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Jensen, Christina Mohr; Breindahl, Torben

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ADHD Attention Deficit and Hyperactivity Disorders
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SHORT COMMUNICATION

Patients in medical treatment for attention deficit/hyperactivity disorder (ADHD): Are they at risk in drug screening?

Christina Mohr Jensen[1] · **Torben Breindahl**[2]

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Abstract
The use of medicines to treat attention deficit/hyperactivity disorder (ADHD) has increased worldwide, including the use of amphetamine-based medicines or prodrugs that metabolise to amphetamine in vivo. At the same time, drugs-of-abuse testing by non-specific, point-of-care immunoassay methods ('quick tests') has increased. This article discusses the risk of 'false positive' results or post-analytical misinterpretations of results when immunoassays are used to analyse biological samples from ADHD patients. A rapid evidence review was conducted to identify studies that have focused on the risk of 'false positive' test results in immunoassay testing of patients treated with atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil. There is only evidence to suggest that bupropion should cause 'false positive' immunoassay results. However, there is a lack of systematic, updated evaluations and validations of cross-reactivity patterns for immunoassays in the literature. Advanced laboratory methods can distinguish the use of medicines from illicit amphetamine by stereospecific analysis of dextro- and levoamphetamine; however, these analytical services are not commonly available for routine drug testing. The present situation calls for more awareness, proper education and information on these critical ethical issues in drug testing, both for clinicians, other healthcare professionals involved in drug testing and for patients in medical treatment for ADHD. The pitfalls of immunoassays due to cross-reactivity and insufficient specificity/sensitivity can have serious negative consequences for patients safety with regard to incorrect laboratory drug-testing results. Consequently, confirmatory laboratory analysis should always be performed for 'presumptive' positive immunoassay screening results.

Keywords Attention deficit/hyperactivity disorder · Drug testing · Immunoassay · False positive · Public health ethics

Introduction

Worldwide attention deficit/hyperactivity disorder (ADHD) affects 4–8% of children and 3–5% of adults worldwide (Fayyad et al. 2007; Giacobini et al. 2014) many of whom receive pharmacological treatment. A Swedish register-based study found that 80% of patients with an ADHD diagnosis received at least one prescription for ADHD medication (Giacobini et al. 2014). During the last two decades, the medical use of stimulants to treat ADHD has increased worldwide (Karlstad et al. 2016; van den Ban et al. 2010). At the same time, the use of immunoassays ('quick tests') for screening of drug use has increased considerably, particularly in the USA with an overall 14,000-fold increase and for general practice a 8700-fold increase during 2000–2009 (Collen 2012). However, this increase may even be underestimated as the data originate from specific procedural codes used to bill the United States Medicare and private insurance for medical procedures. We assume that this is a global trend; however, to our knowledge there is an absence of systematic registration of the use of immunoassays for point-of-care drug testing in most countries.

Due to the rise in both the (often lifelong) use of ADHD medications and the general use of drug testing, they are a population with a high prevalence for routine drugs-of-abuse testing as part of roadside drug testing to screen drivers under the influence of drugs, at emergency departments and somatic and psychiatric hospitals where immunoassay testing is used extensively, in military services, in the primary health sector for diagnostic purposes, in prisons, in doping

✉ Torben Breindahl
torben.breindahl@rn.dk

[1] Child and Adolescent Psychiatry, Aalborg University Hospital, Mølleparkvej 10, Aalborg DK-9000, Denmark

[2] Department of Clinical Biochemistry, North Denmark Regional Hospital, Bispensgade 37, Hjørring DK-9800, Denmark

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testing, and as part of workplace drug testing. Since ADHD is associated with a higher risk of developing substance use disorders (Ottosen et al. 2016), drug testing of these patients may also be more likely, compared to the general population.

As we will discuss in the following, it is crucial that immunoassays are used with the appropriate caution and consideration. We will focus our attention to drug testing for concurrent use of amphetamine. In this paper, we will argue that:

- While the use of immunoassays may have some benefits, they have serious limitations related to risk of 'false positive' results, the risk of overlooking comorbid substance use and problems of correct interpretation even by healthcare professionals.
- Personnel in charge of handling immunoassays should be educated and informed about the proper use of immunoassays and most importantly about their limitations.
- Patients should be informed about how their prescribed medication may affect screening results.
- 'Presumptive positive' screening results should be systematically followed up by confirmatory testing, in order to secure patient safety and to improve decision making.
- More research is needed on patterns of cross-reactivity for new immunoassays, and proper clinical evaluations should be performed on authentic samples.

Issues with ADHD, sports and doping control for stimulants have been reviewed elsewhere (Hickey and Fricker 1999) and will not be included in our discussion as doping testing procedures are internationally standardised and performed with confirmatory methods at laboratories accredited by the World Anti-doping Agency. Forensic laboratories may use immunoassays for pre-screening purposes, but final results are always based on reference methods according to forensic toxicology laboratory guidelines.

The potential consequences of drug screening with immunoassays: general considerations

While there may be good reasons to make rational use of immunoassays for various purposes, it is crucial that the strengths and limitations of these tests are fully acknowledged. Although immunoassays are relatively inexpensive, easy and practical to use, the limitations and intrinsic errors of this technique for drug testing have been known for decades, with numerous, published cases in the literature (Moeller et al. 2008; Reisfield et al. 2009; Saitman et al. 2014). Among the pitfalls immunoassays (1) do not identify the compounds that cause 'presumptive positive' results; (2) show 'false positives' due to cross reactions with medicines, food and drink ingredients or endogenous compounds; (3) are seldom documented properly in logbooks data and patient's medical records; (4) do not test for new psychoactive substances; (5) are often used by non-medically trained personnel; (6) are poorly understood and difficult to interpret even by healthcare professionals; and (7) are not systematically followed by confirmatory analysis because proper guidelines may not be implemented. However, these drawbacks are often not realised by the personnel that carry out the testing at rehabilitation centres, psychiatric hospitals, emergency departments, prisons or in the primary health sector (Reisfield et al. 2007a, c). All aspects discussed above are valid for testing of various biological matrices: blood, urine, oral fluid, sweat, and exhaled breath condensate.

To illustrate our concern, workplace drug testing can be used. Even though workplace drug testing in the USA has been performed under strict legislation since the late 1980s, guidelines and testing procedures have still not been fully implemented in many parts of the world including several European countries (Pierce 2012).

Confirmatory analysis

It is an essential principle that final 'positive' drug-testing results should be confirmed in a laboratory with gas or liquid chromatography coupled to mass spectrometry (GC–MS, LC–MS). These analytical techniques, which are used extensively in forensic and clinical toxicology, provide the most accurate and unequivocal results for drug and drug metabolite identification and quantification. While a number of factors cause 'false negative' confirmatory drug-testing results, avoidance of 'false positive' results is generally thought to be of greater importance. 'False positive' confirmatory results could be caused by various pre-analytical, analytical and post-analytical errors caused by the sampler, the operator, the apparatus or information technology systems. However, when errors occur, they are not related to the analytical principle of the confirmatory method per se (chromatography and mass spectrometry).

Confirmatory analysis often involves shipment of a sample specimen by mail; hence a delay in time to receive the final analytical report must be expected. Therefore, immunoassays fulfil the need for point-of-care testing and fast results, but too often samples may not be forwarded for confirmatory analysis.

When not used with the necessary knowledge and precautions, immunoassays represent a risk for patient safety regarding the correctness of laboratory results. Thus, non-confirmed immunoassay results can misinform clinicians and even cause a risk when drug-testing results are used during judicial decisions. Note that the issues discussed here for ADHD medicines are very similar to the controversy over

urine drug testing in pain management monitoring (McMillin et al. 2013; Reisfield et al. 2007b).

Next we will outline what is known about commonly prescribed ADHD medication, the risk of cross-reactivity causing 'false positive' results when using immunoassays. We also discuss potential consequences for both the clinician and the patient, when knowledge about how ADHD medications interact with drug-testing results is limited.

ADHD medication and the risk of 'false positives' using immunoassays

Today, a range of medications is used to treat ADHD. For the purpose of simplicity, we will divide the medications into amphetamine-based drugs (e.g. dexamphetamine and lisdexamfetamine) and non-amphetamine-based drugs (atomoxetine, bupropion, clonidine, guanfacine, methylphenidate and modafinil). As we will describe below, it can be anticipated that compliant patients treated with amphetamine-based drugs will screen positive for amphetamine on immunoassays, while the risk of screening positive when treated with non-amphetamine-based drugs may be less evident.

'False positive' drug screening results for amphetamine have also been associated with use of other drugs and herbal foods (Baron et al. 2011; Dadlani et al. 2018; Liu et al. 2015; Marin et al. 2016; Olsen et al. 1992; Papa et al. 1997; Pavletic and Pao 2014; Vorce et al. 2011). This also includes case reports for common drugs, e.g. aripiprazole (Kaplan et al. 2015) and metformin (Fucci 2012). In addition, methamphetamine is metabolised to amphetamine in vivo and is in fact an expected finding after ingestion of this drug.

Drug testing and amphetamine-based medication

Patients treated with amphetamines or lisdexamfetamine will generally have positive screening results for amphetamine when using both immunoassays and confirmatory testing, except for very dilute urine samples, where the concentration may be lower than the confirmatory cutoff level. We believe that patients should be informed about this, so they can prepare themselves for potential encounters with drug testing. This could be by notifying a future employer beforehand of likely test outcomes or carrying with them a certificate for medication. This is important, as drugs containing amphetamines or drugs metabolising to amphetamine in vivo do not reveal this by their common brand names, and therefore patients may not be able to foresee their risk status in drug-testing situations.

It is equally important that the personnel performing the screening tests on patients treated with amphetamine-based ADHD medications knows that a positive result should be expected. Also, it is important that they acknowledge that it is not possible, from the immunoassay technique alone, to discern whether the tested person is positive due to administration of licensed medicines or illegal amphetamine use or both.

Another important issue relates to whether or not clinicians can rely on confirmatory analyses to discern whether a positive test result may be caused by use of illegal amphetamine drugs. It does remain a challenge for laboratories to distinguish use of legal medicinal drugs from drugs of an illegal origin. In the case of amphetamine, this would call for chiral (enantiomeric) analysis in order to separate the two optical isomers: dextroamphetamine [*S*-(+)-amphetamine, the pharmacologically most active enantiomer] and levoamphetamine [*R*-(−)-amphetamine, the less active enantiomer]. Providing evidence whether a patient has supplemented a prescribed legal drug dose with 'street-grade' amphetamine is possible, but interpretation depends on the composition of illegal amphetamine found in the specific location (which may not be accessible) and the enantiomeric composition on the drug prescribed in each specific case. If the prescribed drug is pure *S*-(+)-amphetamine, then detection of *R*-(−)-amphetamine (above a certain R/S ratio) may suggest use of amphetamine from an illegal source (Nystrom et al. 2005). A pharmacokinetic study has also shown the applicability of enantiomer compositions in the assessment of 'time since dose' or discrimination between amphetamine from pharmaceutical sources and illicit amphetamine (Cody et al. 2004).

In cases where an ADHD patient is accused of drug use of illicit amphetamine or non-compliance, chiral analysis of various matrices may allow for (1) differentiation of the use of legal drugs from illicit amphetamine; (2) assessment of non-compliance; and (3) evaluation of self-medication with illicit amphetamine. However, chiral analysis of amphetamines is not a routine in neither clinical nor forensic drug testing. It may be difficult to find a laboratory to provide this analytical service, not to mention the challenge of interpreting such complex data.

Nevertheless, patients and clinicians should be aware of the existence of such methodologies for urine, blood or hair testing that may be applicable to monitor compliance of medication with amphetamine-based medical drugs and in some cases also distinguish amphetamine in pharmaceutical drugs from illicit amphetamine (Binz et al. 2017). Immunoassays for stereospecific analysis of amphetamines in urine have been marketed, but these have not been critically evaluated, and we do not advice to use the products. On the contrary, clinicians should contact biochemistry laboratories for guidance on the best choice of analytical services and expertise in post-analytical interpretation of results, and laboratory personnel in charge of drug

testing must be committed to carry out this task in order to improve ADHD patients' safety.

Drug testing and non-amphetamine-based medication

In this section, we will turn to a discussion of the non-amphetamine-based drugs. As mentioned, these include methylphenidate, which is among the most commonly prescribed medical drugs used to treat ADHD in both children, adolescents and adults (Giacobini et al. 2014).

We conducted a rapid evidence review in PubMed the 16th of March 2018, in order to identify any studies that reported on 'false positive' amphetamine immunoassay screening results with relation to either atomoxetine, bupropion, clonidine, guanfacine, methylphenidate or modafinil.[1]

The search returned 44 results of which nine studies were relevant. The reference lists of the nine relevant studies were also searched, in order to identify any relevant studies that could have been missed. In total, we identified one study concerning atomoxetine, six studies concerning bupropion, and three studies concerning methylphenidate. No studies were found concerning clonidine, guanfacine or modafinil. The results are summarised in Table 1.

Cross-reactivity of atomoxetine

We identified one study concerning atomoxetine and 'false positive' screening results on immunoassays. The study was based on a single case report (Fenderson et al. 2013). According to the World Health Organization, single case studies represent the lowest level of evidence (WHO 2000). Single, unexplained events could arise from food ingredients, herbal medicines, endogenous molecules, other drugs or metabolites. Since this single case report has not been supported by supplemental studies, and considering that atomoxetine is not a new type of medication, at present the evidence is insufficient to support a substantial risk of screening 'false positive' for amphetamines on immunoassays in patients treated with atomoxetine. However, in the absence of high-quality and systematic studies of potential cross-reactivity of atomoxetine on screening instruments, it is premature to make final conclusions.

[1] Search string used in Pubmed the 16th of March 2018: (((((((((("Guanfacine"[Mesh] OR guanfacine)) OR ("Clonidine"[Mesh] OR clonidine)) OR ("Bupropion"[Mesh] OR bupropion)) OR ("Atomoxetine Hydrochloride"[Mesh] OR atomoxetine)) OR ("Methylphenidate"[Mesh] OR methylphenidate))) AND (("Substance Abuse Detection"[Mesh]) OR ("Immunoassay"[Mesh] OR immunoassay)))) AND (amphetamine).

Cross-reactivity of bupropion

The systematic search identified one review and five original studies (see Table 1) that all reported on the cross-reactivity of bupropion and its principal metabolites in immunoassays for amphetamine. Thus, based on the review of findings, we believe that patients treated with bupropion are at high risk for being falsely tested positive for amphetamines during initial drug screening. Cross-reactivity by immunoassays can generally be explained as a signal generated by analytes with similarity in chemical structure. In the case of bupropion, the alpha-methylphenylamine structure is changed by the presence of a chlorine atom on the aromatic ring, an oxo group and a bulky *tert*-butyl radical on the amino group. It is not possible to assess the risk of cross-reactivity by simple reasoning based on chemical structures. Laboratory tests must be performed carefully using drug free matrices spiked with reference solutions of drugs and metabolites in the concentrations found in authentic samples.

Cross-reactivity of methylphenidate

In the search, we identified two studies relating to the risk of cross-reactivity of methylphenidate in amphetamine drug screening. One single study has reported methylphenidate as cause of 'false positive' amphetamine screening results (Manzi et al. 2002). Urine samples, originally screened negative for amphetamine, were spiked with a solution prepared from crushed tablets containing methylphenidate. The spiked samples were retested and found positive at the 200 ng/ml concentration level using an immunoassay method. In a commentary, this procedure was questioned, as it is not a good practice to spike urine samples with solutions made from crushed tablets (Breindahl and Hindersson 2012). The same year, three commercial oral fluid immunoassays for amphetamine were evaluated and no cross-reactivity was found for methylphenidate even at high concentrations (Souza et al. 2012). The authors regretted this since they argued for the need to screen for use of 'amphetamine-type stimulants' in Brazilian drivers and methylphenidate was considered belonging to this drug group. Cross-reactivity was in this concept considered as a positive feature, if it in fact would take place.

Methylphenidate and its major metabolite (ritalinic acid) are not connected by any metabolic pathways to other drugs-of-abuse, including amphetamine. However, there is a persistent myth that methylphenidate cannot be distinguished from amphetamine in drug testing. We find no solid published evidence to support that urine samples from patients using methylphenidate are at risk for 'false positive' testing for amphetamine when using immunoassays. As for atomoxetine, we recommend that high-quality research is conducted concerning the risk of cross-reactivity and methylphenidate

Table 1 List of drugs used in medical treatment of attention deficit/hyperactivity disorder (ADHD) and their 'cross-reactivity' in immunoassays

Drug substance name	'Cross-reactivity' in immunoassays used for drug screening	Description and references
Atomoxetine	Reported to cause 'false positive' results for 'amphetamines'	A female (27 years) with past medical history of ADHD presented to the emergency department after a reoccurring episode of acute onset of tonic–clonic seizure. She was prescribed with daily doses of 40 mg atomoxetine per day and had taken 120 mg 12 h prior to presentation. All performed drug tests were negative, except for a positive immunoassay screening result (CEDIA), which was not confirmed by GC–MS analysis. She denied to have taken illicit drugs, herbal medications or any over-the-counter drugs. The blood concentration of atomoxetine and metabolites was not analysed (Fenderson et al. 2013)
Bupropion	Reported to cause 'false positive' results for 'amphetamines' (amphetamine/methamphetamine) and LSD	In a review on 'false positive' urine screens (Brahm et al. 2010), two studies with relevance to bupropion were mentioned (Nixon et al. 1995; Weintraub and Linder 2000) *Case studies* A male with history of polydrug use and with a prescribed dose of 300 mg bupropion per day (for 3 weeks) was found positive for 'amphetamines' during a routine drug screen using an automated monoclonal EMIT II immunoassay, but confirmatory emergency toxicology testing with liquid chromatographic and photo-diode array detection did not confirm this finding. Cross-reactivity by bupropion and three metabolites were further investigated and found to cross-react with the EMIT II immunoassay. The authors suggested that typical doses of bupropion may generate sufficient metabolites to cause 'false positives' amphetamine screening results (Nixon et al. 1995) A woman (66 years) was admitted to an inpatient psychiatric unit with severe depression. Her urine toxicology screen on admission was negative. She was started on bupropion medication bupropion 100 mg b.i.d. Two routine urine samples collected on the 9th and 12th day after starting the medication screened positive for amphetamines when using an immunoassay. However, confirmatory analyses by GC–MS were negative for amphetamines. The authors warned for the potential negative clinical implications when positive drug screening results are released prior to running confirmatory analysis (Weintraub and Linder 2000) An unconscious male (50 years), with seizures on arriving at the hospital, screened positive for amphetamines and LSD when using an automated immunoassay (CEDIA) at a hospital. Subsequent confirmatory analysis (GC–MS, LC–MS) was negative for amphetamine and LSD, but positive for bupropion, which was used by the patient to aid smoking cessation. During the last week the dosage had been doubled to 300 mg bupropion per day. Urine samples spiked with bupropion or LSD (but not metabolites) were tested at different concentrations and demonstrated cross-reactivity for bupropion. For LSD the cross-reactivity was far below 1%, but the assay results were positive in the patients urine (Vidal and Skripuletz 2007) A retrospective study of 'false positive' amphetamine urine drug screens ($N=128$ out of 10,011) by an EMIT immunoassay, revealed 41% prescription use of bupropion in relation to the samples which failed to be confirmed positive by GC–MS analysis (Casey et al. 2011) A laboratory study investigated the cross-reactivity of bupropion and three metabolites. The results showed 'false positive' amphetamine and methamphetamine screening results for an immunoassay kit, but negative for an enzyme-linked immunosorbent assay (ELISA) (Reidy et al. 2011)
Clonidine	Not reported	–
Guanfacine	Not reported	–
Methylphenidate	Reported to cause 'false positive' results for 'amphetamines' in a single study, however, another study found no cross-reactivity for oral fluid testing	Urine samples, initially screened negative for amphetamine, were spiked with a solution prepared from solutions of crushed tablets containing methylphenidate. The spiked samples were retested and found positive at the 200 ng/ml concentration level using an immunoassay method (Manzi et al. 2002) The practical laboratory procedures of this study and the conclusion of the authors has later been criticised (Breindahl and Hindersson 2012) Three commercial oral fluid immunoassays for amphetamine were evaluated and no cross-reactivity was found for methylphenidate even at high concentrations (Souza et al. 2012)
Modafinil	Not reported	–

ADHD attention deficit/hyperactivity disorder, *CEDIA* cloned enzyme donor immunoassay, *ELISA* enzyme-linked immunosorbent assay, *EMIT* enzyme multiplied immunoassay technique, *LSD* lysergic acid diethylamide, *GC–MS* gas chromatography/mass spectrometry, *LC–MS* liquid chromatography/mass spectrometry

treatment. Unfortunately, the biased conclusion by Manzi et al. has found its way into the Summary of Product Characteristics (SPCs) for methylphenidate drugs worldwide causing further confusion and controversies as this misinformation continues to be communicated directly to both prescribers and users of the drug causing anecdotes that may persist for decades.

In summary, the only non-amphetamine-based drug where we have substantial evidence of a risk of 'false positive' results is bupropion. However, when proper confirmatory methods are used that are regarded as mandatory in urine drug testing (Taskinen et al. 2017), substances such as bupropion or methylphenidate will not be mistaken for amphetamine or visa versa, nor will they mask use of amphetamines (Breindahl and Hindersson 2012). We do, however, note that only few studies have looked at the cross-reactivity between non-amphetamine-based drugs used in ADHD treatment and amphetamine screening. In future, we recommend that studies should be set up to systematically evaluate the issue further, in order to provide more robust results, from which guidelines can be developed.

Lack of awareness about the fact that the majority of non-amphetamine-based drugs will not return positive results for amphetamine use could have at least two negative consequences. First, patients prescribed with, e.g. methylphenidate may fear being falsely accused of amphetamine drug use, which could lead to discontinuation of treatment. One of the authors (CMJ) is a board member at the Danish ADHD patient organisation and experiences that members specifically express fear of this. They express being in a dilemma about, on the one hand wishing to continue treatment to harvest the benefits of the medicine, and on the other hand considering discontinuing treatment due to fear of criminalisation, false accusations, losing job privileges, etc. Another risk is that 'true positive' results for amphetamine may be misinterpreted and disregarded as being the result of legitimate methylphenidate or atomoxetine treatment, thus potentially overlooking comorbid substance use.

The lack of a valid or updated cross-reactivity list from manufactures

A list of true negative and positive interactions for immunoassays would be of benefit in an ideal clinical setting. However, it is characteristic for immunoassays in drugs-of-abuse testing that (1) only a limited number of structure-related drugs are included in the manufacturer's validation, mostly performed on drug free matrices spiked with the drugs, but not always with the major metabolites; (2) authentic clinical samples may hold concentrations of drugs and drug metabolites that are much higher than the specimen tested during validation, so that the assay does not function correctly; (3) even in cases where the manufacturer's lists of cross-reactivity may be comprehensive at the time of assay validation (products from the large manufacturers of laboratory assays), such lists may not be updated regularly with new medical drugs and new psychoactive substances; (4) claims of cross-reactivity may not be valid for different batches of anti-body based techniques; (5) drug concentrations causing cross-reactivity and positive results depend on the cutoff of the assay in a nonlinear manner; and (6) although it is clinical relevant that the manufacturers provide updated information on the performance of immunoassays, we acknowledge that this is a costly and time-consuming task, which explains the lack of information from suppliers of the numerous products for on-site testing.

The role of the clinical laboratory

Clinical chemists and specialists in laboratory medicine may have the best understanding of the limitations of screening tests in general, the technical aspects of running such assays in a clinical laboratory or in point-of-care testing as well as the interpretational elements. However, due to the controversies outlined above a strong professional communication and interaction within the networks of patients, clinicians and colleagues is essential. Thus, we identify a need for clinical laboratory professionals to step into a more active and educational role and be involved in the moral and ethical issues of drug screening. It is the potential punitive consequences of 'presumptive positive' drugs-of-abuse screening results that are the main cause of concern and makes it different from other clinical screening tests. Thus, unexpected or unusual drug findings for a patient—also for confirmatory results—should always be questioned in search for a correct interpretation with full consideration to the patients' medical history and prescription drug list.

Conclusion

While drug testing has its benefits and can be justified in certain clinical situations, we have outlined some critical, ethical aspects that needs more attention in both clinical practice and research. The risks for ADHD patients of being falsely accused of drug abuse or discriminated in cases relating to workplace, education, and medical treatment are evident in particular for patients who are prescribed amphetamine-based medications, prodrugs that release amphetamine when metabolised and bupropion. On the other hand, knowledge about the lack of evidence of cross-reactivity, for example for methylphenidate and atomoxetine, is important for those who handle the tests, to avoid overlooking potential use of non-prescribed amphetamine. We believe that our line of argumentation calls for more attention to ensuring that patients are educated about their medication. In addition,

there is a need to inform professionals who administer immunoassays about the patterns of cross-reactivity and that all 'presumptive positive' screening results should be supplemented by confirmatory analysis at a clinical laboratory. With the use of modern laboratory information systems, such requisitions should be made automatically. Finally, more research, critical evaluation and validation are needed to update the current knowledge on immunoassays and cross-reactivity with ADHD drugs.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Research involving human participants and/or animals This research involved no human participants or animal studies.

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