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Guilty or not guilty? — False positive results of common medicines in drug tests: review and practical guide

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Abstract: Drug-abuse detection tests are becoming increasingly commonplace in patient care today and provide a rapid and effective method for identifying illicit substances. Occasionally, they may yield a positive result, indicating the presence of a substance, even though the individual has not consumed the suspected drug what sometimes can significantly impact both medical and legal decisions. The study outlines the substances that can lead to false-positive drug test results for amphetamines, cannabinoids, and benzodiazepines. The study's findings have revealed pivotal insights for patients receiving chronic treatment and their primary care physicians. Notably, amphetamine assays appear to be most prone to cross-reactivity with other substances. The beta-blocker group of medications, confirmed by various studies to interfere with amphetamine assays, could pose a substantial challenge in drug screening given its widespread use. Efavirenz also warrants mention, as it frequently triggers positive results for both benzodiazepine and cannabinoid assays among its users. This research helps highlight new areas for further investigation and aims to guide clinicians in their daily practice, especially when interpreting questionable positive drug-abuse test results. This comprehensive review serves as a valuable resource for clinicians to navigate false-positive scenarios effectively and maintain the highest standard of patient care.

Keywords: urine drug test, false positive, amphetamine, cross-reactivity, cannabinoids, benzodiazepines.

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Introduction

Drug tests are specialized assays widely employed to detect specific substances in biological materials such as blood, plasma, urine, sweat, saliva, or hair [1]. These tests serve various purposes, including investigating the cause of intoxication in medical practice and confirming the use of illicit substances in legal proceedings. However, it is crucial to acknowledge that certain substances may produce false positives (F/P) results in these tests, leading to significant legal ramifications for the individual being tested. Moreover, false positive results can also disrupt the therapeutic process when managing intoxicated patients, potentially leading healthcare personnel to make incorrect diagnoses and decisions [2]. Ongoing advancements in testing methodologies aim to minimize the occurrence of false positives, thereby reducing the potential for misdiagnosis and unwarranted legal consequences. It is essential for healthcare providers, legal professionals, and individuals undergoing drug testing to remain informed about the limitations and potential sources of error associated with these tests [2].

There are several methods available for drug analysing, but currently mass spectrometry (MS) is considered the gold standard for forensic analyses. MS allows for the accurate determination of the molecular mass of ions by considering their mass-to-charge ratio. However very often the initial or even binding decisions are often based on less precise methods, such as immunoassays used in urine drug screening (UDS) [3]. While immunoassay (IA) demonstrates high sensitivity in detecting substances at the microgram range, it can encounter specificity issues resulting in F/P. These issues may arise from structural similarities or the presence of metabolites, compromising the accuracy of the test [3].

Our work aims to enhance the understanding of medical professionals and pharmacology specialists regarding the interpretation of positive drug test results. A comprehensive analysis was performed on a wide array of available literature on commonly used recreational drugs, such as amphetamines (AMP), cannabinoids (CB), and benzodiazepines (BZO) and the substance that could interfere with them. This study holds particular relevance for individuals undergoing long-term drug therapy, those participating in both professional and amateur sports events, and within the sphere of occupational medicine. For these people, false positives can impose significant challenges and disruptions in their lives. The collected data was carefully analyzed to provide insights into the dosage and/or concentration thresholds that trigger positive drug test results, the types of tests that exhibit false positives, potential explanations for this phenomenon and found the populations that could be most commonly affected by false positives.

Amphetamines test cross-reactivity

Amphetamines are now classified as controlled drugs in most countries and only used for limited therapeutic purposes such as treating narcolepsy and ADHD [4]. AMP is highly addictive and known for inducing euphoric effects. As a result, it is commonly included in routine drug tests due to health risks and abuse potential. However, accurately identifying amphetamines and distinguishing them from methamphetamines can be challenging due to their similar chemical structure. Additionally, many drugs that mimic amphetamine effects have similar structural characteristics and are commonly used. Consequently, tests designed to detect amphetamines often face difficulties related to cross-reactivity [5]. In these cases, drug tests may generate a positive result even if the individual has not consumed the specific drug being tested for. F/P in amphetamine tests can arise due to the ingestion of various drugs and substances, as shown in Table 1.

Gastrointestinal medication

Ranitidine: an H2 receptor antagonist, surprisingly can lead to F/P results for amphetamine and methamphetamine in drug tests, despite having a structurally dissimilar composition [22]. Initial reports from 1991, indicating that with a calibration cutoff of 300 μg/L of amphetamine, F/P appeared in specimens with a minimum ranitidine concentration of 91 mg/L. However, achieving such a high urine concentration in routine use is not common, as it is typically prescribed at 150–300 mg doses, with 30–70% of the drug being excreted unchanged [40]. The problem of ranitidine cross-reactivity continues even with technological advances in drug testing, as illustrated by tests conducted on Beckman Coulter DxC 600i and DxC 800 machines. In contrast, the Siemens VIVA E analyzer demonstrated resistance to ranitidine-induced false positives in amphetamine testing [37]. Recently, due to the potential carcinogenic properties of ranitidine, the drug has been withdrawn from numerous countries worldwide. This action has significantly reduced global exposure to this medication. Notably, there is currently insufficient information available regarding the potential cross-reactivity between the amphetamine assay and other drugs belonging to the H2-blocker group, including cimetidine, famotidine, roxatidine, nizatidine, and lafutidine. Further investigations in this area are recommended [22, 37].

Mebeverine, an antispasmodic medication, has the potential to yield false positive results for AMP in fluorescence polarization immunoassay tests. It has been found that even a single oral dose of 405 mg of mebeverine can trigger this effect. Despite these findings, GC/MS analyses revealed no presence of amphetamines or other illicit substances. This suggests that Mebeverine can significantly interfere with IA tests, thereby leading to misleading interpretations for the detection of amphetamines [30].

Table 1. False positive results for amphetamine. The tests performed for detection of amphetamine derivatives and metabolites are not included. [1] — ingested dose of drug; [2] — nominal concentration of drug in urine; N.M. — not mentioned.

Drug name	Type of drug test (cut-off concentration)	Dosage[1] Concentration in urine[2]	Ref.
Amantadine	fluorescence polarization immunoassay ADx® — Abbott Laboratories, Abbott Park, Illinois (N.M.)	N.M.	[6]
Aripiprazole	N.M. (UDS immunoassay with 300 µg/L cut-off) N.M. (UDS immunoassay) Beckman Coulter AU680 Analyzer EMIT II Plus, Brea, CA (500 µg/L)	15–45 mg single dose[1] 15–39 mg/day[1] (256–452.5 µg/L)[2] 30 mg/day[1]	[7–9]
Atenolol	CEDIA amphetamine assay (300 µg/L)	750,000 µg/L[2]	[10]
Atomoxetine	CEDIA amphetamine assay (N.M.)	120 mg — 12 h before test[1]	[11]
Bisoprolol	CEDIA amphetamine assay (300 µg/L)	400,000 µg/L[2]	[10]
Bupropion	CEDIA amphetamine assay (300 µg/L) Syva EMIT II Plus immunoassay (N.M.)	8,500 µg/L[2]	[10] [12]
Erythro-dihydro bupropion	Syva EMIT II Plus immunoassay (300 µg/L)	22,000 µg/L[2]	[13]
(±)-Hydroxybupropion	Syva EMIT II Plus immunoassay (300 µg/L)	62,000 µg/L[2]	[13]
Brompheniramine	monoclonal EMIT d.a.u. Amphetamine Immunoassay (Syva Co., Palo Alto, CA) (N.M.)		[14]
Ceftaroline fosamil	Homogeneous enzyme immunoassay Abbott MULTIGENT® (500 µg/L)	53,100 µg/L[2]	[15]
Chlorpromazine	Syva EMIT-MAM Roche Hitachi 911w platform (1000 µg/L)		[5]
Chloroquine	DRI Amphetamine Assay on an Architect C16000 analyzer — Abbott Diagnostics-Santa Clara, CA (For both 1000 µg/L	155 mg single dose[1] 100,900 µg/L[2]	[16]

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Table 1. cont.

Drug name	Type of drug test (cut-off concentration)	Dosage[1] Concentration in urine[2]	Ref.
	and 500 µg/L) Syva Emit II Plus Amphetamines assay (500 µg/L)		
Clobenzorex Hydrochlorate	GC/MS	30 mg oral dose 1–7 h before test	[17]
Doxepin	Fluorescence Polarization Immunoassay Adx® — Abbott Laboratories, Abbott Park, Illinois (N.M.)	N.M.	[18]
Ephedrine	Triage® DOA kit (650 µg/L) Amphetamine UDT Immunoassays (N.M.)	N.M.	[19] [20] [21]
Esmolol	Homogeneous enzyme immunoassay Abbott MULTIGENT® (500 µg/L)	237,300 µg/L[2]	[15] [22] [23]
Esmolol acid	Homogeneous enzyme immunoassay Abbott MULTIGENT® (500 µg/L)	446,400 µg/L[2]	[15]
Famprofazone	CEDIA immunoassay (N.M.)	100 mg — 6 h before test[1]	[24]
Fenfluramine	Amphetamine immunoassay screens (N.M.)		[20]
Fenofibrate	amphetamine/MDMA CEDIA (1000 µg/L)	daily dose of 267 mg[1]	[25] [26]
Imatinib	Immunoassy-based UDT (N.M.) Homogeneous enzyme immunoassay Abbott MULTIGENT® (500 µg/L)	400 mg/d[1] 216,600 µg/L[2]	[27] [15]
Labetalol	Abbott TDx amphetamine/methamphetamine II kit (N.M.) Syva EMIT d.a.u, polyclonal amphetamine class kit (N.M.) Syva EMIT d.a.u, monoclonal amphetamine kit (N.M.)	800 mg tid[1] 800 mg tid[1]	[28] [29]

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Table 1. cont.

Drug name	Type of drug test (cut-off concentration)	Dosage[1] Concentration in urine[2]	Ref.
Mebeverine	Fluorescence polarization immunoassay (300 µg/L)	single oral dose of 405 mg — 16 h before test[1]	[30]
Metformin	Biosite Triage (N.M.)	N.M.	[5]
Methyldopa	Homogeneous enzyme immunoassay Abbott MULTIGENT® (500 µg/L)	N.M.	[15]
α-Methyldopamine	Homogeneous enzyme immunoassay Abbott MULTIGENT® (500 µg/L)	13,600 µg/L[2]	[15]
Methylphenidate	CEDIA; Microgenics, Pleasanton, CA (1 µM/mL) CEDIA amphetamine assay (300 µg/L)	 125,000 µg/L[2]	[31] [10]
Metoprolol	enzyme immunoassay Abbott MULTIGENT® (500 µg/L) CEDIA (300 µg/L)	20,000 µg/L[2] 300,000 µg/L[2]	[32] [10]
Mexiletine	CEDIA (300 µg/L) Roche integra KIMS (500 µg/L) Roche cobas KIMS (500 µg/L) Noble split specimen POC (1000 µg/L) QuikScreen multi 14 + 3 POC (1000 µg/L) Beckman AU Syva emit II (500 µg/L) Siemens vista Syva emit II (1000 µg/L)	25,000 µg/L[2] 50,000 µg/L[2] 25,000 µg/L[2] 500,000 µg/L[2] 1000,000 µg/L[2] 50,000 µg/L[2] 50,000 µg/L[2]	[10] [33]
Moxifloxacin	Homogeneous enzyme immunoassay Abbott MULTIGENT® (500 µg/L)	350,000 µg/L[2]	[34]
Ofloxacin	TdxFlx AM/MA II (300 µg/L)	N.M.	[5]
Perazine	N.M.	N.M.	[35]

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Table 1. cont.

Drug name	Type of drug test (cut-off concentration)	Dosage[1] Concentration in urine[2]	Ref.
Phendimetrazine	ELISA technique adapted for the detection of amphetamines in hair (N.M.)	N.M.	[36]
Phenethylamine	Amphetamine UDT Immunoassays (N.M.)	N.M.	[21]
Phentermine	EMIT II (300 µg/L) Bio-Quant Direct ELISA (N.M.)	7,500 ng/mL[2]	[10] [21]
Phenylpropanolamine	monoclonal EMIT d.a.u. Amphetamine Immunoassay — Syva Co., Palo Alto, CA (N.M.) KIMS (N.M.)	N.M.	[14] [22]
Procainamide	Homogeneous enzyme immunoassay Abbott MULTIGENT® (500 µg/L)	23,200 µg/L[2]	[15]
N-acetyl-3-hydroxyprocainamide	Homogeneous enzyme immunoassay Abbott MULTIGENT® (500 µg/L)	92,200 µg/L[2]	[15]
Promethazine	Syva EMIT-MAM (1000 µg/L)	N.M.	[5]
Propranolol	Syva EMIT II Plus (200 µg/L)	41,000 µg/L[2]	[13]
Propylhexedrine	Several amphetamine UDT Immunoassays (N.M.)	N.M.	[21]
Pseudoephedrine	Several amphetamine UDT Immunoassays (N.M.)	N.M.	[21]
Ranitidine	monoclonal EMIT d.a.u. Amphetamine Immunoassay — Syva Co., Palo Alto, CA (N.M.) CEDIA (300 µg/L) Beckman Coulter Synchron CX5CE (1000 µg/L)	91,000 µg/L[2] 225,000 µg/mL[2] 43,000 µg/L[2]	[22] [10] [37]
Selegiline	N.M. GC/MS	N.M.	[38]

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Table 1. cont.

Drug name	Type of drug test (cut-off concentration)	Dosage[1] Concentration in urine[2]	Ref.
Sertraline	CEDIA (300 µg/L)	200,000 µg/L[2]	[10]
Sildenafil	CEDIA (300 µg/L)	25,000 µg/L [2]	[10]
Tapentadol	CEDIA (300 µg/L)	25,000 µg/L[2]	[10]
Tetracaine	CEDIA (1000 µg/L)	40,000 µg/L[2]	[39]
Tolmetin	Amphetamine EMIT immunoassay (N.M.)	N.M.	[20]
Tramadol	CEDIA (300 µg/L)	12,500,000 µg/L[2]	[10]
Tranylcypromine	Syva EMIT II Plus (300 µg/L)	20,000 µg/L[2]	[13]
Trazodone (m-CPP)	Syva Ecstasy EMIT II (N.M.) Amphetamines II (300 µg/L)	3,000 µg/L[2] 6,700 µg/L[2]	[5]

Intriguingly, mebeverine could also cause F/P results for other illegal drugs, including MDMA, which could potentially lead to severe consequences [41, 42].

Monoamines and catecholamines derivatives

Ephedrine, pseudoephedrine and phenylephrine: False-positive results have been associated with nonprescription products like cold and cough medications, comprising 8.5% of their usage in assisted living facilities [22]. Ephedrine and its synthetic analogue pseudoephedrine, commonly found in over-the-counter cold medications, share a structural resemblance to amphetamine and methamphetamine, potentially leading to F/P results during initial IA. However, confirmatory analysis with GC-MS effectively differentiates these substances, ensuring reliable results [19, 20]. Moreover, the package inserts of amphetamine UDTs commonly mention a high frequency of cross-reactivity with ephedrine and pseudoephedrine, with both exhibiting a significant cross-reactivity rate of 83.3% in amphetamine UDTs [19–21].

Fenfluramine and phentermine: Weight loss medications like fenfluramine and phentermine can cause F/P results for amphetamines in initial IA screens. However, GC-MS analysis can distinguish these medications from actual amphetamines. The cross-reactivity between fenfluramine/phentermine and amphetamines is due to their structural similarities, similar to what is observed with narcotic analgesics [20, 43].

Cardiovascular medications

Beta blockers: Labetalol is commonly prescribed as a hypertension medication for pregnant women. Interestingly, there have been reports of positive test results among these patients, even though GM/CS tests have failed to detect amphetamine or methamphetamine in their specimens. It is believed that the positive results may be due to a metabolite of labetalol called 3-amino-1-phenylbutane, which is known to cross-react with multiple amphetamine immunoassays [5, 28, 29]. Chemical structures of these substance are shown in Fig. 1.

Esmolol has also been reported to cause F/P results in AMP assays. This finding was described in a case report involving a 27-year-old male patient who underwent esmolol treatment and tested positive for amphetamines in a UDS, despite denying any use of tobacco or recreational drugs [23]. The laboratory findings, which investigate the cross-reactivity of numerous substances, provide additional validation for the potential occurrence of positive results for both esmolol and esmolol acid [15].

Two patients who were poisoned with metoprolol tested positive for AMP and MDMA on MULTIGENT® amphetamine/methamphetamine immunoassay, but GC/MS did not confirm the presence of these substances. To investigate further, urine samples were spiked with metoprolol and its two major phase-I metabolites. The

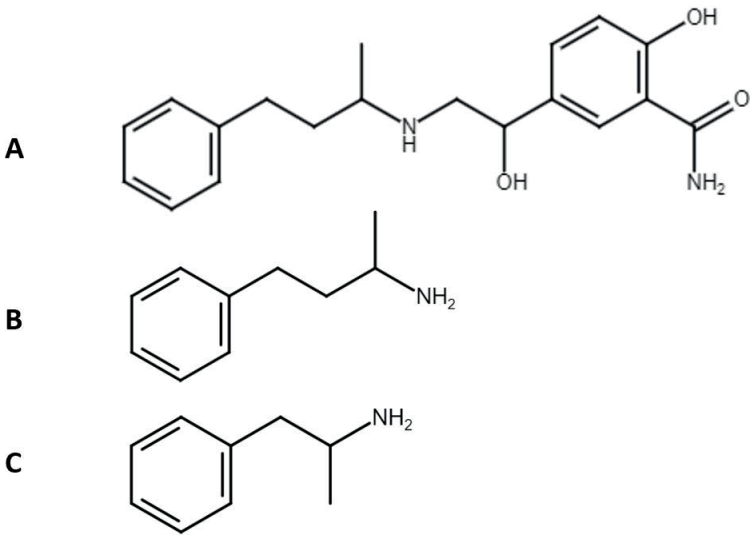

Fig. 1. Chemical structure of (**A**) labetalol, (**B**) 3-amino-1-phenylbutane, (**C**) amphetamine.

results showed that metoprolol gave F/P results for AMP. Metoprolol metabolites cross-reacted only with the amphetamines immunoassay, but at higher concentrations [32].

Additionally, atenolol and bisoprolol have been found to produce F/P results in amphetamine CEDIA tests [10]. This indicates that individuals undergoing antihypertensive therapy with beta-antagonists, particularly pregnant women taking labetalol, are at a higher risk of experiencing false positive amphetamine results.

Fibrats: Fenofibrate also shows an F/P result for amphetamine in some studies [25, 26]. One of them a 60-year-old male patient with a history of alcohol dependency was admitted to an inpatient psychiatry unit. He had been prescribed fenofibrate at a daily dose of 267 mg for the treatment of hyperlipidemia over a period of 3 years. During a routine UDS, the amphetamine/MDMA (CEDIA) test produced a positive result. To confirm the presence of amphetamine and MDMA, GC/MS was conducted. However, subsequent testing using the amphetamine/MDMA and MDMA IA yielded negative results after fenofibrate was discontinued [25].

Mexiletine: A 64-year-old patient prescribed mexiletine medication tested positive for amphetamines twice during urine toxicology screens while hospitalized, despite denying drug use. Additional confirmatory testing yielded negative results, suggesting false positives likely caused by cross-reactivity or other factors [44]. Similarly, two patients on mexiletine treatment tested positive for amphetamines on all screens but showed negative results upon mass spectrometry confirmation, indicating false positives. Introducing mexiletine to drug-free urine samples resulted in positive results in

all tests. The EMIT II Plus and KIMS assays exhibited lower mexiletine cross-reactivity compared to point-of-care assays [33]. These cases, along with other reports, highlight that the risk of false positive results in AMP tests is relatively high in patients taking mexiletine [15, 45].

Patients with elevated cholesterol level taking fibrates, patients with arrhythmias taking beta blockers and mexiletine are at higher risk of false positive result in amphetamine assay.

Antidepressants

Bupropion: In one study, 41% of 53 patients with positive UDS amphetamine results that were not confirmed by GC/MS were found to have been taking bupropion at the time of the test [5]. Poly-substance abuse as the cause was ruled out and it was concluded that a significant portion of the F/P results were directly linked to the patients' bupropion use. However, the study was limited in that it did not include spiking experiments to confirm whether bupropion or its associated metabolites were responsible for the F/P results [5]. Another study, UDS using Syva EMIT II Plus immunoassay reagents confirmed that bupropion is one of the drugs that can cause a false-positive amphetamine test result as it was present in 40% of F/P confirmed by GC. What is more bupropion was also suspected in three cases to give F/P results not only in UDS but even in GC test [12]. This outcome was expected given the structural similarities and even some similarities in the mechanism of action between bupropion and amphetamine. This phenomenon has been already quite widely described in the literature [46].

Trazodone: Dilution experiments with trazodone and meta-chlorophenylpiperazine (m-CPP), a trazodone metabolite showed F/P for amphetamines on the Roche Cobas c501w Amphetamine II assay. Positive results were observed at or below 6,700 µg/L m-CPP concentration. However, subsequent GC-MS testing confirmed these as false positives. The study suggests that the Amphetamines II assay can produce false positives in trazodone users due to the presence of m-CPP. Clinicians should confirm positives with GC-MS [5, 47, 48].

Antipsychotics

Phenothiazines: The medications promethazine and chlorpromazine can cause false-positive results in amphetamine drug tests. A study found that urine samples from patients on these medications tested positive for amphetamines using the SYVA EMIT-MAM test, but further testing with liquid chromatography-photo-diode array (LC-PDA) confirmed these as F/P. Other amphetamine UDS kits produced negative results for these medications, except for the AgilentTM TesTcard 9 kit, which showed

two F/P results. Another study found that promethazine could also lead to false-positive results for amphetamines in urine tests using EMIT II Plus, likely due to its metabolites. In conclusion, promethazine and chlorpromazine can lead to false-positive outcomes in various amphetamine drug tests [5, 49].

Aripiprazole has been identified as a cause of F/P results for AMP in UDS in clinical practice. Two cases involved very young girls who accidentally ingested aripiprazole and tested positive for amphetamines in urine tests [7]. Furthermore literature also reports two cases of adult patients, a 40-year-old woman and a 23-year-old man, who were on aripiprazole therapy for bipolar disorder, also yield false-positive results for amphetamines. In those patients the detected levels of amphetamine steadily decreased after discontinuing aripiprazole therapy [8, 9]. It suggests that individuals with schizophrenia or bipolar disorder are at a higher risk of obtaining false-positive amphetamine results.

Fluoroquinolones

Fluoroquinolone antibiotics, like moxifloxacin or ofloxacin, are commonly prescribed to treat various infections. A laboratory investigation has confirmed the cross-reactivity and interference of moxifloxacin with the detection of amphetamines in the Abbott MULTIGENT amphetamine/methamphetamine assay [34].

Healthy volunteers received two 200 mg doses of ofloxacin, and urine samples collected before and after administration showed all post-administration samples testing positive for amphetamines. This suggests that the presence of ofloxacin in urine can lead to false-positive amphetamine results in the Amphetamine/Methamphetamine II assay on the TdxFlx platform [5].

Local anesthetic agents

The research revealed that the CEDIA Amphetamine/Ecstasy immunoassay yielded F/P AMP results when tetracaine concentrations reached or exceeded 40 mg/L. In a comprehensive analysis of urine samples from 417 patients who initially tested positive for amphetamine, an unexpected finding emerged: 45 of these samples displayed no trace of amphetamine-like substances, thus suggesting F/P outcomes. A deeper look into these specific cases identified tetracaine in 37 (82.2%) samples, with a noteworthy concentration of 40 mg/L or higher found in 22 of them. These results infer that nearly 80% of the reported F/P AMP cases in urine samples obtained from emergency department patients could be attributed to tetracaine. This significant discovery underscores the necessity of considering potential drug interference during the interpretation of immunoassay results and unequivocally affirms tetracaine's interference in the CEDIA Amphetamine/Ecstasy IA [39].

Atomoxetine

A 27-year-old female with ADHD had a F/P result in UDS due to using atomoxetine. Despite positive results for amphetamines in the initial immunochemical cloned enzyme donor immunoassay at the hospital, subsequent urine GC-MS testing did not confirm amphetamine presence. The patient denied using illicit drugs or substances, and her other medications were unlikely to cause false positives. While stimulant treatments for ADHD can result in positive amphetamine urine screens, there are no known reports of false positives specifically linked to atomoxetine. The study suggests that atomoxetine or its metabolites may interfere with UDS immunoassays, causing F/P amphetamine results in cloned enzyme donor immunoassay assays [11].

Our current understanding indicates that immunoassays, utilized to confirm the presence of AMP in specimens, may not possess complete specificity for amphetamines. A positive result could be triggered by an array of substances, particularly phenylalkylamines or some monoamine derivatives. Illicit substances such as MDMA, MDA, 4-MTA, PMA, and MDEA have been also found to yield positive results for AMP, even though the test is not specifically designed to detect these substances [13]. In general results should be interpreted with prudence, considering the potential for cross-reactivity. Certain groups of people, typically characterized by their medical conditions, were initially identified as having an elevated risk of receiving false positive results due to their medication use. The study by Rohrich *et al.* [50], which reveals the cross-reactivity between tyramine and amphetamine assays, is particularly noteworthy. Tyramine, a byproduct of tyrosine decarboxylation typically seen in the putrefaction process, was found to yield a positive result for amphetamines in the TRIAGE immunoassay at concentrations exceeding 5 mg/L. Notably, such concentrations often surpass those found in the urine or serum of cadavers. Considering the structural similarity between tyramine and amphetamines, this finding implicates significant challenges in interpreting test results from cadavers when using methods other than GC-MS [50].

Other substances that can trigger F/P results, and worth noting, are some doping agents used in both professional and amateur sports. A prime example is the synthetic compound 1,3 dimethylamylamine (DMAA). Originally formulated as a nasal decongestant in the 1940s, DMAA despite raising safety concerns, is now a prevalent recreational stimulant that additionally can induce F/P results for AM [51]. Concentrations of DMAA as slight as 3,100 μg/L in certain assays can yield false-positive amphetamine outcomes [5]. Similarly, famprofazone, an active ingredient in the drug Gewodin (a pyrazolone NSAID, available OTC e.g, in Taiwan), undergoes metabolic conversion to amphetamine and methamphetamine, potentially leading to F/P results. This was demonstrated in a case study involving a driver falsely suspected of illicit drug use due to Gewodin consumption [52]. Gewodin was acknowledged as a stimu-

lant drug and is included in the prohibited list by the world anti-doping agency [24, 53]. Surprisingly, the other stimulant kavain, which contributes to the euphoric, sedative, and anxiolytic effects associated with the consumption of kava (a beverage made from the roots of the kava plant), has also been shown to yield positive results for amphetamines (AMP) [54].

It is also worth noting that amphetamine could be a metabolite that appears in the body due to the breakdown of certain drugs. In fact several drugs do metabolize into AMP as part of their metabolic pathway, this include: selegiline — drug used to treat Parkinson's disease, benzphetamine — anorectic drug prescribed short term for obesity treatment, lisdexamphetamine — used in ADHD management, clobenzorex — appetite suppressant and previously mentioned famprofazone [4, 55]. It could be problematic for patients and physicians as also confirmatory test by GC-MS could reveal positive results for AMP.

Interestingly the complexity of F/P results extends to hair assays as well, as evidenced by the Sweeney *et al.* study [36]. The research conducted tests on hair samples from subjects who initially tested positive for amphetamines, revealing cross-reactivity with a range of substances including labetalol, fenfluramine, ephedrine, benzphetamine, phentermine, phenylpropanolamine [36].

Cannabinoids test cross-reactivity

The main method of screening for cannabinoids is urine IA. They work by detecting 11-nor-Δ9-tetrahydrocannabinol-9-carboxylic acid, which is the main metabolite of Δ9-tetrahydrocannabinol (THC). In practice, for positive results obtained by urine immunoassay to be considered reliable they must be confirmed by another independent testing method, for example GC MS. The medications that yield false positive results for THC are detailed in Table 2.

Efavirenz (EFV)

Efavirenz, a non-nucleoside reverse transcriptase inhibitor is a drug used in HIV treatment that can cause F/P results for THC in urine tests, according to several studies. The issue has been seen in three different immunoassays, namely the Cannabinoids ELISA Kit by Immunalysis Corporation, Triage® TOX Drug Screen by Biosite Incorporated, and Cedia® Dau Multi-Level THC by Microgenics Corporation. It's believed that a metabolite of EFV, EFV 8-glucuronide, could be responsible for these false readings [5]. This is exemplified in the case of a 31-year-old transsexual woman, also on HIV therapy with efavirenz, who tested false positive for THC in CEDIA urine immunoassay while other tests proved negative [62]. Moreover, another test, the Rapid Response Drugs of Abuse Test Strips, showed false-positive results for THC

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Table 2. Medications that may potentially yield false positive results in a THC drug screening test. [1] — ingested dose of drug; [2] — nominal concentration of drug in urine; N.M. — not mentioned.

Drug name	Type of drug test (cut-off concentration)	Dosage[1] Concentration in urine[2]	Ref.
Dronabinol	N.M. (UDS)	N.M.	[56]
Diclofenac	EMIT II cannabinoid immunoassay (50 µg/L)	N.M.	[57]
Efavirenz	Microgenics Corporation — Cedia® Dau Multi-Level THC — Immunalysis Corporation (50 µg/L) Cannabinoids THCA/CTHC Direct Elisa (50 µg /L) Biosite Incorporated — Triage® TOX Drug Screen (50 µg/L) BTNX — The Rapid Response™ Single Drug Test Strip (50 µg/L) Rapid Responsew Drugs of Abuse Test Strips (50 µg/L)	600 mg P.O. for 14 days[1]	[5] [58] [59]
Ethacrynic acid	N.M. (UDS)	N.M.	[56]
Ibuprofen	Syva — EMIT® (N.M.)	200 mg/t.i.d. or 400 mg single dose[1]	[60]
Naproxen	Syva — EMIT® (20 µg/L)	N.M.	[5]
Niflumic acid	Roche — KIMS® (50 µg/L)	2,500 µg/L	[5]
Pantoprazole	Alere Triage® TOX Drug Screen assay (50 µg/L)	40 mg/day[1] 1,000,000 µg/L	[61]
Promethazine	N.M. (UDS)	N.M.	[56]
Raltegravir	Homogeneous enzyme immunoassay Abbott MULTIGENT® (50 µg/L)	339,500 µg/L	[15]
Riboflavin	N.M. (UDS)	N.M.	[56]
Rotigotine	Homogeneous enzyme immunoassay Abbott MULTIGENT® (50 µg/L)	415,100 µg/L	[15]

in 28 out of 30 samples tested. This was despite the urine samples being verified as THC-free using a separate method. This cross-reactivity of efavirenz with the tests may be due to the glucuronidated metabolite of the drug [59]. The same issue was found with three other tests: Triage® TOX Drug Screen by BioSite Incorporated, Cedia® Dau MultiLevel THC by Microgenics Corporation, and Cannabinoids ELISA Kit by Immunalysis Corporation. Here, the EFV-8-OH metabolite was suspected of causing false positives [58]. These issues are well-known according to various literature sources. For example, in the ENRICO study, all 24 participants on efavirenz tested positive for THC [63]. However, the inconsistency and lack of reports in recent years suggest a need for more current research in this area [58, 59]. Interestingly, another drug, raltegravir, has also been found to give false-positive results in cannabinoid screenings [15].

Non-steroid anti-inflammatory drugs (NSAIDs)

Niflumic acid, along with NSAIDs like naproxen and ibuprofen, can trigger false positive THC results in urine tests, but the occurrence depends on the test type. Specifically, the Roche's KIMS® test showed consistent F/P, while the EMIT THC® test often produced accurate negatives [5]. On the contrary, the chances of ibuprofen causing a false-positive result in enzyme-mediated immunoassays (EMIA) are low. Out of 60 volunteers who took 1200 mg of ibuprofen per day, only one urine sample tested positive for cannabinoids. Similarly, chronic use of naproxen resulted in a F/P in just one urine sample [22]. Another study involving 120 volunteers found that false positives were generally low for ibuprofen and naproxen use, both acute and chronic. Nevertheless, there were some reported false positives for cannabinoids and barbiturates. The research concluded that the use of ibuprofen and naproxen does not consistently correlate with false positive results. Potential explanations for these findings may include interference from enzymatic activity, inaccuracies in absorbance readings, or the presence of endogenous substances [60].

Rotigotine

It is believed that rotigotine, a dopaminergic agonist utilized in the treatment of Parkinson's disease, has the potential to cause cross-reactions and yield F/P results. It should be noted that no correlation between a patient's intake of rotigotine and the likelihood of a F/P test was found due to the insufficient number of tests performed [15].

Pantoprazole

Research reports suggest that the PPI drug pantoprazole may cause a F/P urine immunochemical screening test for THC, a study was conducted to test the claim [61]. In phase 1 of the study, 3 healthy volunteers took 40 mg of pantoprazole once a day, for 5 days. In the second phase, 9 subjects randomly took 15 mg of lansoprazole, 20 mg of omeprazole or 20 mg of esomeprazole for 5 days, once a day. Urine samples were collected from all subjects, and none had a false positive result using the THC One Step Marijuana Test Strip®. The small number of subjects in the study, the use of only one test and the lack of checking patients' drug intake are limitations of the study. It is therefore advisable to study on a larger scale the effect of PPIs on urine immunochemical screening tests [64].

In a study examining the effect of pantoprazole on the result of the cannabinoid immunoassays, it was shown that adding the said drug to urine not contaminated with drugs or marijuana yielded true negative results of the assays — KIMS® Cannabinoids II and DRI® Cannabinoids, it should be noted that the concentration of pantoprazole was not greater than 12,000 μg/mL. In contrast, the Alere Triage® TOX Drug Screen assay yielded a F/P for cannabinoids. False-positive results in this assay were obtained provided the drug concentration was greater than 1,000 μg/mL [61].

It's also noteworthy to mention the study conducted by Powers *et al.*, which revealed no detectable interference between pantoprazole and THC tests. This finding suggests the need for additional research in this area and emphasizes the importance of documenting and reporting such cases [65].

Research on THC drug tests often focuses on false negative results, with slightly less attention paid to false positives. However, false positives caused by cross-reactivity and substance interference are equally important, as demonstrated by a study that found only 59% of samples retested for THC using a more accurate GC-MS method actually contained THC [66].

Regardless of medication, other substances could also provide test detection and interpretation problems. Detection becomes even more complicated with the recent emergence of synthetic derivatives of Δ9-THC, the primary psychoactive component in cannabis. Despite their structural differences, these derivatives bind to the same CB1 and CB2 receptors as Δ9-THC, often exhibiting more potent effects and longer half-lives. Traditional screening tests, designed mainly to identify THC-COOH and its derivatives, are ineffective against these synthetic substances, as the THC-COOH fragment is not typically found in samples from users of synthetic cannabinoids [67]. The THC-COOH fragment is usually absent in samples from synthetic cannabinoid users, meaning these substances paradoxically do not interfere with the test but present significant detection challenge like in the case of “K2”, “spice”, “JWH-018” that cannot be detected by urine tests [56]. A similar scenario occurs with CBD, another

cannabis-related substance. A study on roadside inspections revealed a low risk of false positive THC results among CBD users. All samples in the study remained negative, even with varying doses of CBD given to the participants [68].

Intriguingly, even everyday substances, such as specific commercial baby soaps, can cause interference with THC detection, leading to false positives in THC urine immunoassays [5, 69]. The underlying mechanism remains uncertain, though multiple studies have confirmed this phenomenon, particularly with a soap named "Head-to-Toe Baby Wash". These studies also indicated a correlation between the volume of soap introduced to the urine sample (ranging from 0.02 to 0.08 mL) and the odds of a false-positive result [57, 66, 69].

Also, substances such as dronabinol (the generic name for THC in pharmaceutical science), promethazine, and ethacrynic acid, as well as dietary supplements such as riboflavin, have been noticed to produce false-positive urine tests for THC [56].

Benzodiazepines test cross-reactivity

Benzodiazepines, a group of substances extensively used in various medical treatments since the early 1960s, includes well-known drugs like diazepam, midazolam, oxazepam, and alprazolam, the latter being the most prescribed benzodiazepine in the US. They quickly became more popular than barbiturates upon their introduction. These substances increase the activity of GABA-A receptors, leading to effects like anxiety reduction, muscle relaxation, seizure prevention, and memory impairment. As a result, benzodiazepines are effective for treating anxiety and insomnia [5]. However, they have a potential for abuse and can lead to global health issues. Long-term use may also result in cognitive problems, including dementia [70]. In 1981 Aleen and Stiles [71] with accomplices checked 162 different substances as a potential cause of false-positive results in urine EMIT DAU system. Drug free urine from healthy volunteers was collected and spiked with different concentrations of those drugs. Authors of the following study were aware that most of the drugs analysed will never reach concentrations over 1 mg/ml in urine, but many substances showed cross reactivity in those concentrations [71]. Several substances can cause F/P results for benzodiazepines in urine drug tests as was shown in Table 3.

Efavirenz

The HIV medication Efavirenz, has also been found to cause F/P (Biosite Triage 8). In a study, 92% of patients on therapeutic doses tested F/P for benzodiazepines, though they were confirmed negative via LC-MS-MS [5]. Furthermore, it was discovered that plasma concentrations of 8-OH-efavirenz between 33.7 and 678.7 μg/ml could lead to F/P in benzodiazepine tests [76]. The cross-reactivity of EFV with benzodiazepine

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Table 3. Medications confirmed to produce false positive results in benzodiazepine drug tests. [1] — ingested dose of drug; [2] — nominal concentration of drug in urine; N.M. — not mentioned.

Drug name	Type of drug test (cut-off concentration)	Dosage[1] Concentration in urine[2]	Ref.
Aspirin	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Benztropine mesylate	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Chlorothiazide	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Chlorzoxazone	EMIT DAU (N.M.)	10,000 μg/L[2]	[71]
Cyproheptadine	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Clonidine	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Cloxacillin	EMIT DAU (N.M.)	100,000 μg/L[2]	[71]
Desipramine	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Dexbrompheniramine	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Dicyclomine	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Diethylpropion	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Diphenhydramine	EMIT DAU (N.M.) EMIT II (N.M.)	1,000,000 μg/L[2] >50,000 μg/L[2]	[71] [73]
Efavirenz	Biosite Triage 8 (N.M.)	33,700–678,700 μg/L[2]	[5]
Ethoheptazine	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]

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Table 3. cont.

Drug name	Type of drug test (cut-off concentration)	Dosage[1] Concentration in urine[2]	Ref.
Fluorometholone	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Fluoxetine	Profile-V MEDITOX scan drugs of abuse test system St Paul Minn (N.M.)		[72]
Furosemide	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Glycopyrrolate	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Hydralazine	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Hydroxyzine	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Indomethacin	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Imipramine	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
L-Hyoscyamine	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Methoxyphenamine	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Nicotinamide	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Orphenadrine	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Oxaprozin	Abbott FPIA urine benzodiazepine assay — TDxFLx analyzer (200 μg/L) EMIT dau urine benzodiazepine assay — Syva ETS analyzer (200 μg/L) BMC CEDIA DAU benzodiazepine assay Ciba Coming Express 550 analyzer (200 μg/L)	12,000 μg/L[2] 10,000 μg/L[2] 11,000 μg/L[2]	[74]

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Table 3. cont.

Drug name	Type of drug test (cut-off concentration)	Dosage[1] Concentration in urine[2]	Ref.
Phenytoin	EMIT DAU assay (N.M.)	1,000,000 μg/L[2]	[71]
Pirfenidone	CEDIA; Architect ci16000, Abbott (N.M.)	133,000 μg/L[2]	[75]
Promethazine	EMIT DAU assay (N.M.)	10,000 μg/L[2]	[71]
Propranolol	EMIT DAU assay (N.M.)	1,000,000 μg/L[2]	[71]
Riboflavin	EMIT DAU assay (N.M.)	1,000,000 μg/L[2]	[71]
Sertraline	the Aeroset and Architect c8000 Systems, Abbott Laboratories, Irving, TX	150 mg/day[1]	[22]
Sulfathiazole	EMIT DAU (N.M.)	1,000,000 μg/L[2]	[71]
Tolmetin	TDx benzodiazepines assay (300 μg/L)	1,800,000 μg/L[2]	[57]
Thiethylperazine	EMIT DAU assay (N.M.)	1,000,000 μg/L[2]	[71]
Tripelennamine	EMIT DAU assay (N.M.)	100,000 μg/L[2]	[71]
Triprolidine	EMIT DAU assay (N.M.)	1,000,000 μg/L[2]	[71]
Warfarin	EMIT DAU assay (N.M.)	1,000,000 μg/L[2]	[71]

tests is particularly noteworthy, given the previously mentioned influence of EFV on false positive outcomes in THC drug tests, suggesting EFV's high potential for cross-reactivity.

NSAIDs

Oxaprozin, a long-acting NSAID used for rheumatoid arthritis and osteoarthritis, can trigger cross-reactivity in urine drug tests for benzodiazepines. This can occur with various analysers like Abbott FPIA TDxFLx, EMIT dau Syva ETS, and BMC CEDIA DAU Ciba Corning Express 550. Despite having a different chemical structure from benzodiazepines, a daily dose of 1200 mg of oxaprozin may lead to false-negative results in these drug tests [74].

Selective serotonin reuptake inhibitors (SSRI)

Sertraline, an SSRI antidepressant, can alter results if taken in doses over 150 mg per day [22]. Studies showed that patients taking sertraline tested false-positive on Abbott Architect and Aeroset platforms but were confirmed benzodiazepine-free via GC/MS [77]. There are suspicions that fluoxetine may have influence on F/P benzodiazepines test results (Profile-V MEDITOXscan drugs of abuse test system St Paul Minn) [72].

As opposed to previously mentioned drugs of abuse, benzodiazepines are not penalized as AMP or CB. However their used are also limited by law due to health consequences in case of inappropriate utilization, as well as legal sanctions tied to operating mechanical vehicles or cars after taking benzodiazepines. Currently, the medical community is in consensus that the use of benzodiazepines should be an ultimacy especially when considering their addictive potential. Despite awareness of medical society about the danger regarding BZD use their recreational use still remaining relatively common with all their consequences. Although it seems that BZD testing is not as developed as in the case of other drugs. The main groups that were noticed for causing F/P result are the SSRIs and some NSAIDs. Interestingly zolpidem, a member of the Z-drugs with high selectivity to alfa1 subunit of GABA A receptors used in insomnia disorders, don't cause cross reactivity in screening urine drug test with benzodiazepines [78]. Interestingly, positive results in benzodiazepine (BZD) testing are commonly found among smokers. It has been suggested that beta-carbolines, which are present in tobacco smoke, may be responsible for this effect due to their structural similarity with BZDs (Fig. 2). Even passive smokers may register F/P results, though this occurs less frequently [79].

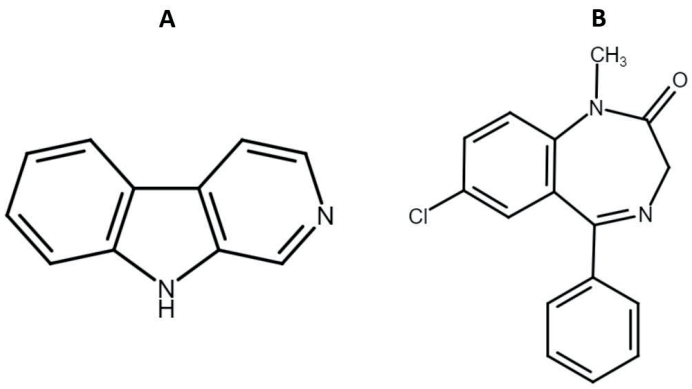

Fig. 2. Chemical structure of (**A**) β-carbolines and (**B**) benzodiazepine.

Conclusions

Numerous substances, as previously mentioned, have been identified in clinical or laboratory settings as potential triggers for F/P results. However, as drug testing methods evolve and become more sophisticated, it becomes increasingly crucial to validate these findings further, especially given the likelihood of high-risk confounding factors in case studies. There are also reports from non-English sources which highlight other substances that could cross-react in certain drug-abuse tests. These findings necessitate independent verification to confirm their credibility and precision [26]. It has been suggested that agents like L-thyroxine, methylprednisolone, and quetiapine may interfere with ELISA/IHRA tests for amphetamines, and group B vitamins, particularly folic acid for the cannabinoid assay. Interestingly, many drug-abuse assay leaflets emphasize the tests' resilience against generating positive results from these listed substances [26]. Yet, these substances often come with an annotation indicating that cross-reactivity was only checked for 100 ng/ml, leaving unanswered questions about the effects of higher doses. Multiple reports remain insufficient to draw definitive conclusions about their impact on amphetamine assays. This ambiguity extends to tolmetin and other potential NSAIDs, which could lead to unexpected positive results.

Importantly, the beta-blocker group displays a significant potential for cross-reactivity. Medications such as metoprolol, propranolol, bisoprolol, atenolol, and labetalol have all been linked to false-positive results under laboratory or clinical conditions. Labetalol, commonly prescribed to pregnant women, is particularly noteworthy as it may lead to false accusations of drug use during pregnancy. It is essential that any clinical interventions for these women are firmly based on results from confirmatory methods like GC-MS or other gold-standard techniques. The potential for F/P results within the beta-blocker group is especially significant due to their widespread usage. For

example, metoprolol was the sixth most frequently sold drug in the United States in 2020, with over 15 million patients. This underscores the need for further investigation into the potential cross-reactivity of other beta antagonists with drug tests [5, 10, 13, 32].

The rising prevalence of THC-based stimulants has led to an increase in cannabinoid screening tests, particularly in corporations, educational institutions, and forensic settings in countries where cannabis is illegal without a prescription, including Poland. Our research highlights those certain medications — including NSAIDs, PPIs, and antivirals — can falsely indicate positive THC use in these tests. As a result, it's important for healthcare providers to inform patients about these potential drug interactions and implications. Additionally, the emergence of new synthetic cannabinoid derivatives that standard urine drug screening can't detect, as well as the challenge of determining the exact timing of THC intake, underscore the need to improve drug screening methods.

Interestingly, even when patients are undergoing treatment with substances known to cross-react, these substances often fail to reach sufficient in vivo concentration. As a result, despite active therapy, these substances may not necessarily lead to F/P results in AMP screenings [5]. It's worth noting that the generation of F/P results depends on a multitude of conditions. These include the cross-reactivity of the substance, the sensitivity and specificity of the test, and the appropriate in vivo drug concentration, which is influenced by the drug's pharmacokinetic properties. Additional substantial factors include the timing of the test, the potential for laboratory errors, and certain patient conditions (e.g., renal or liver diseases, dehydration). All these elements play a role in the accuracy of drug testing, underscoring the need for careful consideration in each individual case.

Moreover, it is imperative for healthcare practitioners to report any instances of false-positive drug test results, which could aid other clinicians in their daily practices. Owing to some information gaps in this research, heightened attention should be directed towards the reporting of drug concentrations in urine or blood, drug dosages, the complete name of the screening test that produced the incorrect positive result, the patient's health status, and any past interactions the patient may have had with illicit drugs. It is also crucial to ascertain if the patient is currently on any medication regimen to accurately interpret drug screening results.

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Conflict of interest

None declared.

References

1. *Verstraete A.G.*: Detection Times of Drugs of Abuse in Blood, Urine, and Oral Fluid. Ther Drug Monit. 2004; 26 (2): 200–205.
2. *Moeller K.E., Kissack J.C., Atayee R.S., Lee K.C.*: Clinical Interpretation of Urine Drug Tests: What Clinicians Need to Know About Urine Drug Screens. Mayo Clin Proc. 2017; 92 (5): 774–796.
3. *Harper L., Powell J., Pijl E.M.*: An overview of forensic drug testing methods and their suitability for harm reduction point-of-care services. Harm Reduct J. 2017; 14 (1): 52.
4. *Heal D.J., Smith S.L., Gosden J., Nutt D.J.*: Amphetamine, past and present — A pharmacological and clinical perspective. J Psychopharmacol. 2013; 27 (6): 479–496.
5. *Saitman A., Park H.D., Fitzgerald R.L.*: False-positive interferences of common urine drug screen immunoassays: A review. J Anal Toxicol. 2014; 38 (7): 387–396.
6. *Merigian K.S., Browning R.G.*: Desipramine and amantadine causing false-positive urine test for amphetamine. Ann Emerg Med. 1993; 22 (12): 1927–1928.
7. *Kaplan J., Shah P., Faley B., Siegel M.E.*: Case reports of aripiprazole causing false-positive urine amphetamine drug screens in children. Pediatrics. 2015; 136 (6): e1625–1628.
8. *Caricasole V., Spagnolo G., Di Bernardo I., Cirnigliaro G., Piccoli E., Dell'Osso B.*: Aripiprazole causing false positive urine amphetamine drug screen in an adult patient with bipolar disorder. Compr Psychiatry. 2019; 94: 152126.
9. *Durmaz O., Özdoğan M.*: An aripiprazole related false positive amphetamine case in urine drug screen. J Subst Use. 2020; 25 (6): 572–574.
10. *Pope J.D., Drummer O.H., Schneider H.G.*: False-Positive Amphetamines in Urine Drug Screens: A 6-Year Review. J Anal Toxicol. 2023; 47 (3): 263–270.
11. *Fenderson J.L., Stratton A.N., Domingo J.S., Matthews G.O., Tan C.D.*: Amphetamine Positive Urine Toxicology Screen Secondary to Atomoxetine. Case Rep Psychiatry. 2013; 2013: 1–3.
12. *Casey E.R., Scott M.G., Tang S., Mullins M.E.*: Frequency of False Positive Amphetamine Screens due to Bupropion Using the Syva Emit II Immunoassay. J Med Toxicol. 2011; 7 (2): 105–108.
13. *Marin S.J., Doyle K., Chang A., Concheiro-Guisan M., Huestis M.A., Johnson-Davis K.L.*: One hundred false-positive amphetamine specimens characterized by liquid chromatography time-of-flight mass spectrometry. J Anal Toxicol. 2016; 40 (1): 37–42.
14. *Olsen K.M., Gulliksen M., Christophersen A.S.*: Metabolites of chlorpromazine and brompheniramine may cause false-positive urine amphetamine results with monoclonal EMIT d.a.u. immunoassay. Clin Chem. 1992; 38 (4): 611–612.
15. *Hughey J.J., Colby J.M.*: Discovering cross-reactivity in urine drug screening immunoassays through large-scale analysis of electronic health records. Clin Chem. 2019; 65 (12): 1522–1531.
16. *Gomila I., Quesada L., López-Corominas V., et al.*: Cross-reactivity of chloroquine and hydroxychloroquine with DRI amphetamine immunoassay. Ther Drug Monit. 2017; 39 (2): 192–196.
17. *Tarver J.A.*: Amphetamine-positive drug screens from use of clobenzorex hydrochlorate. J Anal Toxicol. 1994; 18 (3): 183.
18. *Merigian K.S., Browning R., Kellerman A.*: Doxepin causing false-positive urine test for amphetamine. Ann Emerg Med. 1993; 22 (8): 1370.
19. *Nakae H., Hebiguchi M., Shirasaki S., Okuyama M., Masuda Y.*: Comparison of false-positive reactions for amphetamine analogs after maoto treatment using two urinary drug-screening kits. Tradit Kampo Med. 2014; 1 (1): 2–6.
20. *Neerman M.F.*: Drugs of abuse: Analyses and ingested agents that can induce interference or cross-reactivity. Lab Med. 2006; 37 (6): 358–361.
21. *Reschly-Krasowski J.M., Krasowski M.D.*: A Difficult Challenge for the Clinical Laboratory: Accessing and Interpreting Manufacturer Cross-Reactivity Data for Immunoassays Used in Urine Drug Testing. Acad Pathol. 2018; 5: 2374289518811797.

22. *Brahm N.C.*, *Yeager L.L.*, *Fox M.D.*, *Farmer K.C.*, *Palmer T.A.*: Commonly prescribed medications and potential false-positive urine drug screens. Am J Heal Pharm. 2010; 67 (16): 1344–1350.
23. *Adashek J.J.*, *Khadilkar A.*, *Enciso J.*, *Rane R.*, *Wu R.*: A Case of Esmolol-Induced False-Positive Amphetamine Urine Drug Test. Cureus. 2021; 111 (2): 231–239.
24. *Musshoff F., Kraemer T.*: Identification of famprofazone ingestion. Int J Legal Med. 1998; 111 (6): 305–308.
25. *Kaplan Y.C.*, *Erol A.*, *Karadaş B.*: False-positive amphetamine/ecstasy (MDMA/3,4-methylenedioxymethamphetamine) (CEDIA) and ecstasy (MDMA/3,4-methylenedioxymethamphetamine) (DRI) test results with fenofibrate. Ther Drug Monit. 2012; 34 (5): 493–495.
26. *Sorokina Y.A.*, *Soldatova A.N.*, *Zanozin A.V.*, *Lovtsova L.V.*: Drug Effect on Laboratory Test Result on Narcotic and Psychotropic Substances. Int Res J. 2019; 12 (90): 210–214.
27. *Meyers S., Wachman E.M.*: A Case of False-positive Amphetamine Results on Urine Toxicology Testing Secondary to Imatinib. J Addict Med. 2021; 15 (4): 349–351.
28. *Yee L.M., Wu D.*: False-positive amphetamine toxicology screen results in three pregnant women using labetalol. Obstet Gynecol. 2011; 117 (2 Pt 2): 503–506.
29. *Agrawal N., Tripathi N., Roy N., et al.*: Labetalol or Amphetamine: A Case of Mistaken Identity With Clinical Consequence. Am J Ther. 2019; 26 (6): e748–750.
30. *Kraemer T.*, *Wennig R.*, *Maurer H.H.*: The antispasmodic drug mebeverine leads to positive amphetamine results by fluorescence polarization immunoassay (FPIA) — Studies on the toxicological analysis of urine by FPIA and GC-MS. J Anal Toxicol. 2001; 25 (5): 333–338.
31. *Manzi S.*, *Law T.*, *Shannon M.W.*: Methylphenidate produces a false-positive urine amphetamine screen. Pediatr Emerg Care 2002; 18 (5): 401.
32. *Leclercq M., Soichot M., Delhotal-Landes B., et al.*: False positive amphetamines and 3,4-methylenedioxymethamphetamine immunoassays in the presence of metoprolol — Two cases reported in clinical toxicology. J Anal Toxicol. 2019; 44 (2): 200–205.
33. *Snozek C.L.H., Kaleta E.J., Jannetto P.J., et al.*: False-positive amphetamine results on several drug screening platforms due to mexiletine. Clin Biochem. 2018; 58: 125–127.
34. *Colby J.M.*, *Patel P.C.*, *Fu D.Y.*, *Rutherford N.J.*: Commonly used fluoroquinolones cross-react with urine drug screens for opiates, buprenorphine, and amphetamines. Clin Biochem. 2019; 68: 50–54.
35. *Schmolke M.*, *Hallbach J.*, *Guder W.G.*: False-positive results for urine amphetamine and opiate immunoassays in a patient intoxicated with perazine. Clin Chem. 1996; 42 (10): 1725–1726.
36. *Sweeney S.A., Kelly R.C., Bourland J.A., et al.*: Amphetamines in hair by enzyme-linked immunosorbent assay. J Anal Toxicol. 1998; 22 (6): 418–424.
37. *Liu L., Wheeler S.E., Rymer J.A., et al.*: Ranitidine interference with standard amphetamine immunoassay. Clin Chim Acta. 2015; 438: 307–308.
38. *Shin I., Choi H., Kang S., Kim J., Park Y., Yang W.*: Detection of l-Methamphetamine and l-Amphetamine as Selegiline Metabolites. J Anal Toxicol. 2021; 45 (1): 99–104.
39. *Wijngaard R., Parra-Robert M., Marés L., et al.*: Tetracaine from urethral ointment causes false positive amphetamine results by immunoassay. Clin Toxicol. 2021; 59 (6): 500–505.
40. *Poklis A.*, *Hall K.V.*, *Still J.*: Ranitidine interference with the monoclonal EMIT d.a.u. amphetamine/methamphetamine immunoassay. J Anal Toxicol. 1991; 15 (2): 101–103.
41. *Bedussi F., Acerbis E., Noseda R., Demagistri D., Zamprogno E., Ceschi A.*: False-positive urine screen test for MDMA in a patient exposed to mebeverine. Br J Clin Pharmacol. 2021; 87 (5): 2397–2398.
42. *Sheldon R.J.G.*: A potentially catastrophic outcome from a false-positive urinary drug screen immunoassay. J Forensic Psychiatry Psychol. 2019; 30 (2): 185–188.
43. *Marin S.J.*, *Moore C.*, *McMillin G.A.*: Cross-reactivity of phentermine with an immunoassay designed to detect amphetamine in a meconium specimen. Clin Chem. 2009; 55 (3): 589–590.
44. *Sohal S., Sous M., Pethe G., Padmanabhan S.V., Akbari R., Dadkhah S.*: Mexiletine and False Positive Urine Drug Screen for Amphetamine: A Case Review. Case Rep Med. 2021; 2021: 7134394.
45. *Bui Q.M.*, *Allen L.A.*, *Monte A.A.*, *Page R.L.*, *McIlvennan C.K.*: Amphetamine-positive urine drug screens in the setting of mexiletine use: A case series. J. Heart Lung Transplant. 2016; 35 (8): 1045–1048.

46. *Reidy L.*, *Walls H.C.*, *Steele B.W.*: Crossreactivity of bupropion metabolite with enzyme-linked immunosorbent assays designed to detect amphetamine in urine. Ther Drug Monit. 2011; 33 (3): 366–368.
47. *Roberge R.J.*, *Luellen J.R.*, *Reed S.*: False-positive amphetamine screen following a trazodone overdose. J Toxicol Clin Toxicol. 2001; 39 (2): 181–182.
48. *Baron J.M.*, *Griggs D.A.*, *Nixon A.L.*, *Long W.H.*, *Flood J.G.*: The trazodone metabolite meta-chlorophenylpiperazine can cause false-positive urine amphetamine immunoassay results. J Anal Toxicol. 2011; 35 (6): 364–368.
49. *Melanson S.E.F.*, *Lee-Lewandrowski E.*, *Griggs D.A.*, *Long W.H.*, *Flood J.G.*: Reduced interference by phenothiazines in amphetamine drug of abuse immunoassays. Arch Pathol Lab Med. 2006; 130 (12): 1834–1838.
50. *Röhrich J.*, *Schmidt K.*, *Bratzke H.*: Application of the novel immunoassay TRIAGE to a rapid detection of antemortem drug abuse. J Anal Toxicol 1994; 18 (7): 407–414.
51. *Di Lorenzo C.*, *Moro E.*, *Dos Santos A.*, *Uberti F.*, *Restani P.*: Could 1,3-dimethylamylamine (DMAA) in food supplements have a natural origin?. Drug Test Anal. 2013; 5 (2): 116–121.
52. *Rodriguez A.T.*, *Valtier S.*, *Cody J.T.*: Metabolic profile of famprofazone following multidose administration. J Anal Toxicol. 2004; 28 (6): 432–438.
53. *Tseng Y.L.*, *Lin C.-T.*, *Wang S.-M.*, *Liu R.H.*: Famprofazone as the source of methamphetamine and amphetamine in urine specimen collected during sport competition. J Forensic Sci. 2007; 52 (2): 479–486.
54. *Madhavaram H.*, *Patel T.*, *Kyle C.*: Kavain Interference with Amphetamine Immunoassay. J Anal Toxicol. 2022; 46 (2): 211–215.
55. *Musshoff F.*: Illegal or legitimate use? Precursor compounds to amphetamine and methamphetamine. Drug Metab Rev. 2000; 32 (1): 15–44.
56. *Algren D.A. Christian M.R.*: Buyer Beware: Pitfalls in Toxicology Laboratory Testing. Mo Med. 2015; 112 (3): 206–210.
57. *Joseph R., Dickerson S., Willis R., Frankenfield D., Cone E.J., Smith D.R.*: Interference by nonsteroidal anti-inflammatory drugs in EMIT and TDx assays for drugs of abuse. J Anal Toxicol. 1995; 19 (1): 13–17.
58. *Rossi S., Yaksh T., Bentley H., van den Brande G., Grant I., Ellis R.*: Characterization of interference with 6 commercial delta9-tetrahydrocannabinol immunoassays by efavirenz (glucuronide) in urine. Clin Chem. 2006; 52 (5): 896–897.
59. *Oosthuizen N.M., Laurens J.B.*: Efavirenz interference in urine screening immunoassays for tetrahydrocannabinol. Ann Clin Biochem. 2012; 49 (2): 194–196.
60. *Rollins D.E.*, *Jennison T.A.*, *Jones G.*: Investigation of interference by nonsteroidal anti-inflammatory drugs in urine tests for abused drugs. Clin Chem. 1990; 36 (4): 602–606.
61. *Gomila I., Barceló B., Rosell A., Avella S., Sahuquillo L., Dastis M.*: Cross-reactivity of pantoprazole with three commercial cannabinoids immunoassays in urine. J Anal Toxicol. 2017; 41 (9): 760–764.
62. *Döğer R.*, *Yayayürük A.E.*, *Koç P.Ü.*, *Aydemir N.*, *Akgür S.A.*: False positivity for marijuana in immunoassay analysis due to Efavirenz use. A case report. Rom J Leg Med. 2016; 24 (2): 135–136.
63. *la Porte C.J.L.*, *Droste J.A.H.*, *Burger D.M.*: False-positive results in urine drug screening in healthy volunteers participating in phase 1 studies with efavirenz and rifampin. Ther Drug Monit. 2006; 28 (2): 286.
64. *Vohra V.*, *Marraffa J.M.*, *Wojcik S.M.*, *Eggleston W.*: An assessment of urine THC immunoassay in healthy volunteers receiving an oral proton-pump inhibitor. Clin Toxicol. 2020; 58 (6): 498–500.
65. *Powers J.L.*, *Rasmussen N.N.*, *Hurst D.*, *Strathmann F.G.*: Up in smoke: Uncovering a lack of evidence for proton pump inhibitors as a source of tetrahydrocannabinol immunoassay false positives. Pain Med. (United States) 2018; 19 (11): 2196–2200.
66. *Fucci N.*, *De Giovanni N.*: False-positive cannabis results in Italian workplace drug testing. Drug Test Anal. 2012; 4 (2): 71–73.

67. *Metternich S., Fischmann S., Münster-Müller S., et al.*: Discrimination of synthetic cannabinoids in herbal matrices and of cathinone derivatives by portable and laboratory-based Raman spectroscopy. Forensic Chem. 2020; 19: 100241.
68. *McCartney D., Kevin R.C., Suraev A.S., et al.*: Orally administered cannabidiol does not produce false-positive tests for Δ9-tetrahydrocannabinol on the Securetec DrugWipe® 5S or Dräger DrugTest® 5000. Drug Test Anal. 2022; 14 (1): 137–143.
69. *Cotten S.W.*, *Duncan D.L.*, *Burch E.A.*, *Seashore C.J.*, *Hammett-Stabler C.A.*: Unexpected interference of baby wash products with a cannabinoid (THC) immunoassay. Clin. Biochem. 2012; 45 (9): 605–609.
70. *Votaw V.R.*, *Geyer R.*, *Rieselbach M.M.*, *McHugh R.K.*: The epidemiology of benzodiazepine misuse: A systematic review. Drug Alcohol Depend. 2019; 200 (1): 95–114.
71. *Allen L.V., Stiles M.L.*: Specificity of the EMIT drug abuse urine assay methods. Clin Toxicol. 1981; 18 (9): 1043–1065.
72. *Callaghan K., Rappaport D.I.*: False-Positive Urine Drug Screen for Benzodiazepines in a Child Taking Fluoxetine. Pediatr Emerg Care. 2021; 37 (5): e283.
73. *Rogers S.C.*, *Pruitt C.W.*, *Crouch D.J.*, *Caravati E.M.*: Rapid urine drug screens: Diphenhydramine and methadone cross-reactivity. Pediatr Emerg Care. 2010; 26 (9): 665–666.
74. *Fraser A.D., Howell P.*: Oxaprozin cross-reactivity in three commercial immunoassays for benzodiazepines in urine. J Anal Toxicol. 1998; 22 (1): 50–54.
75. *Jennings D.L.*: Increase in short-term of rejection in heart transplant patients receiving granulocyte colony-stimulating factor. J. Heart Lung Transplant. 2018; 37 (12): 1475.
76. *Blank A., Hellstern V., Schuster D., et al.*: Efavirenz treatment and false-positive results in benzodiazepine screening tests. Clin Infect Dis. 2009: 48 (12): 1787–1789.
77. *Nasky K.M.*, *Cowan G.L.*, *Knittel D.R.*: False-Positive Urine Screening for Benzodiazepines: An Association with Sertraline?: A Two-year Retrospective Chart Analysis. Psychiatry (Edgmont). 2009; 6 (7): 36–39.
78. *Piergies A.A.*, *Sainati S.*, *Roth-Schechter B.*: Lack of cross-reactivity of Ambien (zolpidem) with drugs in standard urine drug screens. Arch Pathol Lab Med. 1997; 121 (4): 392–394.
79. *Haj Mouhamed D., Ezzaher A., Mabrouk H., et al.*: Interference of tobacco smoke with immunochromatography assay for urinary drug detection. J Forensic Leg Med. 2012; 19 (7): 369–372.