CAT
Critically Appraised Topic

Evaluation of a next generation screening assay for ketamine in urine: added value and implementation in routine clinical practice

Author: Xanthe De Kimpe
Supervisor: Dorien Leenaerts, Juul Boes
Search/methodology verified by: Dorien Leenaerts
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CLINICAL BOTTOM LINE

Ketamine use has increased sharply in recent years, accompanied by growing clinical and public health concerns. Despite its legitimate medical applications, its widespread recreational use poses clinical challenges. Current laboratory diagnosis often relies on hyphenated mass spectrometry techniques, which, although highly sensitive and specific, are limited by prolonged turnaround times. This CAT evaluated the feasibility and clinical value of implementing a rapid next generation ketamine screening assay in the core clinical laboratory of AZ Turnhout.
The ARK Ketamine II assay demonstrated good analytical performance and excellent diagnostic concordance with liquid chromatography tandem mass spectrometry (LC-MS/MS). Implementation of the immunoassay can significantly reduce turnaround times, ensuring that results remain clinically relevant for diagnosis, acute decision making and patient counselling. Furthermore, by enabling faster diagnostic clarification, unnecessary laboratory testing, imaging and workload may be avoided, resulting in more efficient use of healthcare resources.
The assay provides a clear added value in acute intoxications and suspected drug-facilitated or spiking incidents. The assay might also help identify ketamine abuse as an underlying cause of unexplained lower urinary tract symptoms or cystitis, thereby enabling appropriate management and follow-up care. In addition, the high prevalence of ketamine abuse (approximately 5%) and its frequent underdiagnosis, further support implementing the assay in routine clinical practice. Moreover, the popularity of ketamine abuse, its health care challenges, and societal impact justify reconsideration of ketamine inclusion in routine urine drug screening panels.

CLINICAL/DIAGNOSTIC SCENARIO

KETAMINE (AB)USE

Ketamine, a derivative of phencyclidine (PCP), acts primarily as an antagonist of the glutamate N-methyl-D-aspartate (NMDA) receptor, which contributes to its dissociative anaesthetic and analgesic effects [1–3] (*Figure 1*). Ketamine has a relatively short half-life (± 2-3h) and produces hemodynamically stable anaesthesia with minimal respiratory depression, making it particularly useful for anaesthesia in short surgical procedures requiring rapid induction and recovery [1,3–6]. Over time, ketamine's unique pharmacological profile has led to broader clinical applications, including pain management, treatment-resistant depression, compulsive eating disorders, etc. [1,4]. However, in parallel with these legitimate applications, ketamine's dissociative effects and low cost have led to its increasing and widespread use as a recreational drug, particularly among young adults in nightlife settings and at festivals [1–3,5,7–9]. When used illicitly, ketamine is also known as K, Special K, Ket, Kit-Kat, Cat Valium, and Vitamin K [1,3,6]. A marked increase in ketamine abuse is reflected not only in self-reported surveys [2,3,10], but also in data on wastewater-based epidemiology (WBE), monitoring population-level consumption patterns [8,9,11]. One study reported a 7- to 11-fold increase in ketamine use in Belgium over approximately a decade, comparing results from 2012 and 2020-2023 [8]. Another recent Sciensano report showed a continued increase in ketamine use across Belgium, without clear weekend patterns suggesting diverse usage contexts [11]. Among users, polydrug intoxications are a common finding; other co-used substances often include alcohol, cannabis, cocaine, GHB and/or ecstasy [1–3,7,10].

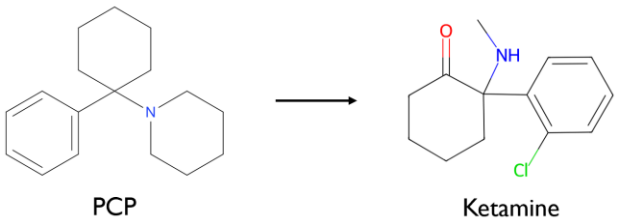

Figure 1: Structures of phencyclidine (PCP) and ketamine.

Clinical manifestations

Ketamine is typically consumed as a white powder for nasal insufflation (snorting), but it can also be dissolved in beverages, inserted rectally or less commonly smoked or injected (IV or IM) [1,7,10]. Following administration, ketamine is rapidly absorbed and widely distributed due to its high lipophilicity, consistent with the rapid penetration of the blood-brain barrier to exert its central nervous system effects [1,7].

These psychological effects include euphoria, vivid imagining, disinhibition, altered space and body perception, and hallucinations. Adverse effects are agitation, impaired consciousness, ataxia, anxiety, tachycardia, hypertension, blurred vision, and abdominal pain and vomiting ("K-cramps"). At higher doses, users may experience a so-called "K-hole", which is an intense detachment from reality, often described as a near-death-experience [1,2,6,7].

Chronic ketamine abuse can lead to several complications, such as psychological dependence and addiction, cognitive impairment, gastrointestinal toxicity, cholangiopathy, and most notably urological complications [1–5,7,12]. Ketamine-induced uropathy (KIU) manifests as lower urinary tract symptoms (LUTS), with increased frequency, high urgency, dysuria, nocturia, suprapubic pain, and haematuria associated with ketamine-induced cystitis (KIC) [1,3–5,12]. KIU is a common finding among long-term ketamine users: prevalence estimates are up to 30% among regular users [1,3,4]. Moreover, damage can further extend to the upper urinary tract, causing hydronephrosis, ulceration, ureteral stenosis, and renal failure and it may even be irreversible and require surgical intervention [1,4,5,12].

Metabolisation and excretion of ketamine

Ketamine undergoes extensive hepatic metabolism, primarily via cytochrome P450 isoenzymes, to form norketamine (primary active metabolite), and subsequently dehydronorketamine and hydroxynorketamine (*Figure 2*) [1,3]. These metabolites, which all retain pharmacological activity, are then conjugated and predominantly excreted via the kidneys [1,3]. Consequently, unchanged ketamine (2%), norketamine (2%) and dehydronorketamine (16%) are detectable in urine for variable periods post-use, depending on dose, frequency of use, metabolic capacity and renal function [1,3,13]. In general, ketamine can be detected in urine for five days, norketamine for up to six days, whereas dehydronorketamine remains present the longest with up to ten days [1]. Markedly prolonged detection times are reported in chronic heavy users, in which detection times for ketamine, norketamine and dehydronorketamine can extend to weeks or even months [13,14].

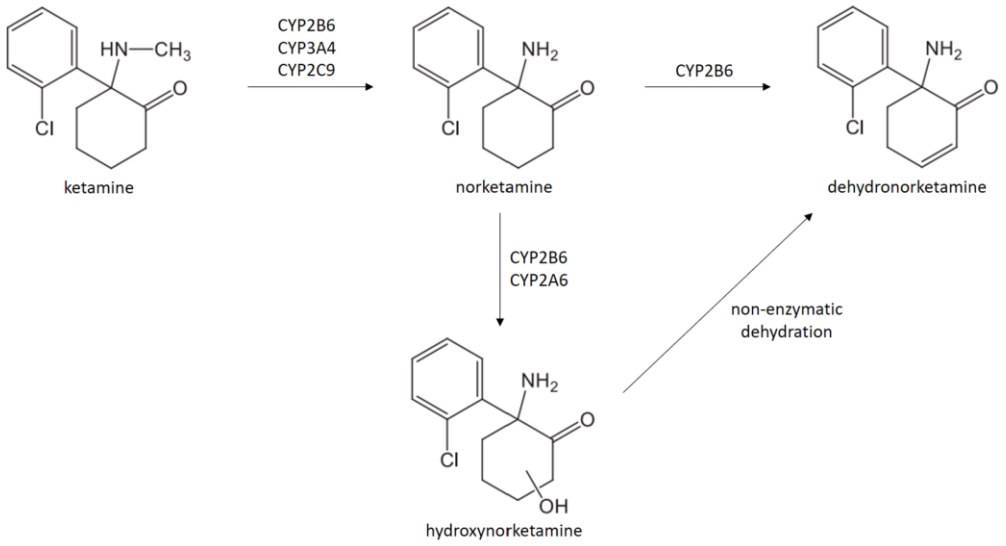

Figure 2: Metabolisation of ketamine into norketamine, dehydronorketamine and hydroxynorketamine. Figure adapted from Schep et al [1].

LABORATORY DIAGNOSIS OF KETAMINE INTOXICATIONS

The diagnosis of a ketamine intoxication may be supported by the patient's clinical presentation and history of drug abuse. Often, confirmation from the laboratory is required for a definitive diagnosis. Moreover, clinical symptoms can overlap with the use of other substances, which means that laboratory tests play a valuable role in confirming or ruling out ketamine use.

Current practice

The following drugs can be detected in a routine urine drug screening panel in the clinical laboratory HETUMO (AZ Herentals, AZ Turnhout, AZ Mol): amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine,

methadone, opiates, cannabinoids and tricyclic antidepressants (Triage TOX Drug Screen, Alere Inc., USA). Within HETUMO, it is also possible to detect GHB in urine using an automated immunoassay (Bühlmann GHB Enzymatic Assay on Abbott Alinity).

When the test 'ketamine in urine' is requested by clinicians, the urine sample is sent directly to an external laboratory for the quantification of ketamine and its metabolites (i.e. norketamine and dehydronorketamine) using liquid chromatography tandem mass spectrometry (LC-MS/MS). The response time for this test is approximately five days.

Diagnostic problem

Hyphenated mass spectrometry techniques (LC-MS/MS or GC-MS) are considered the gold standard due to their excellent performance characteristics [14,15]. However, these techniques also have limitations, such as long turnaround times (TAT), making them less suitable for the rapid diagnosis of ketamine toxicity [1,14]. As a result, clinicians often only receive results for ketamine when:

- the patient is no longer admitted to the hospital;
- the result no longer has an impact on acute decision-making;
- the result no longer has an impact on counselling patients about their substance use.

Therefore, the following question was asked from the emergency physicians in AZ Turnhout: "Is it possible to detect ketamine more quickly and possibly in-house?"

Moreover, due to this current practice and the lack of a rapid in-house test for ketamine, this could lead to potential underuse of the laboratory test and, consequently, underdiagnosis of ketamine abuse. This hypothesis was reviewed by requesting the latest request numbers of toxicological screenings in urine (*Table 1*), which show that ketamine lags far behind other drugs (drugs included in the Triage TOX Drug Screen, as well as the GHB immunoassay).

Table 1: Request number of toxicological screenings in urine (in HETUMO: AZ Herentals, AZ Turnhout, AZ Mol).

Drugs of abuse (in urine)	**2023**	**2024**	**2025**
Amphetamines	1382	1418	1475
Methamphetamines	1334	1368	1425
Barbiturates	1140	1187	1226
Benzodiazepines	1461	1530	1633
Cocaine	1391	1424	1536
Methadone (EDDP)	1121	1178	1220
Opiates	1285	1322	1392
Cannabinoids (THC)	1472	1467	1527
Tricyclic antidepressants	1028	1093	1144
GHB	843	1068	1287
Ketamine	**38**	**43**	**35**

QUESTION(S)

1) *Question 1: How can a screening assay for ketamine in urine be implemented in routine clinical practice?*
   - *What screening tests for ketamine in urine are available?*
   - *Reviewing the feasibility of implementing a next generation immunoassay for ketamine in a regional hospital.*
2) *Question 2: In which clinical settings can a screening test for ketamine be of added value?*

SEARCH TERMS

1) *MeSH Database (PubMed): MeSH term: "Ketamine/pharmacokinetics", "Ketamine/urine", "Ketamine/poisoning", "Ketamine/toxicity", "Liquid Chromatography-Mass Spectrometry", "Tandem Mass Spectrometry", "Immunoassay"*
2) *International organisations: National Committee for Clinical Laboratory Standards (NCCLS / CLSI), The LEAP checklist for laboratory evaluation and analytical performance characteristics reporting of clinical measurement procedures, United Nations Office on Drugs and Crime (UNODC) Guidance for the Validation of Analytical Methodology and Calibration of Equipment used for Testing of Illicit Drugs in Seized Materials and Biological Specimens*
3) *UpToDate Online: "Urine drug testing", "General approach to drug poisoning in adults", "Ketamine poisoning"*

RELEVANT EVIDENCE/REFERENCES

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APPRAISAL

QUESTION 1: How can a screening test for ketamine in urine be implemented in routine clinical practice?

1. What screening tests for ketamine in urine are available?

To aid the diagnosis of a ketamine intoxication, multiple analytical methods are available for the detection of ketamine (and its metabolites) in urine: GC-MS, LC-MS/MS, hair analysis, GC-FID, capillary electrophoresis, immunoassays, etc [16]. An overview of common used analytical methods for clinical applications is given in the table below (*Table 2*). GC-MS and LC-MS/MS are considered reference techniques or gold standards due to their high sensitivity and specificity, and their ability to distinguish parent drug from its metabolites and other structurally related compounds [14]. However, these techniques (1) can be labour-intensive, with sometimes time-consuming sample preparation steps, (2) require specialised, expensive instrumentation, (3) require technical expertise with training of laboratory staff, (4) require the need to work in batch (with long turnaround times) and may therefore not be suitable for high-throughput and around-the-clock screening in all laboratory settings [14,15]. Consequently, fast screening methods for ketamine were identified, with the following available options: point-of-care lateral flow assays, rapid oral fluid devices, and homogeneous immunoassays. Manual methods, like lateral flow tests, are often more expensive than automated methods, utilise high cut-off concentrations and suffer from possible observer-variability, transcription errors, and sometimes poor performance [14]. Homogeneous immunoassays offer full automation on open-access chemistry analysers, making them robust, easily available, and thus the most suitable option for implementation in a clinical laboratory [15]. These immunoassays are widely used for drug screening owing to simple operation, simple methodology with no sample preparation, and a quick turnaround time [15]. Therefore they can meet the limitations of current analytical methods. However, they often include the risk of false-positive (and false-negative) results, as well as potential cross-reactivity, lot-to-lot variation and dependence on a well-chosen cut-off concentration [1,14,15,17]. Therefore, a fast, yet reliable commercially available immunoassay was searched for in the literature and at manufacturer sites [18–21].

Table 2: Available analytical methods for the detection of ketamine.

	Hyphenated mass spectrometry	**Lateral flow assays and rapid oral fluid devices**	**Homogeneous immunoassays**
Matrix	urine, blood, hair, saliva	urine, saliva	urine
Use	- emergency toxicology - addiction medicine - forensic toxicology	- emergency toxicology - roadside testing (oral fluid)	emergency toxicology
Advantages	- high sensitivity - high specificity - no cross-reactivity	- rapid test result - no expertise needed - portable	- no need for specific equipment - full automation - no need for analysis in batch → rapid test result
Disadvantages	- expensive equipment - can be labour-intensive - expertise and training needed - analysis in batch → long turnaround times	- more expensive than automated methods - lack of sensitivity / specificity - observer-variability - possible transcription errors	- risk of false-positive (and false-negative) results - potential cross-reactivity - lot-to-lot variation - cut-off dependent performance

Recently, ARK Diagnostics, Inc. (Fremont, CA, USA) had introduced a second-generation ketamine immunoassay for use on random-access chemistry analysers [21]. Analysis time on the Abbott Alinity analyser is only seven minutes. Based on prior positive experience within our laboratory with the small molecules of this manufacturer (e.g. the ARK Lamotrigine and Voriconazole assay), we chose to proceed with this new ARK assay.

The ARK Ketamine II assay is a homogeneous, enzyme-based immunoassay (EMIT-principle) designed for the qualitative and semi-quantitative detection of ketamine in urine. Its test principle relies on a competitive binding

principle, in which enzyme-labelled ketamine (reagent R2) competes with ketamine present in the urine specimen for a limited number of antibody binding sites (reagent R1). The resulting change in enzyme activity leads to the conversion of NAD+ to NADH, which can be measured spectrophotometrically at 340 nm. This signal – i.e. increase in absorbance – is directly proportional to the concentration of ketamine present in the urine sample. Results are reported relative to a defined cut-off concentration (50 ng/mL or 100 ng/mL).

The ARK assay's screening capabilities, together with full automation, aligned well with our diagnostic needs and met the emergency physicians' requirement for a rapid in-house assay.

2. Reviewing the feasibility of implementing a next generation immunoassay for ketamine in a regional hospital.

To assess the ARK immunoassay's suitability for implementation in routine clinical practice, several aspects must be taken into account. First, the analytical performance of the assay on an Abbott Alinity platform was reviewed in the core laboratory of AZ Turnhout. Second, a method comparison study was performed with an established hyphenated tandem mass spectrometry method (LC-MS/MS) to assess its diagnostic performance. Finally, the financial impact, clinical value and organisational aspects of the test were reviewed.

Analytical performance

Precision and trueness

Accuracy studies were performed using quality control material, according to the CLSI EP15-A3 protocol [22]. To this end, three levels of controls (25, 75, 125 ng/mL) were tested five times consecutively over five days. The manufacturer data contains no quantitative claims for imprecision and bias, and could therefore not be verified. Following the United Nations Office on Drugs and Crime (UNODC) guidelines, (1) precision is acceptable when control material with concentrations close to the cut-off is correctly classified by the immunoassay as being either higher or lower than the cut-off level, and (2) imprecision and bias are acceptable when they are better than 20% [23]. All samples (n=75) were identified correctly (*Table 3A and Table 3B*) and imprecision and bias were found acceptable (*Table 4*), all within UNODC guidelines.

Table 3: Imprecision results: qualitative interpretation for the 50 ng/mL cut-off and 100 ng/mL cut-off.

A) 50 ng/mL cut-off

Quality control	Target concentration (ng/mL)	Relative % to cut-off	Qualitative results
Low	25	-50%	25 negative
Mid	75	50%	25 negative
High	125	150%	25 positive

B) 100 ng/mL cut-off

Quality control	Target concentration (ng/mL)	Relative % to cut-off	Qualitative results
Low	25	-75%	25 negative
Mid	75	-25%	25 negative
High	125	25%	25 positive

Table 4: Imprecision and bias of the ARK Ketamine II assay on an Abbott Alinity platform.

Quality control	Target concentration (ng/mL)	Mean (ng/mL)	Repeatability		Within-laboratory imprecision		Bias
			SD	CV	SD	CV	
Low	25	27.4	0.9	3.4%	1.8	6.4%	9.5%
Mid	75	77.3	1.2	1.5%	2.8	3.6%	3.1%
High	125	131.6	3.2	2.4%	6.3	4.8%	5.2%

Analytical specificity

Potential cross-reacting compounds were thoroughly tested by the manufacturer, with the assay showing a substantial (wanted) cross-reactivity with the metabolites norketamine and dehydronorketamine, but no cross-reactivity with other structurally related compounds. Analytical specificity is considered sufficient, as no significant cross-reactivity with other drugs or substances was observed (cfr. UNODC-guidelines) [23]. Notably, these findings were further supported in our method comparison study, which included numerous samples from multi-drug users, none of which yielded false-positive ketamine results.

Diagnostic performance

The ARK Ketamine II assay was compared with liquid chromatography tandem mass spectrometry (LC-MS/MS), carried out at the clinical laboratory AML Antwerp (Sonic Healthcare Benelux). A number of 50 positive and 57 negative samples, determined by the reference method, were used to compare both methods (cfr. CLSI EP12-A protocol) [24]. For this purpose, we used anonymised left-over urine samples collected at AZ Turnhout and AML. Urine samples were tested with both the ARK assay and LC-MS/MS, when (1) ketamine in urine has been requested, or (2) a standard urine drug screening (without ketamine) was requested. Approval was obtained from the Ethics Committee of AZ Turnhout.

Contingency tables (*Table 5A and Table 5B*) showed the best percent agreement (96%) and Cohen's kappa coefficient (0.92) for the 50 ng/mL cut-off. Agreement of the test method with a positive LC-MS/MS result (sensitivity) was 92% and agreement with a negative LC-MS/MS result (specificity) was 100%. Discrepant results were further investigated, with the ARK assay's numerical values – which are 'total concentrations' of ketamine, ±50% norketamine and ±15% dehydronorketamine – showing good agreement with LC-MS/MS (*Table 6*). In all cases, the assay correctly indicated the presence of ketamine in the urine sample. Discrepancies (false-negatives) can be explained solely by the difference in cut-off levels for positivity: the ARK assay's cut-off (50 ng/mL or 100 ng/mL) is higher compared to the LOQ of LC-MS/MS (25 ng/mL for ketamine and 28 ng/mL for norketamine).

Table 5: Method comparison results in contingency tables.

A) 50 ng/mL cut-off

ARK Ketamine II assay	LC-MS/MS		
	Negative	Positive	Total
Negative	57	4	61
Positive	0	46	46
Total	57	50	107

ARK Ketamine II assay	LC-MS/MS		
	Negative	Positive	Total
Negative	56	0	56
Below cut-off	1	4	5
Weak positive	0	0	0
Strong positive	0	46	46
Total	57	50	107

Percent agreement = 96.3%
Agreement of test method with LC-MS/MS positive = 92%
Agreement of test method with LC-MS/MS negative = 100%
Cohen's kappa coefficient = 0.92

B) 100 ng/mL cut-off

ARK Ketamine II assay	LC-MS/MS		
	Negative	Positive	Total
Negative	57	6	63
Positive	0	44	44
Total	57	50	107

ARK Ketamine II assay	LC-MS/MS		
	Negative	Positive	Total
Negative	57	4	61
Below cut-off	0	2	2
Weak positive	0	3	3
Strong positive	0	41	41
Total	57	50	107

Percent agreement = 94.4%
Agreement of test method with LC-MS/MS positive = 88%
Agreement of test method with LC-MS/MS negative = 100%
Cohen's kappa coefficient = 0.89

Remark: If ketamine or norketamine on LC-MS/MS > LOQ (25 ng/mL for ketamine; 28 ng/mL for norketamine), the result is classified as positive (LC-MS/MS). If ketamine and norketamine on LC-MS/MS ≤ LOQ, the result is classified as negative.
Remark: Semi-quantitative interpretation of the ARK Ketamine II assay, using the 50 ng/mL cut-off: negative < 25 ng/mL; below cut-off 25-49 ng/mL; weak positive 50-75 ng/mL; strong positive > 75 ng/mL.
Remark: Semi-quantitative interpretation of the ARK Ketamine II assay, using the 100 ng/mL cut-off: negative < 50 ng/mL; below cut-off 50-99 ng/mL; weak positive 100-150 ng/mL; strong positive > 150 ng/mL.

Table 6: Discrepant results in the method comparison study.

Discrepancies	LC-MS/MS		ARK Ketamine II assay (ng/mL)
	Ketamine (ng/mL)	Norketamine (ng/mL)	
#1	37	< 28	38.2
#2	44	< 28	46.0
#3	< 25	40	43.5
#4	65	< 28	30.0
#5	134	62	93.2
#6	26	68	92.8

Remark: #1-4 for 50 ng/mL cut-off, #1-6 for 100 ng/mL cut-off.

Costs

Costs are another important aspect in reviewing the feasibility of implementing the ARK assay in routine practice. In the table below (*Table 7*) the price of a ketamine test was estimated. As shown, this estimated cost is strongly dependent on the request numbers: the more the test is requested by clinicians, the more financially advantageous it becomes for the laboratory.

Table 7: Estimation of the total cost for a ketamine test.

Parameter	1100 tests/year	500 tests/year	250 tests/year
Fixed costs			
→ Reagent (small kit = 190 tests)	389.7 euro	389.7 euro	389.7 euro
→ Controls (2x 2 levels iQC)	210.4 euro	210.4 euro	210.4 euro
→ Calibrator set (5 cal)	262.9 euro	262.9 euro	262.85 euro
→ EQA Sciensano / SKML / …	already in use	already in use	already in use
➢ Total fixed costs	862.9 euro	862.9 euro	862.9 euro
Tests per day			
→ Patient tests per day	3.0 tests	1.4 tests	0.7 tests
→ Loss of useful tests			
Quality control loss (2x iQC/day)	2.0 tests	2.0 tests	2.0 tests
Calibration loss (every 10 days)	0.5 tests	0.5 tests	0.5 tests
➢ Total tests per day	5.5 tests	3.9 tests	3.2 tests
Usable fraction of kit for patients			
→ Usable days per kit	34.5 days	49.1 days	59.7 days
→ Patient tests per kit	103.8 tests	67.3 tests	40.6 tests
→ Usable fraction of kit	55%	35%	21%
Annual fixed costs			
→ Kits required per year	10.6 kits	7.4 kits	6.1 kits
→ Fixed costs per year	9146 euro	6385 euro	5263 euro
Total cost per patient test	**8.3 euro / test**	**12.8 euro / test**	**21.1 euro / test**

Reimbursement for the execution of the test can be obtained through the Belgian National Institute for Health and Disability Insurance (RIZIV/INAMI) via nomenclature codes 547794 (ambulatory) and 547805 (hospitalised patients). This nomenclature corresponds to: "Detection of xenobiotics using a qualitative immunological test. A positive result must be confirmed by a specific chromatographic method (maximum 5; cumulation rule 73; diagnostic rule 49)." The reimbursement is based on a B-value of 250, corresponding to €0.031803 per unit, resulting in a total reimbursement of €7.95 per test. However, only 25% of the B250-value is effectively allocated to the laboratory, corresponding to approximately €1.99 per test.

In addition, reimbursement is limited to a maximum of five tests per urine sample. If the proposed ketamine assay were to be incorporated into the routine urine drug screening panel (i.e. in combination with the Triage TOX Drug Screen with or without the GHB immunoassay), the laboratory would perform 10 or 11 tests in total, of which only five would be reimbursed (5x €1.99 per test = 9.94 euro). Consequently, the current nomenclature framework does not allow implementation and inclusion of this additional ketamine assay within a standard urine drug screening panel without financial loss. However, by implementing this ketamine assay, a lot of confirmatory testing and associated costs can be potentially avoided. Costs can also be saved elsewhere in the hospital, e.g. by avoiding unnecessary further investigations, like imaging or other laboratory tests.

Clinical and organisational impact

Impact on routine clinical practice

Given the prolonged turnaround times of the current workflow, implementation of the ARK Ketamine II assay may provide considerable added value by enabling rapid ketamine screening while maintaining excellent analytical and diagnostic performance. Screening results should be considered presumptive and require in many clinical scenarios confirmation by a more advanced analytical method for definitive identification and quantification [14,15]. Nevertheless, this immunoassay balances speed with excellent performance characteristics, making it a suitable screening tool to support reliable acute clinical decision-making. Implementation of the ARK assay would lead to optimisation of the current workflow for ketamine (*Figure 3*).

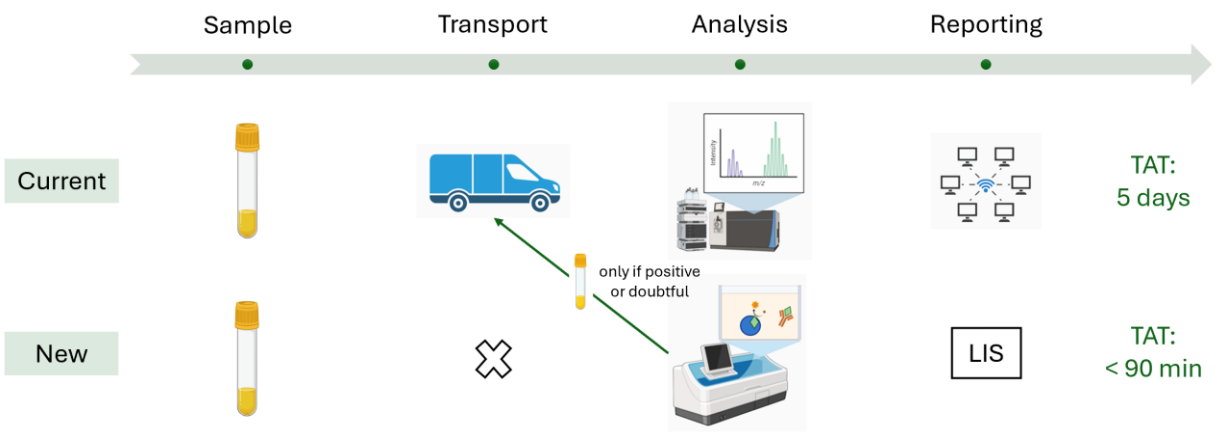

Figure 3: Workflow optimisation for ketamine.

The new proposed workflow contains: (1) screening by the ARK assay, and (2) if positive or doubtful confirmation by LC-MS/MS at an external laboratory. Transport to this external lab remains the same (once daily), and as a result, the response time for the confirmation test will also remain the same (approximately five days). However, as no transport is needed with the new workflow and the ARK assay provides results in only seven minutes, implementation of the assay can substantially reduce turnaround times for ketamine reporting, thereby enabling clinicians to receive screening results while the patient is still admitted. This ensures that test results remain clinically relevant, with the potential to directly confirm or rule out diagnosis, and the potential to have an impact on acute-decision making, patient management and counselling patients regarding substance use during admission.

In addition, our method comparison results revealed a clinically relevant underdiagnosis of ketamine abuse. Ketamine was detected in 6 of 155 urine samples (3.9%) for which a routine urine drug screening – without ketamine – had been requested. Overall prevalence of ketamine positivity in the dataset was 5.2%, which indicates that more than 5% of patients undergoing routine drug screening, test positive for ketamine. Most patients presented with mixed intoxications, where ketamine was used together with other substances like THC, benzodiazepines, and cocaine.
In some cases, this finding of ketamine was anticipated as patients had already disclosed ketamine abuse. However, in other cases, although substance use was suspected, no drugs could be identified using the traditional urine drug screening. Importantly, in such cases where drug use is suspected but the toxicology screen is entirely negative, this diagnostic pathway is often excluded. As a consequence, clinicians may pursue alternative investigations, including additional laboratory testing, imaging, follow-up consultations, which may ultimately prove unnecessary. Ketamine screening may therefore enable earlier diagnostic clarification and may facilitate more timely and targeted management. This may reduce unnecessary diagnostic work-up and potentially shorten hospital length of stay, thereby lowering healthcare costs and conserving valuable time of hospital staff.

Global impact
Ketamine abuse has risen sharply in recent years, with a clear global impact across multiple domains. Reports highlight this increased use, along with its increasing availability, diversification of trafficking routes and an additional burden on police, boarder control and law enforcement. This rise is also reflected in public safety concerns, with growing evidence of ketamine involvement in traffic incidents, as well as its use in spiking and drug-facilitated crimes [3,25,26]. Furthermore, in the healthcare setting, clinicians are encountering more cases of ketamine toxicity and long-term complications, including urological damage (such as KIC), placing additional strain on healthcare resources. Taken together, the increasing prevalence of recreational ketamine use is not merely a clinical issue but a broader public health and societal challenge, with implications for healthcare systems, public safety, and economic burden. Improving access to adequate diagnostic testing will be essential to improve clinician awareness and better characterise the true burden of ketamine-related harm.

QUESTION 2: In which clinical settings can a screening test for ketamine be of added value?

The ARK Ketamine II assay has proven to be a fast and reliable screening method for ketamine in urine. The question arises as to in which clinical scenarios a screening test for ketamine could be of added value.

Clinical utility of a screening assay for ketamine in urine
A ketamine screening assay is especially suitable to support fast diagnosis of acute ketamine toxicity (including mixed intoxications), and support further management in emergency or acute care settings. The assay can also help identify ketamine-related health risks (e.g. KIU), and guide timely treatment, appropriate follow-up care and counselling (e.g. referral to specialists, like urologists, and addiction care) [4,5,7,12]. As an example, several scenarios are listed below that should indicate the use of a ketamine screening test:

- In intoxicated patients in the emergency department ketamine should be tested to differentiate between drugs that come with similar symptoms (e.g. ketamine, GHB, and ethanol) and exclude alternative causes;
- In patients with LUTS without infection or other identifiable aetiology and in patients with unexplained cystitis or haematuria ketamine use should be investigated to identify the cause (diagnosis), guide ketamine abstinence and timely treatment and follow-up to prevent (further) ketamine-induced urinary damage;
- In patients who are being monitored by their general practitioner (GP) in relation to their drug use;
- In psychiatry departments the assay can be used for screening ketamine addicted patients where ketamine abstinence is an absolute requirement for (continued) admission to the department.

Due to its dissociative effects and its ability to be dissolved in beverages, usage of ketamine has also been reported in some criminal cases involving spiking and drug-facilitated sexual assault [1,27]. The literature reports ketamine not yet being widely used in these scenarios in comparison to other substances, like benzodiazepines and GHB [1,3,28,29]. However, due to the rising prevalence of ketamine as a recreational drug, a similar increase in its use as a date-rape drug may also develop. Laboratories do not routinely test for ketamine and therefore there is a potential for undetected cases. Consequently, the assay might be suitable as well for screening of drugs potentially involved in spiking, amongst other frequently used substances like alcohol, GHB, flunitrazepam, other benzodiazepines, or other sedative drugs [27–30].

In summary, the ketamine immunoassay can be requested by the emergency department or in acute care settings, as well as by the GP or departments like urology and psychiatry. The assay should be intended for screening purposes only and is not appropriate for non-clinical drug testing, workplace or forensic drug testing, nor for legal or judicial investigations, where confirmation by a more advanced analytical method is required [13,15]. Detection times in chronic heavy users can extend to weeks or even months post-use, implying that the assay cannot be used either in the follow-up of patients in abstinence treatment programs, where frequent measurements of urine samples are required [13].

Inclusion of ketamine in routine urine drug testing

When substance use is suspected, a routine urine drug screening can be performed. Despite increasing abuse, ketamine is currently not part of this routine urine drug testing and clinicians must request it separately. Although a fast screening assay can be implemented in the core laboratory, the exclusion of ketamine in routine urine drug screening may still lead to potential underdiagnosis of ketamine intoxications and its associated long-term complications. As a recent review on laboratory practices for urine drug testing suggests, laboratories should continually update and review provided drug panels as drugs in circulation change over time [15]. Currently, ketamine is even among the most commonly used drugs of abuse in Belgium, following cannabis, cocaine, and ecstasy [10,11]. Its high (and still rising) prevalence could therefore demand an update of these routine urine drug screening panels.

Several studies in the Netherlands advocate for the need to expand the routine urine drug screening to include ketamine. Marongiu et al [7] stated: "Routine inclusion of ketamine in toxicological screening could improve diagnostic precision and better address the health risks associated with its growing prevalence". Another study similarly reports the increasing ketamine abuse and the potential for undetected cases, which might indicate adding the drug to the standard screening panel [26]. In addition, Van der Schaar et al [31] determined how many drugs were detected by comprehensive toxicological screening, that could not be detected with the Triage TOX Drug Screen, and whether these drugs were clinically relevant to detect. Many additional drugs were detected, but only two were considered relevant, leading to adding GHB and ketamine to the screening panel of drugs in Amsterdam. In line with these studies, our results also showed high prevalence and important underdiagnosis of ketamine, which argues for the implementation and inclusion of ketamine in routine urine drug testing. Moreover, the absence of ketamine in these current screening panels may contribute to its increasing abuse, supporting this recommendation [26].

In summary, the rising recreational use of ketamine worldwide, its associated health-risks and societal challenges, warrant the need for laboratories to consider adding ketamine to the routine urine drug screening panels.

COMMENTS

Study approval was obtained from the Ethics Committee of AZ Turnhout.

Acknowledgement: We would like to thank clinical biologists Lisbeth Patteet and Delphine Cappelle (AML Antwerp) for their contribution to the evaluation of assay performance in comparison to LC-MS/MS.

TO DO/ACTIONS

1) Implementation of the ARK Ketamine II assay in HETUMO (AZ Herentals, AZ Turnhout, AZ Mol).
2) Follow-up of the assay after implementation
   - Comparing turnaround time before and after implementation;
   - Follow-up of concordance between screening and confirmatory results;
   - Assess on-board reagent stability, including optimal calibration frequency;
   - Monitor test request numbers;
   - Collect and evaluate feedback from clinicians.
3) Review current routine drug screening strategy and evaluate the cost-effectiveness of full automated practice.

ATTACHMENTS

None.