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Toxicological screening in the Amsterdam acute setting becomes more relevant if the standard panel of the drugs-of-abuse point-of-care test is expanded with GHB and ketamine

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ABSTRACT

Objective: For diagnosis and treatment in the acute setting, it is crucial to know whether the clinical status of patients might be explained by the effects of drugs.

The objective of this study was to determine how many drugs were detected by comprehensive toxicological screening, that could not be detected with a routine drugs-of-abuse point-of-care test (DOA-POCT) and which drugs of abuse (DOA) were relevant. A secondary objective was to determine in how many patients comprehensive toxicological screening provided additional clinically relevant information.

Methods: In this prospective study, patients were included in whom a DOA-POCT was performed and residual urine and serum samples were available.

DOA-POCT were performed using the Triage® TOX Drug Screen. Comprehensive toxicological screening was performed using 1) the Toxtyper™ LC–MS^N method and 2) two GC-FID methods for alcohols and GHB respectively.

The clinical relevance of the comprehensive toxicological screening results regarding diagnosis and patient management was quantified.

Results: A total of 100 patients were included. In 91 of these patients, comprehensive toxicological screening identified 234 drugs that were not identified by DOA-POCT. However, DOA-POCT identified 34 DOA that were not identified by comprehensive toxicological screening.

Seven percent of comprehensive toxicological screening results were found to be clinically relevant, all with regard to diagnosis. GHB and ketamine were the drugs involved. Another 38 % strengthened confidence in diagnosis and patient care decisions.

Conclusion: GHB and ketamine should be added to the panel of drugs we screen at the point of care in the Amsterdam acute setting.

1. Background

1.1. Background

For adequate diagnosis and patient care in the Emergency Department (ED), it is often important to know if the patient's condition might be explained by the effects of drugs-of-abuse (DOA) or other drugs. Therefore, toxicological screening analysis of biological material is usually performed when a patient presents with undefined symptoms or has a history of drug ingestion [1–3].

In most hospitals in the Netherlands, toxicological screening of DOA and other therapeutic drugs in blood or urine takes place at the laboratory of the Department of Clinical Pharmacy. For comprehensive toxicological screening in blood a High Performance Liquid Chromatography equipped with a Diode Array Detector (HPLC-DAD) is normally used. This method is time-consuming, due to sample preparation, and expensive, due to the need of trained laboratory technicians in a central laboratory. For the screening of DOA and a couple of other drugs in urine, immunoassay based tests can be used. Previous research has shown good results regarding sensitivity and specificity for the point-of-care-test (POCT) Triage TOX Drug Screen. As a result of this study OLVG introduced the use of this DOA-POCT which can detect a number of drugs in urine within 10 min [1].

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1.2. Importance

DOA-POCTs are frequently used in EDs. However, previous research at our ED has shown that the clinical value of this DOA-POCT is limited in our setting, despite the rapid availability of the results [3].

We wondered if this is due to the limited number of drugs that can be tested with the standard panel on the DOA-POCT, or the limited sensitivity of the DOA-POCT for new designer drugs [1,4,5].

Since 2016, our hospital has implemented the Toxtyper™ (Bruker, Bremen, Germany), a new type of drug screener for comprehensive screening. The Toxtyper™ is based on Ultrahigh Performance Liquid Chromatography (UHPLC) coupled to an MS^N ion trap system, equipped with a comprehensive and editable spectral library of about 900 DOA and therapeutic drugs. The sample pre-processing technique is fast and simple and run times are short, in contrast to generally used HPLC-DAD methods [6–10].

The Toxtyper™ cannot detect volatile substances. Therefore, comprehensive toxicological screening should consist of a Toxtyper™ run plus specific GC methods for the detection or exclusion of gammahydroxybutyric acid (GHB) and alcohols.

A disadvantage of comprehensive toxicological screening is that the analysis takes longer and results become available later. An advantage could be that comprehensive toxicological screening may detect additional relevant compounds and may have additional clinical value in cases of intoxications.

1.3. Goals of this investigation

This study aimed to determine how many additional drugs were detected by comprehensive toxicological screening in both blood and urine, that were not detected with a routine DOA-POCT in urine and which of these DOA were clinically relevant. Our secondary objective was to determine in how many patients comprehensive toxicological screening did provide additional clinically relevant information for diagnosis and patient management..

2. Materials and methods

2.1. Study design and setting

The study was designed as a non-comparative, prospective, observational study. No interventions were made.

The study was performed from June to September 2017 in OLVG, a teaching hospital in the middle of Amsterdam, the Netherlands. The local Medical Ethical Committee approved the study.

2.2. Selection of participants

The Emergency Department (ED) of OLVG has a census of 90.000 patients each year and a high prevalence of drug abuse and misuse complications.

All patients for whom a physician ordered a DOA-POCT and enough residual urine and serum were available, were eligible for inclusion into this study.

During this study the DOA-POCT and comprehensive toxicological screening were applied as in routine clinical practice. Patients were not treated differently. Therefore, informed consent was not required.

2.3. DOA-POCT

Routinely, DOA-POCTs in urine were performed by laboratory technicians of the Haematological and Clinical Chemical Laboratory using the Alere Triage® TOX Drug Screen. This competitive fluorescence immunoassay can be used to determine the presence of DOA and a panel of therapeutic drugs in urine. The drug panel consists of amphetamine, methamphetamine, barbiturates, benzodiazepines, cocaine, methadone, phencyclidine, opiates, tetrahydrocannabinol (THC, the main active component of cannabis) and tricyclic antidepressants. [2,5] The cut-off values were: 1000 ng/mL (amphetamine, methamphetamine, tricyclic antidepressants), 300 ng/mL (barbiturates, benzodiazepines, cocaine methadone, opiates), 25 ng/mL (phencyclidine) and 50 ng/mL (11-nor-9-carboxy-Δ9-THC (THC(COOH)), the main inactive metabolite of cannabis) [5]. Analytical validation and the application of control samples in the study setting were performed according to the instructions of the manufacturer and according to International Guidelines. [5]. All tests were performed within a few hours after urine collection.

2.4. Comprehensive toxicological screening

Comprehensive toxicological screenings in residual urine and residual serum were performed by laboratory technicians of the Department of Clinical Pharmacy. Comprehensive toxicological screening contained 1) qualitative toxicological drug screening in both serum and urine with validated Toxtyper (TT) methods and 2) quantitative screening for GHB and alcohols (ethanol, methanol, acetone, acetonitrile and isopropyl alcohol) in both serum and urine with validated gass chromatography-coupled with flame ionization detection (GC-FID) methods.

The TT is an LC-ESI-MS^N, an Ultra High Performance Liquid Chromatography (UHPLC) coupled to a tandem Mass Spectrometer (MS^N) ion trap system. The TT uses electrospray ionization (ESI) as an ionization technique. [6–8] The library used for this study was the Toxtyper 1.1 library, which contains around 900 DOA and other drugs. In addition, agents can be added manually, including in our case 4-fluoramphetamine [9].

Protein precipitation was used as the sample preparation technique prior to injection into the TT. [10] For this purpose the TT methods in urine and serum were validated in our own laboratory.

Until comprehensive toxicological screening was performed, residual urine and serum samples were stored at −80 °C. Serum samples have been stored for a maximum of 2 weeks. Urine samples have been stored for a maximum of 2 weeks for analysis with GC-FID and for a maximum of one year for analysis with the TT.

2.5. Confirmation of the results

The primary objective was to determine how many drugs were detected by comprehensive toxicological screening, that were not detected by DOA-POCT. Therefore, all positive results of comprehensive toxicological screening were compared with all positive results of DOA-POCT. The number of extra substances found was expressed in absolute numbers.

The secondary objective was to determine in how many patients comprehensive toxicological screening did provide additional clinically relevant information with regard to diagnosis and patient management and to determine which types of drugs were relevant to detect. To answer this question, the clinical value of comprehensive toxicological screening for diagnosis and patient management was assessed by an independent expert panel. The expert panel consisted of an internal medicine physician, an emergency physician and a hospital pharmacist-toxicologist. They individually, retrospectively assessed the clinical value of comprehensive toxicological screening with regard to:1) diagnosis, 2) hospital admission and monitoring and 3) treatment. The clinical relevance of the comprehensive toxicological screening results for diagnosis and patient management were quantified using a previously validated 5-point scale (Table 1) [2]. We derived the 5-point scale from a diagnostic value questionnaire that was used in a study of the clinical value of DOA-POCT in an emergency department setting [2]. The expert panel had access to information from the electronic patient file (Table 2).

The average of the scores of the three members of the expert panel

Table 1
Scales used to assess the influence on diagnosis, admission into the hospital, patient monitoring and patient care.

Diagnosis	
D1	CTS provided false information and led to extra (unnecessary) investigations
D2	CTS did not provide relevant diagnostic information
D3	CTS confirmed what I already thought
D4	CTS contributed to my diagnostic understanding, but other factors were more important
D5	CTS was the most important factor on diagnosis
Admission and Monitoring	
M1	CTS led me to choose an admission and monitoring which was not the best choice for the patient at that time
M2	CTS did not influence my choice of admission and monitoring
M3	CTS did not alter my choice of admission and monitoring, but reassured me that I made the right choice
M4	CTS influenced my choice of admission and monitoring, but other factors were more important
M5	CTS was the most important factor in choosing an admission and monitoring
Treatment	
T1	CTS led me to choose a treatment which was not the best choice for the patient at that time
T2	CTS did not influence my choice of treatment
T3	CTS did not alter my choice of treatment, but reassured me that I made the right choice
T4	CTS influenced my choice of treatment, but other factors were more important
T5	CTS was the most important factor in choosing a treatment

CTS = comprehensive toxicological screening.

was calculated. All average scores of 4 and 5 for either 1) diagnosis, 2) admission and monitoring and 3) treatment were regarded as clinically relevant. The number of patients for whom additional clinical relevance was demonstrated was expressed as a percentage. The responsible compounds were named by their generic name.

Analyses were performed using Excel 2010 and SPSS for Windows, version 22.0. The demographic data were described in median with interquartile range. Categorical data were described in frequencies and/or percentages. Because Glascow Coma Scale (GCS) values were not normally distributed, the non-parametric Mann-Whitney *U* test was used to test significance. A p-value < 0.05 was considered statistically significant.

3. Results

A total of 236 DOA-POCT analyses were performed for 235 patients. Only the results of 100 patients were included for analysis. Reasons for exclusion were:

- The residual urine and/or serum was not available or insufficient amounts for comprehensive toxicological screening (132 patients, 55.9 %).
- The DOA-POCT did not produce a valid result (3 patients, 1.3 %).
- The DOA-POCT was performed twice for one person; only the results of one DOA-POCT were used (1 patient, 0.42 %).

From the 100 DOA-POCT, 78 were found to be positive for at least one drug. In total, 160 DOA were found by DOA-POCT (Table 4, orange column).

From the 100 comprehensive toxicological screenings, 94 were found to be positive for at least one drug in urine and/or serum. In total, 360 DOA and other (therapeutic) drugs (DOA (n = 169), other (therapeutic) drugs (n = 127), alcohols or GHB (n = 64)) were found by comprehensive toxicological screening.

If comprehensive toxicological screening was only performed in urine or serum, a total of 206 respectively 161 DOA and other drugs were found by comprehensive toxicological screening which were not found by DOA-POCT (Figs. 1–3). Comprehensive toxicological screening in urine detected more compounds than screening in serum. However, benzodiazepines were missed more often by screening in urine.

TT found 9 designer drugs in urine and/or serum, all were amphetamine-like (4-fluoroamphetamine (4-FA (n = 4), benzodioxazoylbutamin (BDB) (n = 2), mephedrone (n = 1) and methylone (n = 2)).

DOA-POCT was found positive for amphetamine and negative for methamphetamine in the cases comprehensive toxicological screening revealed 4-FA and mephedrone in patients. DOA-POCT was found negative for both amphetamine and methamphetamine in the cases comprehensive toxicological screening revealed the presence of BDB and methylone in patients.

TT found 43 DOA in urine and/or serum which were not found positive by DOA-POCT (Fig. 1). In 26 of the 43 cases the DOA did belong to the DOA-POCT panel and in 17 of the 43 cases the DOA did not (Table 4, green column, numbers with *). Fig. 1 also shows 4-FA and mephedrone.

DOA-POCT were found positive for 29 DOA which were not found by TT (Table 4, green column, numbers underlined). In 23 of the 29

Table 2
Patient data available for expert panel.

General information	gender, age, nationality, date and time of admission, date and time of intoxication, date and time of collectingurine and serum samples
Anamnesis	
Home medication	
Medical history	
Medication administered in the ambulance	
Information reported by the emergency care physician	ABCD, lab values, other diagnostic workup (eg CT, ECG)
Results DOA-POCT	
Diagnosis reported by the emergency care physician	
Admission, monitoring and patient care reported by the emergency care physician	admission in which department, main problems, interventions (eg oxygen supply, supporting medication, fluid, antidote, dialysis), expected complications (eg convulsions, QT prolongation, rhabdomyolysis)
Results comprehensive toxicological screening	

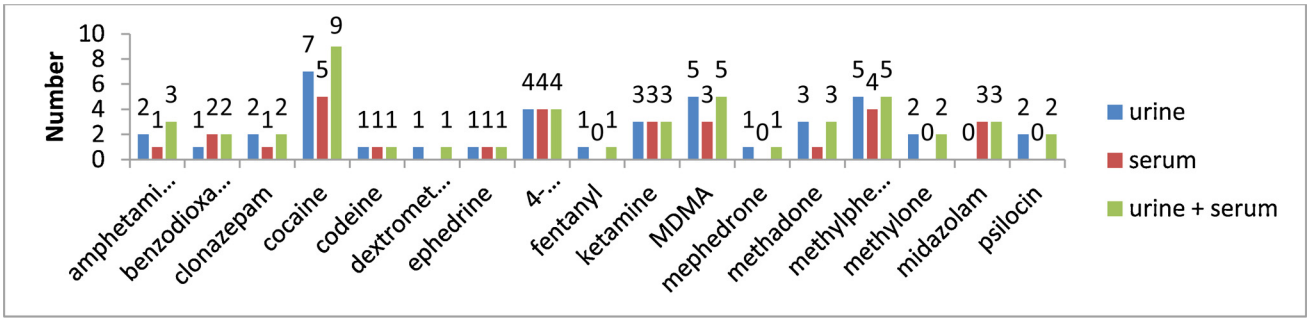

Fig. 1. Extra detected DOA by the TT compared to the detected drugs on the DOA POCT.

cases it concerned THC(COOH), the metabolite of cannabis.

In 7 patients (7%), the expert panel was of the opinion that the results of comprehensive toxicological screening would have contributed significantly to the correct diagnosis (D4 + D5 (n = 7)) (Fig. 4). 5 of 7 patients had used GHB, including 1 in combination with cocaine. 2 of 7 patients had used ketamine, including 1 in combination with methadone and 1 in combination with amphetamine and alcohol (Table 5). In all cases, GHB or ketamine were judged the decisive factor, leading to the conclusion that identifying these drugs was considered clinically relevant.

In none of the patients (0%) comprehensive toxicological screening made a significant contribution to patient management and decision to admit (Fig. 4).

For the patients where comprehensive toxicological screening provided relevant additional information, the median GCS score was considerably lower than for the other patients although this difference was not statistically significant (Mann-Whitney U test: P = 0.168) (Table 3).

In 38 patients (38 %), the results of comprehensive toxicological screening boosted confidence in diagnosis (D3 (n = 31)), and / or admission and monitoring (M3 (n = 4)), and / or treatment (T3 (n = 14)) (Fig. 4). For these patients, Table 5 shows the involved DOA or therapeutic drugs.

4. Discussion

In our study, a DOA-POCT was performed on 235 patients in only 3 months of time. This large number was more than revealed by previous research [2,3]. This can be explained by the fact that 1) with the start of this study the DOA-POCT has been brought to the attention of the emergency physicians and 2) inclusion took place during the summer festival season where many DOA are used [13]. Our study involved a very heterogeneous group of patients since every patient with a suspected intoxication was eligible for inclusion. Only 100 patients could be included, because in many cases residual material was not available. The hectic environment of the ED is probably the main reason for this. Nevertheless, we feel that this has not affected the results of this study, since the patient characteristics of the included patients are comparable to those of the whole group of eligible patients.

Comprehensive toxicological screening in urine and/or serum identified much more DOA and other drugs (234 extra) than DOA-POCT. This was what we expected, because 1) the TT library that was used contains around 900 drugs, 2) GHB and alcohols were also screened for and 3) screening was performed in both urine and serum. Of all the DOA and therapeutic drugs identified by comprehensive toxicological screening, the expert panel found the results predominantly relevant for a correct diagnosis in patients who had used amphetamine, cocaine, ethanol, GHB, ketamine and methadone. Since GHB and ketamine were the determining factor in all cases, extending the DOA-POCT with GHB and ketamine could provide important additional information.

The TT appeared to identify 47 amphetamine-like drugs, of which 9 were new designer drugs (19 %).Of these, 4 were missed with DOA-POCT. In the case of 4-FA and mephedrone, DOA-POCT tested positive for amphetamine. In the Dutch drugs of abuse scene, around 16 % of amphetamines are new designer drugs, which is confirmed by our study [11,12].

The TT identified 26 DOA in urine and/or serum that belonged to the DOA-POCT panel, but were not identified by DOA-POCT. 6 of these 26 DOA were only found in serum. For the remaining 20, several reasons may explain for this discrepancy. First of all, the detection limits for TT and DOA-POCT are not the same. DOA that are present in very low concentration can be detected by TT, but cannot be detected by DOA-POCT. [13] Furthermore, it is possible that DOA-POCT has produced a false negative result, because this is inherent to the analysis technique [1]. Finally, the TT sometimes appeared to give false positive results for cocaine in urine through carry-over [13]. This may have been the case in 7 patients where DOA-POCT was negative for cocaine.

DOA-POCT identified 29 DOA that were not identified by the TT in

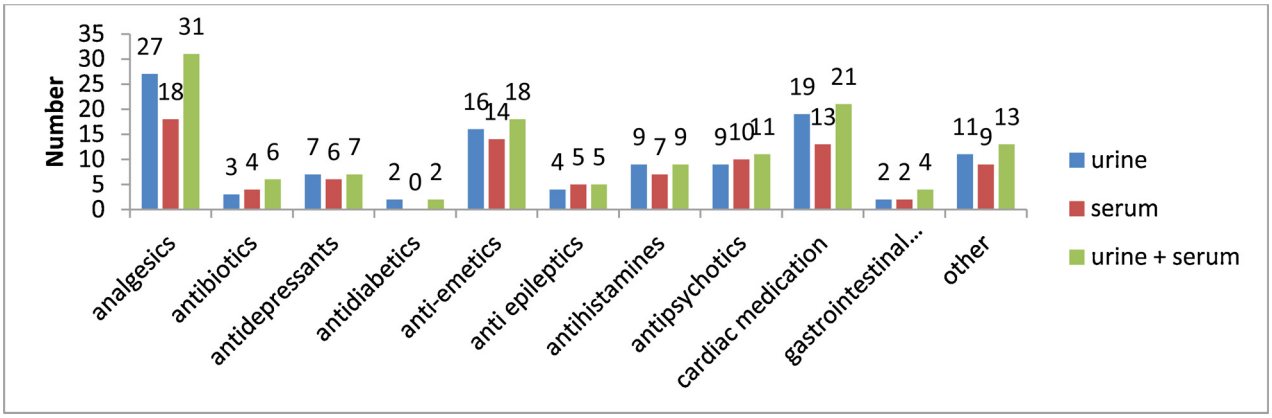

Fig. 2. Extra detected other (therapeutic) drugs by the TT compared to the detected drugs on the DOA POCT.

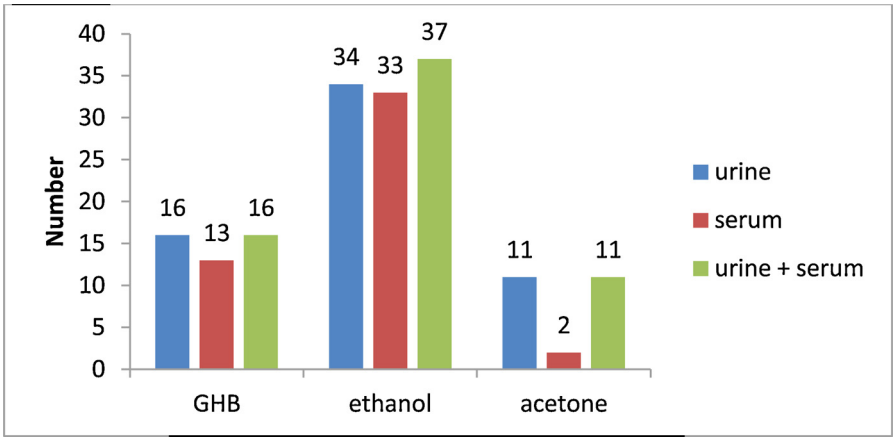

Fig. 3. Extra detected volatile substances by GC-FID.

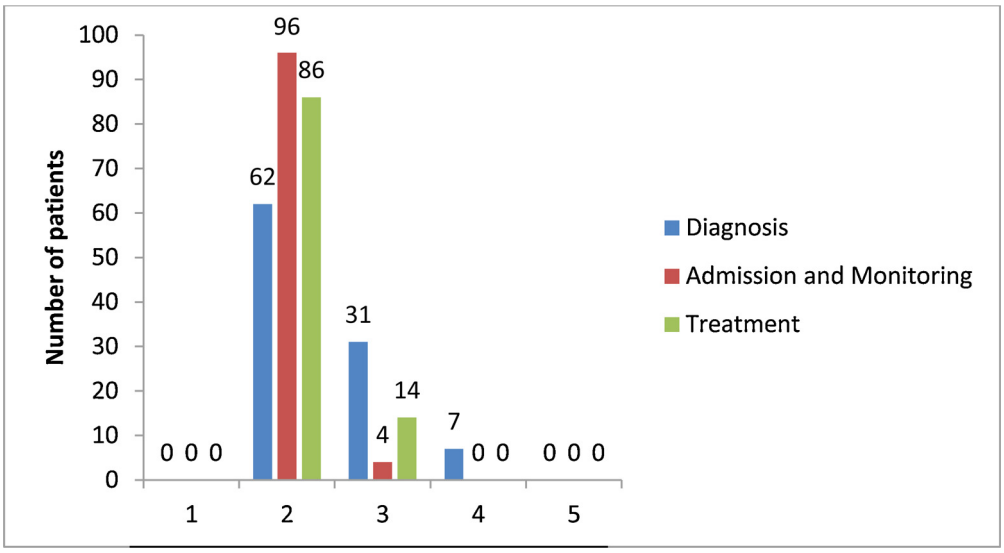

Fig. 4. The influence of comprehensive toxicological screening on diagnosis, admission and monitoring and treatment. A higher score means that comprehensive toxicological screening had more influence on diagnosis, admission and monitoring and treatment. See Table 1 for an explanation of the scales.

urine and/or serum. Additionally, benzodiazepines were regularly missed by the TT, especially in urine. Since the specificity of Triage for most DOA is > 99 % [1], this cannot be explained by possible false-positive results from DOA-POCT. In recent studies, the specificity and sensitivity of the TT was found to be ≥97.7 % for amphetamine, methamphetamine, benzodiazepines, cocaine, methadone and opiates. Also, the sensitivity for THC of TT might have been insufficient [13]. If the 29 discrepancies are examined in more detail, then in most cases it appears to be THC, which has been missed by the TT in both urine and serum. In contrast, the DOA-POCT is sensitive for the inactive THC(COOH) metabolite (by antibody binding) in urine. This may result in a longer window of THC detection by DOA-POCT as compared by TT in serum and urine and may explain why DOA-POCT in urine identified more positive cannabis cases as compared to TT. Stability may also have played a role in the urine samples, as they were stored for one year before analysis with the TT took place. In this regard, it is known that levels of THC metabolites show a decline of ± 30 %, whereas benzodiazepines appear quite stable after 1 year of storage at -20 °C. [14,15]. Another possibility is that ion suppression has occurred in LC-ESI-MS of cannabinoids. For cannabinoids, solid phase extraction is preferably used as the sample pre-processing technique., Since protein precipitation in serum has been used in this study, matrix effects may have caused ion suppression leading to lack of detection of THC in serum samples [16,17]. In addition, benzodiazepines are mainly present in conjugated form in urine, which can be detected by DOA-POCT. However since benzodiazepine-conjugates were not included in the TT library used, they were not identified by TT [5,9,18].

Comprehensive toxicological screening in urine identified more DOA and therapeutic drugs (n = 206) than comprehensive toxicological screening in serum (n = 161).

Psilocin (the active component of hallucinating mushrooms), methylone (amphetamine-like), amphetamine, cocaine, analgesics (in particular paracetamol) and cardiac agents were identified more often in urine than in serum.

On the other hand, benzodiazepines were identified more often in serum than in urine. An explanation for this is that the phase II metabolites (glucuronides) of benzodiazepines were not included in the TT library [9,18].

In our study, 7 % of comprehensive toxicological screening results, in addition to the routine DOA-POCT in urine, substantially supported the physician in diagnosis and did not substantially influence patient management. This is a lower impact than we expected, since the combination TT and GC-FID captures almost all DOA and other drugs.

It should be noted that a large percentage of comprehensive toxicological screening confirmed a suspected diagnosis or reassured physicians in making their decision to admit and for patient monitoring and treatment. Though we did not consider this a substantial influence, confirmation and reassurance is valuable for physicians [2].

Table 3
Patient characteristics.

	Patients excluded (n = 136)	Patients included (n = 100)	Patients for whom clinical added value has been demonstrated (n = 7) *(Scores D4 − 5, M4 − 5 and/or T4 − 5)*	Patients for whom no clinical added value has been demonstrated (n = 93) *(Scores D1 − 3, M1 − 3 and/or T1 − 3)*
Age, median	33 (IQR26 − 44)	34 (IQR27 − 43)	38 (IQR33 − 52)	33 (IQR25 − 43)
Men, number (%)	101 (74 %)	62 (62 %)	6 (857%)	56 (602%)
Dutch, number (%)	102 (75 %)	64 (64 %)	6 (857%)	58 624%)
Foreign, number (%)	34 (35 %)	36 (36 %)	1 (143%)	35 (376%)
EMV, median	15 (IQR12 − 15)	14 (IQR8 − 15)	8 (IQR7 − 14)	14 (IQR8 − 15)

IQR = interquartile range. See Table 1 for an explanation of the codes D1 − 5, M1 − 5 and T1 − 5.

One explanation for the limited clinical value may be that comprehensive toxicological screening probably has the most added value in intoxications with unclear clinical presentation, while a very heterogeneous patient group has been included in our study. In previous research, the DOA-POCT was found to have most influence on diagnosis and patient management when used for patients with a decreased GCS and patients with psychiatric and neurological symptoms. [2] In our study, the median GCS score of patients with clinical added value was 6 points lower compared to other patients. Although this difference was not significant, the additional clinical value appears to be greater in patients with a lower GCS.

It should be mentioned that the TT only provides qualitative information. Usually this will provide sufficient knowledge on the type of intoxication, but it does not provide information on the extent of drug exposure in the body. With regard to estimation of the extent of drug exposure a semi-quantitative TT toxicology screen that has become available may have additional clinical value in the future.

GHB and ketamine were the main recreative drugs that were missed by the routine POCT-DOA test in urine. GHB is a recreational drug with central nervous system depressing effects that is often abused. Recreational doses of 1–2 g generally provide a feeling of euphoria. [19] Apart from its role as a drug in pain management and anaesthesia, ketamine has also become a recreational drug since it may produce euphoria and dissociative hallucinogenic effects [20]. Interestingly for both of these drugs urinary POCT-tests have become available. GHB can be picked up by a GHB point-of-care test in urine [21–23]. It should be noted that alcohol and other compounds may interfere with these GHB urinary tests [23]. Recently, also for ketamine, tests in urine and oral fluid have become available [24]. These tests may have sensitivities and specificities > 90 %. [23]. Therefore these tests may become of value for testing potentially intoxicated patients at the emergency department.

5. Conclusion

Comprehensive toxicological screening with the combination of TT and GC-FID for GHB and alcohols, in addition to the routine DOA-POCT in urine, aids in the diagnosis of intoxicated patients but does not affect patient management. Identification of GHB and ketamine was found to be particularly relevant for this purpose. GHB and ketamine should be added to the panel of drugs we screen at the point of care in the Amsterdam acute setting.

CRediT authorship contribution statement

J.A.J. van der Schaar: Conceptualization, Methodology, Investigation, Writing - original draft. **M.E. Attema-de Jonge:** Conceptualization, Methodology, Validation, Writing - review & editing. **F.M.J. Gresnigt:** Conceptualization, Writing - review & editing. **E.J.F. Franssen:** Conceptualization, Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing interest.

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Table 4
Identified drugs from the DOA-POCT panel in our 100 patients.

DOA	Detected by DOA-POCT	Detected by TT in urine		Detected by TT in serum		Detected by TT in urine and/or serum	
			Total		*Total*		*Total*
Amphetamine	14	14 / 2*	16	9 / 1*	10	14 / 3*	17
Methamphetamine	20	20 / 5*	25	20 / 3*	23	20 / 5*	25
Barbiturates	0	0	0	0	0	0	0
Benzodiazepines	47	28 / 2*	30	41 / 4*	45	42 / 5*	47
Cocaine	29	29 / 7*	36	25 / 5*	30	29 / 9*	38
Methadone	3	3 / 3*	6	3 / 1*	4	3 / 3*	6
Opioids	1	1 / 1*	2	0 / 1*	1	1 / 1*	2
Phencyclidine	0	0	0	0	0	0	0
THC	45	17 / 0*	17	14 / 0*	14	22 / 0*	22
TCAs	1	0	0	0	0	0	0
Total	*160*	*112 / 20**	*132*	*112 / 15**	*127*	*131 / 26**	*157*

The numbers underlined mean the number of DOA that have been detected by DOA-POCT and also by the TT.
The numbers with an asterisk (*) mean the number of DOA that have been detected by the TT, but not by DOA-POCT.
TT = Toxtyper™.

Table 5
. DOA and volatile substances for which the expert panel indicated that knowledge of their presence in the body was relevant for diagnosis and or treatment.

Diagnosis D3	Diagnosis D4	Admission and monitoring M3	Admission and monitoring M4	Treatment T3	Treatment T4
4-FA (3x)	Amphetamine (1x)	Cocaine (1x)	None	Amphetamine (1x)	None
Benzodiazepines (1x)	Cocaine (1x)	Ethanol (1x)		Cocaine (7x)	
Clozapine (1x)	Ethanol (1x)	Fentanyl (1x)		Ethanol (2x)	
Cocaine (7x)	GHB (5x)	GHB (2x)		Fentanyl (1x)	
Codeine (1x)	Ketamine (2x)	Methadone (1x)		GHB (6x)	
Ephedrine (1x)	Methadone (1x)	Methylphenidate (1x)		Ketamine (1x)	
Ethanol (5x)		Paracetamol (2x)		MDMA (1x)	
Fentanyl (1x)				Methadone (1x)	
GHB (9x)				Methylphenidate (1x)	
Ketamine (1x)				Paracetamol (2x)	
MDMA (3x)					
Methadone (2x)					
Methylphenidate (1x)					
Mirtazapine (1x)					
Paracetamol (4x)					
Sertraline (1x)					
Venlafaxine (1x)					

See Table 1 for an explanation of the codes D1 − 5, M1 − 5 and T1 − 5.

making this study possible.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.toxrep.2020.04.007.

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