of adulterants (such as methamphetamine, MDMA, and diphenhydramine) [10, 11].

In addition, other drugs that strongly affect the CNS may also exhibit cross-reactivity in fentanyl immunoassays. A study analyzing 11,873 urine samples reported that 10.4% initially tested positive for fentanyl, with 8.8% of these results being confirmed upon subsequent testing. The positive predictive value of these screens was 85.7%. Among the 4,398 unique patients tested, 13.2% had at least one confirmed positive result for non-prescription fentanyl. Common medications, including haloperidol, trazodone, labetalol, fluoxetine, and amitriptyline, were identified as potential contributors to F/Ps in these assays [12].

Recent reports have also highlighted the misuse of loperamide, which acts as a μ-opioid receptor agonist. Although loperamide has a low potential for abuse due to its poor bioavailability and extensive first-pass metabolism, instances of misuse have been documented, particularly when combined with P-glycoprotein and/or CYP450 enzyme inhibitors [13]. Loperamide has been found to cause F/Ps results in various IAs drug screens [13].

Buprenorphine

Buprenorphine, a medication extensively utilized in the treatment of opioid dependence and pain management, undergoes metabolic conversion to norbuprenorphine, which is further metabolized into norbuprenorphine-glucuronide (primary metabolite excreted in urine). The sensitivity of assays for detecting free buprenorphine or norbuprenorphine can be significantly enhanced by treating urine samples with glucuronidase [14, 15].

Challenges in buprenorphine assays arise from cross-reactivity with other substances. For instance, levofloxacin demonstrates significant cross-reactivity with the CEDIA Buprenorphine, although it does not affect oxycodone or methadone tests [16]. Also, tramadol, (5 ng/mL cutoff), causes interference, which can be mitigated by increasing the cutoff to 20 ng/mL [4]. Additionally minor cross-reactivity has been observed with amisulpride/sulpiride, which is particularly significant due to their high urinary concentrations [4]. Hughey *et al.* further identified several substances as potential F/P triggers in buprenorphine assays [17]. The specific concentrations at which these substances induce F/Ps results are detailed in Table 1.

A study comparing the results of urine analysis obtained by CEDIA buprenorphine with those LC-MS/MS revealed instances of F/Ps among patients using codeine. Specifically, 1.1% of drug-dependent patients tested positive for buprenorphine using CEDIA but were negative when tested with LC-MS/MS. Raising the assay cutoff from 5 ng/mL to 10 ng/mL significantly improved specificity to 99.7% [18]. Additionally, loperamide has been found to cause positive results in the CEDIA buprenorphine test [13].

Methadone

Methadone, a synthetic opioid widely used in pain management and the treatment of opioid dependence, presents significant challenges in drug screening due to the potential for F/Ps results (Table 1) [4]. UDS reveal methadone and its primary metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) [19]. Unlike morphine and other semi-synthetic opioids, methadone and EDDP do not share structural similarities with fentanyl, rendering traditional morphine-specific opiate immunoassays ineffective for their detection [9].

Research conducted by Cherwinski *et al.* has demonstrated that quetiapine, even at doses as low as 125 mg/day, can result in false positives in methadone screenings [4]. Furthermore, F/Ps have been associated with the use of diphenhydramine and doxylamine. Specifically, daily doses of 100–200 mg of diphenhydramine have been reported to cause misleading urine drug screening results, while intoxication with doxylamine has led to F/Ps for both methadone and opiates, despite the absence of opiates in alternative testing methods [5]. The impact of psychotropic medications on methadone testing varies, with certain assays showing cross-reactivity with chlorpromazine, clomipramine, and thioridazine. Additionally, F/Ps for methadone have been linked to the presence of verapamil metabolites in specific testing kits [5].

Oxycodone

Testing for oxycodone is important for medication compliance monitoring due to the limited reactivity of standard opiate immunoassays with oxycodone itself. Utilizing assays that detect both the parent drug and its major metabolites, noroxycodone and oxymorphone, minimizes the risk of false negatives, especially in samples with low oxycodone concentrations. A retrospective analysis showed that many samples initially screened negative for oxycodone tested positive for its metabolites upon more sensitive analysis. The oxycodone DRI (100 ng/mL cutoff), exhibits robust cross-reactivity with oxymorphone, ensuring positive screens even at lower oxycodone levels [20].

Research indicates that the DRI oxy assay, with a 50 ng/mL cutoff, reliably identifies oxycodone and oxymorphone in urine samples. When combined with an opiate immunoassay like the

CEDIA opiate test, this method effectively screens for opiates in urine, reducing the need for GC-MS testing of negative specimens [21].

Table 1. List of substances detected by various opioids drug tests, including tests type, cutoff concentrations, dosages, and concentrations in serum/urine. Abbreviations: CEDIA — Cloned Enzyme Donor Immunoassay; FTS — Fentanyl Test Strips; EIA — Enzyme Immunoassay; HEIA — Homogeneous Enzyme Immunoassay; KIMS — Kinetic Interaction of Microparticles in Solution; EMIT — Enzyme Multiplied Immunoassay Technique; DAU — Drug Abuse Urine; DRI — Diagnostic Reagents Immunoassay; [1] — ingested dose of drug; [2] –concentration of detected drug in serum; [3] — nominal concentration of drug in urine; N.M. — not mentioned.

Drug name	Type of drug test/assay (cut-off concentration)	Dosage[1] Serum concentration[2] Urine concentration[3]	Ref.
Buprenorphine			
Amisulpride, sulpiride	CEDIA buprenorphine (5 ng/mL)	130 mg/L amisulpride[3] 250 mg/L sulpiride[3]	[22]
Ceftaroline fosamil		709.6 μg/mL[3]	[17]
Codeine, dihydrocodeine		30 mg/L (codeine)[3,A] 60 mg/L (dihydrocodeine)[3,A] N.M (dihydrocodeine)[B] 60 mg (codeine)[1,C]	[23][A] [24][B] [18][C]
Donepezil		681.5 μg/mL[3]	[17]
Hydroxychloroquine		200 mg/day[1]	[15]
Levofloxacin		250 μg/mL[3]	[16]
N-Desmethyl loperamide		12.2 mg/L [3]	[15]
Methadone		N.M.	[15]
Morphine		120–900 mg[1]	[25]
Procainamide		92.8μg/mL[3]	[17]
Propafenone		180.7 μg/mL[3]	[17]
Rotigotine		0.13 μg/mL[3]	[17]
Tramadol	CEDIA buprenorphine (5 ng/mL)[A] CEDIA buprenorphine (5 ng/mL)[B] ABMC Rapid One buprenorphine (12.5 ng/mL)[B] QuikStrip OneStep buprenorphine (2.5 ng/mL)[B]	N.M.[A] 12.4 mg/L[3,B] 5.5 mg/L [3,B] 0.9 mg/L[3,B]	[15][A] [26][B]
Trimethoprim	CEDIA buprenorphine (5 ng/mL)	47.2 μg/mL [3]	[17]
Fentanyl			
Dextromethorphan	FTS (20 ng/mL)	N.M.	[27]
Diphenhydramine	FTS (20 ng/ml)	N.M.	[28]
Heroin	FTS (20 ng/mL)	N.M.	[27]
Labetalol	HEIA (2 ng/mL)	100mg/day[1]	[29]

Drug name	Type of drug test/assay (cut-off concentration)	Dosage[1] Serum concentration[2] Urine concentration[3]	Ref.
Methamphetamine	FTS (20ng/ml) EIA fentanyl kit (1 ng/mL)	N.M.[A] 40 μg/mL[3,B]	[28][A] [30][B]
Risperidone **9-Hydroxyrisperidone**	JusCheck™, a multi-drug test panel urine kit DRI fentanyl (2-ng/mL)	50 mg/month[1,A] N.M.[B]	[11][A] [31][B]
Loperamide	DRI fentanyl (2 ng/ml) Fentanyl Urine HEIA (2 ng/ml) Fentanyl Assay (1 ng/ml)	7.25 mg/L[3] 5.72 mg/L[3] 23.7 mg/L[3]	[13]
Methadone			
Amitriptyline	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Benaphetamine	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Benzophenone	CEDIA DAU methadone (300 ng/mL)	N.M.	[33]
Benztropine mesylate	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Bethanechol	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Brompheniramine maleate	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Carbamazepine	CEDIA DAU methadone (300 ng/mL)	N.M.	[34]
Chlorpromazine	KIMS methadone, (300 ng/mL)	20 mg/L[3]	[35]
Clindamycin hydrate	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Clorazepate dipotassium	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Clomipramine	KIMS methadone, (300 ng/mL)	100 mg/L[3]	[35]
Cloxacillin	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Cyamemazine	KIMS methadone, (300 ng/mL)	8 mg/L[3]	[35]
Desipramine	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Digoxin	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Diphenhydramine	One-step Multidrug, methadone (300 ng/mL)[A] N.M. (206 ng/mL)[B] Methadone DAU (N.M.)[C]	100 μg/mL[3,A] >50,000 ng/mL[3,B] 100 μg/mL[3,C]	[36][A] [34][B] [32][C]
Disopyramide	CEDIA DAU methadone (300 ng/mL)	N.M.	[37]
Ephedrine sulfate	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Ethambutol	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
L-Hyoscyamine sulfate	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Ibuprofen	Methadone DAU[A] CEDIA DAU methadone (300 ng/mL)[B]	1,000 μg/mL[3,A] N.M.[B]	[32][A] [34][B]
Imipramine	Methadone DAU (N.M.)	100 μg/mL[3]	[32]
Idomethacin	Methadone DAU (N.M.)	1,000 μg/mL[3]	[32]
Levomepromazine	KIMS methadone, (300 ng/mL)	5 mg/L[3,A] N.M.[B]	[35][A] [33][B]

Drug name	Type of drug test/assay (cut-off concentration)	Dosage[1] Serum concentration[2] Urine concentration[3]	Ref.
Methoxyphenamine	Methadone DAU (N.M.)	1,000 µg/mL[3]	[32]
Paracetamol	CEDIA DAU methadone (300 ng/mL)	N.M.	[33]
Pazopanib	HEIA 300 ng/mL	198.4 µg/mL[3]	[17]
Perphenazine	Methadone DAU (N.M.)	100 µg/mL[3]	[32]
Promethazine	Methadone DAU (N.M.)	100 µg/mL[3]	[32]
Propafenone	HEIA (300 ng/mL)	83.2 µg/mL[3]	[17]
Propranolol	Methadone DAU (N.M.)	1,000 µg/mL[3]	[32]
Quetiapine	KIMS methadone, (300 ng/mL)	N.M.[A] 200 mg/day[1], 80 ng/mL[3,B] 900 mg/24 h[1,C] 125 mg/day[1,D]	[38][A] [39][B] [40][C] [41][D]
Tapentadol and metabolites	DRI (130 ng/ml)	6,500 ng/ml[3] (Tapentadol) 20,000 ng/ml[3] (N-Desmethyl) 25,000 ng/ml[3] (Glucuronide) 3,000 ng/ml[3] (Sulfate)	[42]
Thioridazine	KIMS methadone, (300 ng/mL)	100 mg/L[3]	[36]
Triethyperazine maleate	Methadone DAU (N.M.)	100 µg/mL[3]	[32]
Trihexyphenidyl	Methadone DAU (N.M.)	1,000 µg/mL[3]	[32]
Trimethobenzamide	Methadone DAU (N.M.)	1,000 µg/mL[3]	[32]
Tripellenamine	Methadone DAU (N.M.)	100 µg/mL[3]	[32]
Verapamil	DRI (300 µg/L)	20 mg/L	[43]
Opiates & Opioids			
Amitriptyline	Opiate DAU (N.M.)[A] CEDIA opiates (300µg/l)[B]	1,000 µg/mL[3,A] N.M.[B]	[32][A] [33][B]
Atropine sulfate	Opiate DAU (N.M.)	1,000 µg/mL[3]	[33]
Codeine **Dihydrocodeine**	KIMS opiate (300 ng/mL)[A] N.M. (300 ng/mL)[B]	N.M.[A] N.M (dihydrocodeine)[B]	[44][A] [45][B]
Cyproheptadine	Opiate DAU (N.M.)	1,000 µg/mL[3]	[32]
Desipramine	Opiate DAU (N.M.)	1,000 µg/mL[3]	[32]
Dexbrompheniramine	Opiate DAU (N.M.)	1,000 µg/mL[3]	[32]
Dicyclomine	Opiate DAU (N.M.)	1,000 µg/mL[3]	[32]
Diphenhydramine	Opiate DAU (N.M.)[A] N.M. (143 ng/mL)[B]	1,000 µg/mL[3,A] >50,000 ng/mL[3,B]	[32][A] [34][B]
Doxylamine	EMIT-ST opiates (0.3 mg/l)	1,000 mg[1]	[39]
Flurometholone	Opiate DAU (N.M.)	1,000 µg/mL[3]	[32]
Gatifloxacin	Beckman Synchron analytical system (2,000 ng/ml)	400 mg/day[1]	[46]
L-Hyoscyamine sulfate	Opiate DAU (N.M.)	1,000 µg/mL[3]	[32]
Imipramine	Opiate DAU (N.M.)	1,000 µg/mL[3]	[32]

Drug name	Type of drug test/assay (cut-off concentration)	Dosage[1] Serum concentration[2] Urine concentration[3]	Ref.
Orphenadrine citrate	Opiate DAU (N.M.)	1,000 µg/mL[3]	[32]
Oxycodone	DRI Opiate (300 ng/mL)[A] CEDIA opiates (300 ng/ML)[B]	N.M.[A] N.M.[B]	[47][A] [19][B]
Oxymorphone	DRI Opiate (300 ng/mL)[A] CEDIA opiates (300 ng/ML)[B]	N.M.[A] N.M.[B]	[48][A] [19][B]
Perazine	FPIA (100 µg/L)	1 g/L[3]	[49]
Promethazine	Opiate DAU (N.M.)	100 µg/mL[3]	[32]
Propranolol	Opiate DAU (N.M.)	1,000 µg/mL[3]	[32]
Rifampin	Syva RapidTest (300 mg/L)[A] Genix RapidTech (300 mg/L)[A] KIMS (300 µg/l)[B,C] KIMS (2,245 µg/L)[D]	300 mg/L[3,A] 0.05 mg/L[3,A] 2,500 µg/l[3,B] 900 µg/l[3,C] 600 mg[1,D]	[48][A] [50][B] [51][C] [52][D]
Triethyperazine	Opiate DAU (N.M.)	1,000 µg/mL[3]	[32]
Tripellenamine	Opiate DAU (N.M.)	1,000 µg/mL[3]	[32]
Triprolidine	Opiate DAU (N.M.)	1,000 µg/mL[3]	[32]
Levofloxacin	CEDIA (375ng/ml)[A] Abbott MULTIGENT (300 ng/ml)[B]	500 mg[1,A] 434 µg/mL[3,B]	[53][A] [16][B]
Ofloxacin	CEDIA (375ng/ml)[A] EMIT II (300 µg/L)[B] Fluorescence immunoassay for opiates (N.M.)[C]	400 mg[1,A] 400 mg[1,B] N.M.[C]	[53][A] [54][B] [55][C]
Oxazepam	CEDIA (300µg/l)	N.M.	[33]
Propoxyphene			
Amitriptyline	DRI propoxyphene (300 ng/mL)	100 mg/L[3]	[56]
Brompheniramine	Propoxyphene DAU (N.M.)	1,000 µg/mL[3]	[32]
Cyproheptadine	Propoxyphene DAU (N.M.)	1,000 µg/mL[3]	[32]
Desipramine	Propoxyphene DAU (N.M.)	1,000 µg/mL[3]	[32]
Diphenhydramine	EMIT II propoxyphene, (300 ng/mL)[A] DRI propoxyphene (300 ng/mL)[B]	200 mg/L[3,A] 100 mg/L[3,B]	[31][A] [56][B]
Doxepin	DRI propoxyphene (300 ng/mL)	100 mg/L[3]	[56]
Imipramine	DRI propoxyphene (300 ng/mL)[A] Propoxyphene DAU (N.M.)[B]	100 mg/L[3,A] 1,000 µg/mL[3,B]	[56][A] [32][B]
Nortriptyline	DRI propoxyphene (300 ng/mL)	100 mg/L[3]	[56]
Promethazine	Propoxyphene DAU (N.M.)	1,000 µg/mL[3]	[32]
Triethyperazine	Propoxyphene DAU (N.M.)	1,000 µg/mL[3]	[32]
Tripellenamine	Propoxyphene DAU (N.M.)	1,000 µg/mL[3]	[32]

Tricyclic antidepressants test cross-reactivity

Despite the shift from tricyclic antidepressants (TCAs) to selective serotonin reuptake inhibitors for treating depression, the detection of TCAs in clinical settings remains challenging. Routine drug abuse assays often exclude TCAs, yet their detection in urine is crucial during emergencies, such as overdoses or toxicity incidents, where early patient management is vital [57]. TCAs, which are characterized by their three-ring nucleus, often exhibit cross-reactivity in immunoassays with other medications, including cyproheptadine, carbamazepine, cyclobenzaprine, and quetiapine [57, 58]. Even structurally distinct antihistamines, such as diphenhydramine and hydroxyzine, can interfere with TCA assays, particularly during overdose situations [57].

Current TCA immunoassays are designed to target compounds such as desipramine and imipramine; however, significant cross-reactivity occurs with non-TCA drugs like phenothiazines, due to structural similarities. Drugs that exhibit Tanimoto similarities to desipramine include carbamazepine, chlorpromazine, cyclobenzaprine, doxepin, nortriptyline, prochlorperazine, and quetiapine [59]. A comprehensive list of substances that have yielded F/Ps results for TCAs is provided in Table 2.

Recent studies have particularly highlighted the cross-reactivity of quetiapine with TCA assays. Notably, main quetiapine metabolites, such as N-desalkylquetiapine (norquetiapine), quetiapine S-oxide, and 7-hydroxyquetiapine, did not show cross-reactivity in Biosite assays, even at high concentrations [59]. Additionally, hydroxyzine and its metabolite cetirizine have been shown to disrupt TCA quantification when using FPIA methods [60].

Table 2. Substances causing F/Ps results in TCA drug tests. Abbreviations: EMIT — Enzyme Multiplied Immunoassay Technique; FPIA — Fluorescence Polarization Immunoassay; eSTAD — Serum Tricyclic Antidepressant Screen; EIA — Enzyme Immunoassay; DAU — Drug Abuse Urine; DS — drug screen; [1] — ingested dose of drug; [2] –concentration of detected drug in serum; [3] — nominal concentration of drug in urine; N.M. — not mentioned.

Drug name	Type of drug test/assay (cut-off concentration)	Dosage[1] Serum concentration[2] Urine concentration[3]	Ref.
Carbamazepine	Abbott TDx/TDxFlx TCA (20 ng/mL) [A] Abbott TDx FPIA (50 ng/mL TCA) [B] Biosite Triage (1,000 ng/mL multiple TCA) [C]	2 × 200 mg/d[1]; 121 μM[2,A] 8 mg/L[2,B] N.M.[C]	[61][A] [62][B] [56][C]
Cetirizine	Abbott TDx FPIA (20 ng/ml)	500 ng/mL[2]	[59]
Chlorpromazine	Syva EMIT (1,000 ng/mL desipramine) [A] DS Test (1,000 ng/mL Amitriptyline) [B]	N.M.[A] 50,000 ng/mL[3,B]	[50][A] [63][B]
Cyclobenzaprine	Syva EMIT (1,000 ng/mL desipramine)[A] Triage Plus TCA (1,000 ng/mL)[B] DS Test (1,000 ng/mL Amitriptyline)[C]	N.M.[A] 1,000 ng/mL[3,B] 5,000 ng/mL[3,C]	[59][A] [56][B] [63][C]
Cyproheptadine	Syva EMIT (200 ng/mL nortryptyline)	400 μg/L[2]	[64]
Diphenhydramine	AccusignTCA kit (1,000 ng/mL nortryptyline)	2,000 mg[1]	[65]
Hydroxyzine	Abbott TDx FPIA (20 ng/mL)	500 ng/mL[2]	[60]
Perphenazine	Signify ER DS (1,000 ng/mL Amitriptyline)	50,000 ng/mL[3]	[63]
Prochlorperazine	Biosite Triage (1,000 ng/mL multiple TCAs)	N.M.	[50]

Drug name	Type of drug test/assay (cut-off concentration)	Dosage[1] Serum concentration[2] Urine concentration[3]	Ref.
Promazine	Signify ER DS (1,000 ng/mL Amitriptyline)	10,000 ng/mL[3]	[63]
Quetiapine	Microgenics® Roche (300 ng/mL Nortriptyline)[A] Abbott TDx (20 ng/ml)[B] Abbott TDxFLx FPIA (20 ng/ml)[B] Syva Emit tox Serum TCA Assay (300 ng/mL)[B] eSTAD (300 ng/mL)[B] Status DS™ (N.M.)[B] Microgenics, Tricyclic Serum Tox EIA (N.M.)[C] Tox/See ® (N.M.)[E]	600 mg/d[1]; 7.0 mg/mL[3,A] N.M.[B] N.M.[B] ≥320 ng/mL[1,B] ≥160 ng/mL[1,B] 5.1 ng/ml (2)[2,C] 400 mg/d[1,E]	[66][A] [67][B] [68][C] [69][E]
Trihexyphenidyl	Syva EMIT (1,000 ng/mL desipramine)	N.M.	[50]

Cocaine test cross-reactivity

Cocaine, a central nervous system stimulant, is widely abused for its euphoric effects, enhanced focus, appetite suppression, and reduced need for sleep. Immunoassays are effective in detecting cocaine by targeting its primary metabolite, benzoylecgonine, which generally exhibits minimal cross-reactivity with other substances. However, exposure to products derived from coca leaves, contaminated edibles, and environmental exposure to cocaine smoke — especially in children — can lead to F/Ps results [57, 70].

F/Ps in drug tests can occur due to various non-illicit substances. For instance, coca leaf tea, an herbal product, and mugwort have been reported to trigger positive results in the AxSym system (300 ng/mL) despite their non-narcotic nature [57, 71, 72]. Additionally, metabolites such as cocaethylene, ecgonine, and norcocaine can be detected by the Roche DAT assay (3 ng/mL), potentially leading to F/Ps results [73]. Table 3 presents substances yielding F/Ps results for cocaine, along with corresponding doses and test names.

Table 3. List of substances that can yield F/Ps results for cocaine. Abbreviations: DAU — Drug Abuse Urine N.M. — not mentioned.

Drug name	Type of drug test/assay (cut-off concentration)	Urine concentration	Ref.
Amitriptyline	Cocaine DAU (N.M.)	100 µg/mL	[32]
Amoxicillin trihydrate		1,000 µg/mL	[32]
Doxylamine succinate		1,000 µg/mL	[32]
Ephedrine		1,000 µg/mL	[32]

Discussion

In summary, it is essential to consider the clinical context in which the patient is situated, including the concurrent use of specific medications, and to carefully interpret positive test results. Patients who deny using certain substances may indeed be truthful, and this should prompt a thorough

investigation by the clinician. Analyzing F/Ps results for opioids, TCAs, and cocaine requires an understanding of the pharmacokinetics of these substances and the sensitivity of detection methods. Opioids like codeine and heroin are detectable for about 48 hours, while oxycodone and hydromorphone can be detected for 2–4 days (see Table 4) [57]. Fig. 1 details the duration of drug detection in urine.

Table 4. Detailed information regarding the detection windows, screening cut-offs, and confirmation cut-offs for various drugs [5].

Drug/drug class	Detection window	Screening cut-off	Confirmation cut-off
Cocaine	2–4 days	150 ng/mL	100 ng/mL
Opiates	3 days	2,000 ng/mL	2,000 ng/mL
Heroin	12–24 h	10 ng/mL	10 ng/mL
Hydrocodone/Hydromorphone	3 days	300 ng/mL	100 ng/mL
Oxycodone/oxymorphone	3 days	100 ng/mL	50 ng/mL
Methadone	3 days	300 ng/mL	100 ng/mL

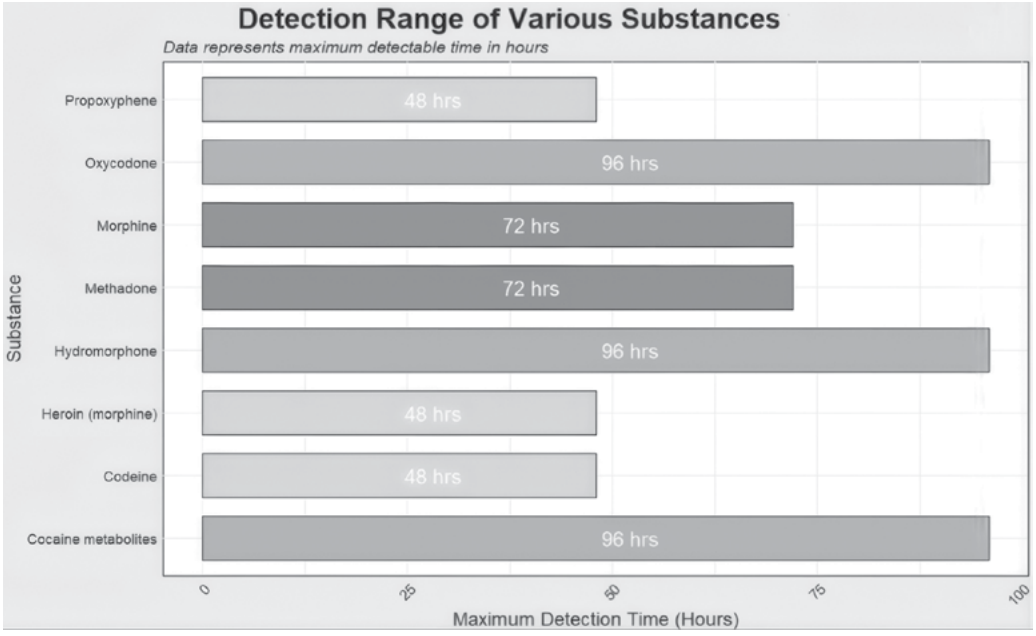

Fig. 1. Detection windows for drugs of abuse in urine. Based on [57].

Another critical aspect in accurately interpreting UDS results is obtaining a comprehensive patient history, as the intake of certain medications has been demonstrated to lead to F/P results. While occurrences of F/P results are relatively rare, vigilance is essential. One study highlighted that the positive predictive value of a urine fentanyl screen was 85.7%, underscoring the importance of confirmatory testing to avoid misdiagnosis [12]. Additionally,

challenges like stealing medications, stockpiling drugs, irregular use (such as occasional or increasing doses in opioid treatment), and false-negative results from infrequent dosing, which leads to undetectable low drug levels, might further complicate the interpretation of UDS results [1]. Although immunoassay testing is relatively specific, abnormal results often necessitate confirmatory testing. It is estimated that approximately 20% to 32.9% of patients may require such confirmation [74].

Recent advances in drug testing have introduced alternative specimens beyond traditional blood or urine samples, with oral fluid testing emerging as a convenient and efficient method for detecting drugs in saliva. Unlike urine testing, oral fluid collection can be directly observed by clinicians, reducing tampering risks while maintaining patient privacy. Adulterants like Clear Choice® and Listerine® have minimal impact on drug concentrations in oral fluids when samples are collected 30 minutes after use [1]. Oral fluid testing holds promise in drug screening by offering a shorter detection window compared to urine, making it suitable for specific clinical application. Although challenges like contamination from food and drink and individual metabolic differences can affect accuracy, implicating further research to refine its clinical use [1].

Urine drug testing remains essential for verifying self-reported drug use, especially in opioid therapy management. High rates of noncompliance, including illicit drug use, additional prescriptions, and specimen tampering, have been documented. A study in a nonprofit healthcare system found a 30.6% noncompliance rate, involving issues like missing prescribed opioids and the presence of nonprescribed substances [75]. These findings highlight the critical role of urine drug testing in optimizing patient care and understanding drug-related behaviors [75].

Conclusions

Accurate interpretation of urine drug screen results necessitates careful consideration of the clinical context, including a comprehensive patient history and an understanding of substance pharmacokinetics. While F/Ps are rare and false negatives may occur due to factors like irregular dosing, confirmatory testing is crucial to avoid misdiagnosis and ensure appropriate clinical management. Proper interpretation and diligent follow-up are essential for optimizing patient care and supporting informed clinical decisions. This research aims to assist physicians in quickly identifying substances that may interfere with opioid, TCA, and cocaine assays.

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Conflict of interest

None declared.

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