

False-positive drug test results in patients taking psychotropic drugs. A literature review

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Summary

Aim. The study reviews the literature on false-positive drug test results in patients taking psychotropic medications.

Method. A narrative review of available literature in English and Polish was conducted by searching MEDLINE/PubMed and Google Scholar databases using the search phrase ‘false-positive drug test’ and names of selected registered antidepressant, antipsychotic and mood stabilizing medications as well as pharmaceuticals used in the treatment of ADHD. Review articles, case reports and original papers from years 1990–2019 were analyzed.

Results. False-positive drug test results have been reported for many psychiatric drugs: clomipramine, amitriptyline, bupropion, trazodone, sertraline, venlafaxine, hydroxyzine, haloperidol, sulpiride, perazine, levomepromazine, aripiprazole, risperidone, amisulpride, quetiapine, lamotrigine, carbamazepine, methylphenidate, and atomoxetine. No such reports have been found for other drugs considered in this study.

Conclusions. When interpreting urine drug tests, caution should be exercised, especially when the tested person categorically denies the use of psychoactive substances. In such situations, the patient’s medication list should be analyzed to ascertain that the obtained result is not false-positive. When test results are unclear, the presence of drugs in the urine can be effectively confirmed or excluded using gas chromatography. Unfortunately, most of the data available in the literature are case reports, which means they require further support from studies of large cohorts of patients taking psychotropic medications.

Key words: urine, false-positive reactions, medications

Introduction

Screening for drugs of abuse is now uncomplicated and quick due to the broad use of urine tests [1]. Screens are usually performed using commercial immunoassay kits, which are based on complex reactions between antigens and specific antibodies. More specific tests, based on gas or liquid chromatography coupled with mass spectrometry

(GC-MS/LC-MS), are rather the domain of specialist toxicology laboratories [2]. Urine drug of abuse screens are used by the police, healthcare institutions and some employers, which is why it is crucial that they should be highly sensitive and highly specific. Psychiatrists should take special care in interpreting the results of drug tests because a false-positive screen may hinder proper diagnosis, undermine the mutual trust between the doctor and the patient, and, in the case of patients treated for addiction, result in dismissal from a drug treatment program [3]. For this reason, it should be born in mind that some psychotropic drugs may trigger false-positive results in commonly used drug tests. Several groups of such drugs have been analyzed in medical studies and reports: tricyclic antidepressants – TCAs (clomipramine, amitriptyline), selective serotonin reuptake inhibitors – SSRI (sertraline), serotonin and noradrenaline reuptake inhibitors – SNRI (venlafaxine), other antidepressants (bupropion, trazodone), antipsychotics (haloperidol, sulpiride, perazine, levomepromazine, aripiprazole, risperidone, amisulpride, quetiapine), mood stabilizers (lamotrigine, carbamazepine), drugs used in the treatment of hyperkinetic disorders (methylphenidate and atomoxetine), and hydroxyzine [4–6].

Because these medications are widely used in the treatment of mental disorders, it is important to be aware that they can give a false-positive result on urine drug screens.

Aim

The study reviews available literature on false-positive drug test results in patients taking psychotropic medications.

Method

The source articles were found in MEDLINE/PubMed and Google Scholar databases using the following key words: clomipramine, imipramine, amitriptyline, moclobemide, mianserin, mirtazapine, reboxetine, tianeptine, agomelatine, bupropion, trazodone, fluoxetine, fluvoxamine, citalopram, escitalopram, sertraline, paroxetine, vortioxetine, venlafaxine, duloxetine, zolpidem, zopiclone, zaleplon, hydroxyzine, pregabalin, haloperidol, zuclopenthixol, flupentixol, sulpiride, perazine, tiapride, levomepromazine, chlorprothixene, aripiprazole, olanzapine, risperidone, amisulpride, quetiapine, ziprasidone, sertindole, clozapine, lithium salts, valproic acid, lamotrigine, carbamazepine, methylphenidate and atomoxetine, and time descriptors 1990–2019. The search was conducted in English and Polish. Review articles, case reports and original papers were considered.

Results

For the sake of clarity, the results are presented in Table 1 and the subsections of this article in the order consistent with a therapeutic classification of drugs: 1. Antidepressants; 2. Antipsychotics; 3. Drugs from various therapeutic groups (including mood stabilizers used in the treatment of ADHD).

Table 1. False-positive test results for psychoactive substances depending on a psychotropic drug usage

Medication	Psychoactive substance	Type of source	Source
Antidepressants			
Clomipramine	Methadone	1. Case report	1. Lancelin F et al. 2005 [32]
Amitriptyline	LSD	1. Case report	1. Detlef R et al. 1997 [16]
Bupropion	Amphetamine	1. Study confirming false-positives in 53 patients using bupropion	1. Casey ER et al. 2011 [11]
		2. Case report	2. Weintraub D et al. 2000 [8]
		3. Case report	3. Nixon AL et al. 2007 [9]
		4. Case report	4. Vidal C 2007 [10]
Trazodone	Amphetamine	1. Case report	1 Roberge RJ 2001 [13]
		2. Case report	2 Craig RJ 1996 [14]
		3. Case report	3 Jason M 2011 [15]
	LSD	1. Study confirming false-positives in 13 patients using trazodone	1. Detlef R et al. 1997 [16]
Sertraline	Benzodiazepines	1. Study confirming false-positives in 26 patients using sertraline	1. Nasky KM 2009 [18]
		2. Case report	2. Gear JL 1996 [17]
	LSD	1. Case report	1. Citterio-Quentin A 2012 [19]
Venlafaxine	Phencyclidine (PCP)	Case report	Bond GR et al. 2003 [20]
		Case report	Sena SF et al. 2002 [21]
		Case report	Santos PM et al. 2007 [22]
		Case report	Brahm N et al. 2006 [23]
Antipsychotics			
Haloperidol	LSD	1. Study confirming false-positives in 11 patients using haloperidol	1. Detlef R et al. 1997 [16]

table continued on the next page

Sulpiride	Buprenorphine	Case report	1. Birch MA et al. 2013 [37]
Pemazine	Opioid	Case report	1. Schmolke M et al. 1996 [36]
	Amphetamine		
Levomepromazine	Methadone	Case report	1. Lancelin F 2005 [32]
Aripiprazole	Amphetamine	Case report	1. Kaplan J 2015 [35]
Risperidone	LSD	Case report	1. Detlef R et al. 1997 [16]
	Fentanyl	Case report	1. Wang BT et al. 2014 [38]
Amisulpride	Buprenorphine	Case report	1. Birch MA et al. 2013 [37]
Quetiapine	Methadone	Study confirming false-positives in 12 patients using quetiapine	Cherwinski et al. 2007 [27]
		Case report	Widsichwendter CG et al. 2007 [28]
		Case report	Lasić D et al. 2012 [29]
	TCAs	Case report	Chathanchirayil SJ 2011 [31]
Mood stabilizer			
Lamotrigine	Phencyclidine (PCP)	Case report	Geraci MJ et al. 2010 [34]
Carbamazepine	TCAs	Case report	Fleischman A et al. 2001 [45]
		Case report	Matos ME et al. 2000 [46]
		Case report	Chattergoon DS et al. 1998 [47]
ADHD medications			
Methylphenidate	Amphetamine	1. Description of the in vitro experiment	1. Souza DZ et al. 2012 [40]
Atomoxetine	Amphetamine	Case report	1. Fenderson JL et al. 2013 [41]
Other medications			
Hydroxyzine	TCAs	1. Description of the in vitro experiment	1. Dasgupta A et al. 2007 [44]

Antidepressants

Bupropion

Bupropion is a selective catecholamine (norepinephrine and dopamine) reuptake inhibitor indicated in the treatment of major depressive episodes, and as a treatment adjunct in smoking cessation programs. It exerts a minimal effect on serotonin metabolism without affecting monoamine oxidase (MAO) [7].

Case reports point to a direct relationship between the use of bupropion and false-positive results of rapid immunoassays for the determination of amphetamine in urine. In the mentioned cases, the use of amphetamine was ruled out by LC-MS [8–10]. Particularly worth mentioning are the results of a study conducted in 2010 by Casey et al. [11]. Those authors analyzed over 10,000 urine samples taken from emergency department patients at Barnes-Jewish Hospital, of which 362 (3.62%) had positive amphetamine drug screens. These samples were subjected to GC-MS, which showed that 128 (35.4%) of the test results were false-positive. As many as 53 (41%) patients with false-positive urine amphetamine immunoassay results had an active prescription for bupropion. The remaining false-positive results were due to the use of other antidepressants (13%), antipsychotics (11%), and labetalol (7%), and in 28% of cases the factor responsible for the false-positive result was unknown. To compare, among true positives, bupropion use accounted for only 1.3% of cases. The study shows that prescription use of bupropion is the most common cause of false-positive urine drug screens for amphetamine [11]. It has been shown that the false-positive test results are not directly attributable to bupropion but to its metabolite threo-Hydroxybupropion [12].

Trazodone

Trazodone belongs to the group of serotonin reuptake inhibitors and at the same time is a 5-HT₂ receptor antagonist. Used as an antidepressant, it has the additional benefit of regulating the sleep-wake cycle [7]. Several case reports indicate that therapeutic use of this drug may elicit false-positive urine drug screens for amphetamine. In these studies, chromatographic tests did not confirm the presence of amphetamine in the urine [13, 14]. The few studies available in the literature suggest that it is probably not trazodone itself that elicits false-positive results but its metabolite 1-(3-Chlorophenyl) piperazine (mCPP). These reports also show that the probability of receiving a false-positive result appears to increase with increasing blood trazodone concentration. However, false-positive screens have also been observed in patients with trazodone levels within the therapeutic reference range [15]. In another study, false-positive LSD (lysergic acid diethylamide) results were obtained in 13 patients treated with trazodone [16]. It is worth noting that Angelini in the leaflet attached to preparations whose active substance is trazodone places information on the possibility of obtaining false-positive results for the presence of amphetamine in the urine

Sertraline

Sertraline is a SSRI and is used as an antidepressant, an anxiolytic and in the treatment of obsessive-compulsive disorder [7]. Descriptions of three cases indicate that sertraline may elicit false-positive drug test results for benzodiazepines [17]. In a retrospective study of urine drug screen results, Nasky et al. analyzed 522 urine

screens positive for benzodiazepines. After confirmatory GC-MS and exclusion of those patients who were documented to be taking benzodiazepines at the time of screening, 98 (18.8%) of the records turned out to be false-positive. Of these, 26 (26.5%) were from patients treated with sertraline [18]. Some rare reports also indicate the possibility of receiving false LSD-positive drug screens in both patients who overdosed sertraline and those who took the doctor-recommended dose [19].

Venlafaxine

The SNRI venlafaxine is another antidepressant that can lead to false-positive drug test results. An example is the case of a 13-year-old girl who took 48 tablets of 150 mg venlafaxine at a time to commit suicide. A urine drug test indicated the presence of phencyclidine (PCP), which was not confirmed by subsequent GC-MS [20]. The medical literature describes several other cases of patients treated with venlafaxine who tested false-positive for PCP, as determined later by gas chromatography. However, a false-positive screen for PCP does not necessarily point to an overdose [21–23]. False-positive PCP results have also been obtained after administration of desvenlafaxine – a PCP derivative [24].

Antipsychotics

Phenothiazine derivatives – chlorpromazine and promethazine

Chlorpromazine is an aliphatic derivative of phenothiazine. It exerts strong antipsychotic, sedative, anti-autistic, anxiolytic, and antiemetic activities. Indications for the use of chlorpromazine include psychosis, anxiety, psychomotor agitation, impulsive behavior, childhood schizophrenia, autism, hiccups, nausea, vomiting, and hypothermia (as an adjunct to prevent shivering) [7].

Promethazine, another derivative of phenothiazine, is a first-generation H1-receptor antagonist. It shows antihistamine, CNS-depressive, cholinolytic, antiemetic, sedative, and hypnotic effects. Indications for the use of promethazine include allergic conditions of the upper respiratory tract and skin, urticaria, itchy skin rashes, anaphylactic reactions, post-transfusion reactions, prevention and treatment of motion sickness, pre-operative sedation, and post-operative vomiting [7].

In a study conducted by Melanson et al., 22 urine samples collected from patients of the Massachusetts General Hospital emergency department who had positive serum drug test results for promethazine were screened for the presence of amphetamine and methamphetamine. 36% of the patients who were taking promethazine had false-positive urine drug screens for amphetamine. Six false-positive urine amphetamine tests were associated with therapeutic use of chlorpromazine. The researchers suggest that positive amphetamine, methamphetamine and methadone tests should be confirmed by

chromatography [25]. A study of 135 urine samples taken from Norwegian prisoners treated for psychiatric conditions also confirms the association between chlorpromazine and promethazine and false-positive urine amphetamine results. No such relationship was observed for alimemazine, levomepromazine, flupentixol or chlorprothixene [26]. One study also points to the possibility of obtaining false-positive LSD test results in patients treated with chlorpromazine [16].

Quetiapine

Quetiapine, which is a second-generation antipsychotic drug, is used in the treatment of both schizophrenia and bipolar disorder [7]. Case reports indicate that quetiapine may elicit false-positive results. For example, Cherwinski et al. describes cases of 12 adolescents treated with quetiapine each of whom had at least one false-positive result on a urine drug screen for methadone. Two of these cases were subjected to a chromatographic analysis, which did not reveal the presence of methadone [27]. Another study reports false-positive methadone test results in three patients on quetiapine monotherapy. In none of them, methadone was detected by chromatographic methods [28]. A case report of a 30-year-old patient treated at the University Hospital in Split also suggests there is a relationship between false-positive urine methadone tests and quetiapine treatment [29].

The literature also contains a description of two patients with active prescriptions for quetiapine who had false-positive screens for ketamine, however, these patients also took other medications, so there is no absolute certainty as to which of the drugs caused this effect [30]. It seems that quetiapine may, in some cases, also mimic TCAs in urine drug screens [31].

Other psychotropic drugs (including mood stabilizers used in ADHD treatment)

The literature mentions a few cases of false methadone-positive results in patients taking cyamemazine, alimemazine, levomepromazine, chlorpromazine, clomipramine and thioridazine [32]. Desipramine in turn has been observed to elicit false-positive amphetamine screens [33]. A description of two cases shows that false-positive drug test results for PCP can be encountered in patients treated with lamotrigine [34]. One study reports cases of false-positive LSD results in patients taking amitriptyline, buspirone, thioridazine, haloperidol, fluoxetine, risperidone, prochlorperazine, and doxepin [16]. There are also two known cases of false-positive drug test results for amphetamine in children who had accidentally taken aripiprazole [35].

It has been reported that intoxication with formulations comprising perazine may result in false-positive results of urine amphetamine and opiate immunoassays [36].

In a study by Birch et al., several patients with active prescriptions of sulphiride or amisulpride had false-positive findings of buprenorphine by CEDIA (Cloned Enzyme

Donor Immunoassay Technology), not confirmed by other tests [37]. Another prescription medication – risperidone may interfere with the results of fentanyl tests [38].

Mention should also be made here of methylphenidate, an amphetamine derivative used in the treatment of hyperkinetic disorders [7]. Manzi et al. showed that an addition of methylphenidate to urine samples in which no amphetamine had previously been detected, elicited an amphetamine-positive result [39]. This finding was not confirmed in a study using oral fluid immunoassays for amphetamine detection. In that study methylphenidate did not cause false amphetamine-positive results *in vivo* [40]. There are, however, cases in which false amphetamine-positive drug screens were elicited by another medication used in the therapy of hyperkinetic disorders – atomoxetine [41].

False-positive test results for TCAs

Sometimes urine immunoassays, in addition to screening for drugs of abuse, are also used to test for other substances, such as TCAs. As mentioned earlier, quetiapine is a drug that can mimic TCAs in urine screens. Case reports indicate that false-positive results can be obtained both in patients who have overdosed the antipsychotic drug to commit suicide and in patients who comply with medical recommendations [31, 42, 43]. Another drug that increases urine TCA levels and, when overdosed, may elicit a false TCA-positive screen is hydroxyzine [44]. A similar effect may be produced by an overdose of carbamazepine, which occurs relatively frequently in children [45–48].

Recapitulation

The problem of obtaining false-positive drug test results in patients taking psychotropic medications is still poorly explored in the medical literature. Most investigations are based on case reports or small cohort studies. However, because the potential repercussions of testing positive for a drug of abuse one has not actually taken may be severe, reliable larger cohort studies are requisite to address this issue. It is worth mentioning here that false-positive screening results are not a problem that concerns only medications used in psychiatry. False-positive test results can be elicited by many other, sometimes commonly used, substances, such as ibuprofen, which has been shown to mimic PCP in drug screens [49].

The potential for false-positive results in immunochemical tests is related to the similarity of the chemical structure of some drugs and their metabolites with the molecules that these tests are to detect, and thus with drugs and their metabolism products [6].

In case of high probability of a false-positive result of a standard immunochemical test for the presence of drugs, the optimal standard of conduct should be confirmation using methods based on liquid or gas chromatography, which are higher selectivity and

sensitivity methods [50, 51]. It should be kept in mind that different biological materials allow to obtain a different detection window. Urine tests can detect psychoactive substances taken up to several days before, and blood test, depending on the drug, from several hours to a day. When using hair analysis, it is possible to determine the substance intake up to 10 months before. Sometimes hair analysis can also determine how long the subject has been in contact with a particular substance [50]. It is worth remembering because the physician's belief that the patient is deliberately trying to mislead him/her or is not fulfilling the therapeutic contract may be detrimental to the doctor-patient relationship and thus reduce the chances of fruitful cooperation in treatment [52].

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