

LZI Ketamine Enzyme Immunoassay – EU Only

IVD For In Vitro Diagnostic Use Only



REF 0660 (100/37.5 mL R₁/R₂ Kit)
0661 (1000/375 mL R₁/R₂ Kit)



Lin-Zhi International, Inc.

Intended Use

The LZI Ketamine Enzyme Immunoassay is intended for the qualitative and semi-quantitative determination of norketamine in human urine at the cutoff value of 50 ng/mL when calibrated against norketamine. The assay is designed for prescription use with a number of automated clinical chemistry analyzers. The semi-quantitative mode is for purposes of enabling laboratories to determine an appropriate dilution of the specimen for verification by a confirmatory method such as GC/MS or LC/MS, or permitting laboratories to establish quality control procedures.

The assay provides only a preliminary analytical result. A more specific alternative chemical confirmatory method (e.g., gas or liquid chromatography and mass spectrometry) must be used to obtain a confirmed analytical result (1, 2). Clinical consideration and professional judgment should be exercised with any drug of abuse test result, particularly when the preliminary test result is a preliminary positive.

Summary and Explanation of Test

Ketamine (2-[2-chlorophenyl]-2-[methylamino]-cyclohexanone) is a pharmaceutical derived from phencyclidine (PCP) and cyclohexamine. Mechanistically, it acts as a non-competitive N-methyl-D-aspartate (NMDA)-receptor antagonist. The NMDA-receptor is involved in sensory input at the spinal, thalamic, limbic and cortical levels (3, 4). Ketamine has been shown to have a number of beneficial pharmacological properties. It is primarily considered an anaesthetic with a good safety profile. (5) Its major drawback, limiting its clinical use, is the occurrence of emergence reactions or dissociative effects (e.g., hallucinations, vivid dreams, floating sensations and delirium.) (3, 6). Recently, extensive research has been carried out on the antidepressant properties of ketamine (7-9).

The frequent use of ketamine can lead to addiction and dependence (10). Ketamine possesses narcotic effects similar to phencyclidine (PCP) and hallucinogenic effects similar to lysergic acid diethylamide (LSD) (11, 12). The recreational use of ketamine as a rave, party, and nightclub drug has increased over time, thus increasing public concerns about the potential hazards of this drug (13-15).

Ketamine undergoes rapid N-demethylation by liver microsomal cytochrome P450 enzymes CYP 3A4, CYP 2B6, and CYP 2C9 to form its primary metabolite, norketamine, which is pharmacologically active, and an inactive metabolite, 6-hydroxynorketamine (16, 17). A small percentage of unchanged ketamine (2.3%), norketamine (1.6%), and dehydronorketamine (16.2%) are eliminated in urine, whereas 80% is present as the glucuronide conjugates of hydroxylated metabolites of ketamine (18-21). While dehydronorketamine is present at higher levels and for a longer period of time than ketamine and norketamine in urine, dehydronorketamine has a lower stability, potentially limiting its utility in the detection of ketamine abuse (22).

Assay Principle

The LZI Ketamine Enzyme Immunoassay is a homogeneous enzyme immunoassay ready-to-use liquid reagent. The assay is based on competition between drug in the sample and drug labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for a fixed amount of antibody in the reagent (23). The drug-labeled G6PDH conjugate is traceable to a commercially available ketamine standard and referred to as ketamine-labeled G6PDH conjugate. Enzyme activity decreases upon binding to the antibody, and the norketamine concentration in the sample is measured in terms of enzyme activity. In the absence of ketamine and/or norketamine in the sample, ketamine-labeled G6PDH conjugate is bound to antibody, and the enzyme activity is inhibited. On the other hand, when ketamine and/or norketamine is present in the sample, antibody would bind to free ketamine and/or norketamine; the unbound ketamine-labeled G6PDH then exhibits its maximal enzyme activity. Active enzyme converts nicotinamide adenine dinucleotide (NAD) to NADH, resulting in an absorbance change that can be measured spectrophotometrically at 340 nm.

Reagents Provided

Antibody/Substrate Reagent (R₁): Contains a mouse monoclonal anti-ketamine antibody, glucose-6-phosphate (G6P), nicotinamide adenine dinucleotide (NAD), stabilizers, and sodium azide (0.09 %) as a preservative.

Enzyme-drug Conjugate Reagent (R₂): Contains glucose-6-phosphate dehydrogenase (G6PDH) labeled with ketamine in buffer with sodium azide (0.09 %) as a preservative.

Calibrators and Controls*

*Calibrators and Controls are sold separately or as a semi-quantitative set and contain negative human urine with sodium azide as a preservative.

Ketamine Cutoff Calibrators	REF
Negative Calibrator	0001
Low Calibrator: Contains 25 ng/mL norketamine	0662
Cutoff #1 Calibrator: Contains 50 ng/mL norketamine	0663
Cutoff #2 Calibrator: Contains 100 ng/mL norketamine	0664
Intermediate Calibrator: Contains 250 ng/mL norketamine	0665
High Calibrator: Contains 500 ng/mL norketamine	0666

Ketamine Cutoff Controls	REF
Level 1 Control: Contains 37.5 ng/mL norketamine	0667
Level 2 Control: Contains 62.5 ng/mL norketamine	0668

Precautions and Warning

- This test is for in vitro diagnostic use only. Harmful if swallowed.
- Reagent contains sodium azide as a preservative, which may form explosive compounds in metal drain lines. When disposing such reagents or wastes, always flush with a large volume of water to prevent azide build-up. See National Institute for Occupational Safety and Health Bulletin: Explosive Azide Hazards (24).
- Do not use the reagents beyond their expiration dates.

Reagent Preparation and Storage

The reagents are ready to use. No reagent preparation is required. All assay components should be refrigerated at 2-8°C when not in use.

Specimen Collection and Handling

Use fresh urine specimens for the test. If the sample cannot be analyzed immediately, it may be refrigerated at 2-8°C for seven days. For longer storage, keep sample frozen at -20°C and then thaw before use (22). Adulteration may cause erroneous results. If sample adulteration is suspected, obtain a new sample and both samples should be forwarded to a laboratory for testing.

Handle all urine specimens as if they are potentially infectious.

Instrument

Clinical chemistry analyzers capable of maintaining a constant temperature, pipetting sample, mixing reagents, measuring enzyme rates at 340 nm and timing the reaction accurately can be used to perform this homogeneous immunoassay.

Performance characteristics presented in this package insert have been validated on the Beckman Coulter AU480 automated clinical analyzer.

Assay Procedure

Refer to the specific parameters used for each analyzer before performing the assay. For qualitative analysis use the 50 ng/mL as the cutoff calibrator. For semi-quantitative analysis, use all six calibrators including the universal negative calibrator. Recalibration should be performed after reagent bottle change or a change in calibrators or reagent lot. Two levels of controls are available for monitoring of each cutoff level. Use the 37.5 ng/mL and 62.5 ng/mL controls for the 50 ng/mL cutoff level.

Calibration and Quality Control

Good laboratory practices recommend the use of at least two levels of control specimens (one positive and one negative control near the cutoff) to ensure proper assay performance. Controls should be run with each new calibration and after specific maintenance or troubleshooting procedures as detailed in the instrument system manual. Each laboratory should establish its own control frequency. If any trends or sudden change in control value are observed, review all operating parameters, or contact LZI technical support for further assistance. Laboratories should comply with all federal, state, and local laws, as well as all guidelines and regulations.

Results

Note: A positive test result does not necessarily mean a person took a specific drug and a negative test result does not necessarily mean a person did not take a specific drug. There are a number of factors that influence the reliability of drug tests.

Qualitative: The cutoff calibrator, which contains 50 ng/mL of norketamine, is used as a reference for distinguishing positive from negative samples. A sample with a change in absorbance (Δ MAU) equal to or greater than that obtained with the cutoff calibrator is considered positive. A sample with a change in absorbance (Δ MAU) lower than that obtained with the cutoff calibrator is considered negative.

Semi-Quantitative: The semi-quantitative mode is for purposes of (1) enabling laboratories to determine an appropriate dilution of the specimen for verification by a confirmatory method such as GC/MS, LC/MS or (2) permitting laboratories to establish quality control procedures. When an approximation of concentration is required, a calibration curve can be established with six calibrators. The concentration of norketamine in the sample may then be estimated from the calibration curve.

Limitations

1. A preliminary positive result from this assay indicates only the presence of norketamine. The test is not intended for quantifying this single analyte in samples.
2. A preliminary positive result does not necessarily indicate drug abuse.
3. A negative result does not necessarily mean a person did not take illegal drugs.
4. Care should be taken when reporting results, as numerous factors (e.g., fluid intake, endogenous or exogenous interferants) may influence the urine test result.
5. Preliminary positive results must be confirmed by other affirmative, analytical methods (e.g., chromatography), preferably GC/MS or LC/MS.
6. The test is designed for use with human urine only.
7. This test should not be used for therapeutic drug monitoring.

Typical Performance Characteristics

The results shown below were performed with a single Beckman Coulter AU480 automated chemistry analyzer.

Precision:

Semi-quantitative analysis: The following concentrations were determined with reference curves from six calibrators. Typical results (ng/mL) are as follows:

50 ng/mL Cutoff		Within Run (N = 22)		Run-to-Run (N = 88)	
Norketamine Concentration	% of Cutoff	# Samples	EIA Result	# Samples	EIA Result
0 ng/mL	0 %	22	22 Neg	88	88 Neg
12.5 ng/mL	25 %	22	22 Neg	88	88 Neg
25 ng/mL	50 %	22	22 Neg	88	88 Neg
37.5 ng/mL	75 %	22	22 Neg	88	88 Neg
50 ng/mL	100 %	22	3 Neg/ 19 Pos	88	15 Neg/ 73 Pos
62.5 ng/mL	125 %	22	22 Pos	88	88 Pos
75 ng/mL	150 %	22	22 Pos	88	88 Pos
87.5 ng/mL	175 %	22	22 Pos	88	88 Pos
100 ng/mL	200 %	22	22 Pos	88	88 Pos

Qualitative analysis: The following concentrations were evaluated. Typical qualitative results (measured by Δ OD, mAU) are as follows:

50 ng/mL Cutoff		Within Run (N = 22)		Run-to-Run (N = 88)	
Norketamine Concentration	% of Cutoff	# Samples	EIA Result	# Samples	EIA Result
0 ng/mL	0 %	22	22 Neg	88	88 Neg
12.5 ng/mL	25 %	22	22 Neg	88	88 Neg
25 ng/mL	50 %	22	22 Neg	88	88 Neg
37.5 ng/mL	75 %	22	22 Neg	88	88 Neg
50 ng/mL	100 %	22	1 Neg/ 21 Pos	88	8 Neg/ 80 Pos
62.5 ng/mL	125 %	22	22 Pos	88	88 Pos
75 ng/mL	150 %	22	22 Pos	88	88 Pos
87.5 ng/mL	175 %	22	22 Pos	88	88 Pos
100 ng/mL	200 %	22	22 Pos	88	88 Pos

Accuracy: One hundred eleven (111) urine specimens and pooled urine samples spiked with norketamine were tested with the LZI Ketamine Enzyme Immunoassay and confirmed with LC/MS. Specimens with a combined norketamine and ketamine concentration greater than or equal to 50 ng/mL by LC/MS are defined as positive, and specimens with a combined norketamine and ketamine concentration below 50 ng/mL by LC/MS are defined as negative in the table below. Near cutoff samples are defined as \pm 50 % of the cutoff value. The correlation results are summarized as follows:

Semi-Quantitative Accuracy Study:

50 ng/mL Cutoff	Neg	< 50 % of the cutoff	Near Cutoff Neg	Near Cutoff Pos	High Pos	% Agreement
Positive	0	2*	2**	6	62	100.0 %
Negative	20	4	15	0	0	90.7 %

The following table summarizes the results for the semi-quantitative discordant samples:

Sample #	NKET LC/MS (ng/mL)	KET LC/MS (ng/mL)	Total NKET + KET LC/MS (ng/mL)	Pos/ Neg Result	AU480 EIA Semi-Quantitative Result (ng/mL)	Pos/ Neg Result
24*	17	0	17.0	-	227.9	+
26*	19.6	0	19.6	-	228.2	+
31**	14.3	12.8	27.1	-	133.2	+
34**	0	32.3	32.3	-	58.3	+

Qualitative Accuracy Study:

50 ng/mL Cutoff	Neg	< 50 % of the cutoff	Near Cutoff Neg	Near Cutoff Pos	High Pos	% Agreement
Positive	0	2*	2**	6	62	100.0 %
Negative	20	4	15	0	0	90.7 %

The following table summarizes the results for the qualitative discordant samples:

Sample #	NKET LC/MS (ng/mL)	KET LC/MS (ng/mL)	Total NKET + KET LC/MS (ng/mL)	Pos/ Neg Result	AU480 EIA Qualitative Result (ng/mL)	Pos/ Neg Result
24*	17	0	17.0	-	308.2	+
26*	19.6	0	19.6	-	312.1	+
31**	14.3	12.8	27.1	-	190.8	+
34**	0	32.3	32.3	-	90.9	+

Calibration Cutoff Average = 69.3 mAU

* Discordant between negative and <50 % cutoff concentration (0.1 – 24.9 ng/mL)

** Discordant between 50 % of cutoff and cutoff concentration (25 – 49.9 ng/mL)

Analytical Recovery: To demonstrate recovery for purposes of sample dilution and quality control of the entire assay range, a drug free–urine pool spiked with norketamine at 500 ng/mL was serially diluted. Each sample was run in 10 replicates and the average was used to determine percent recovery compared to the expected target value.

Target Concentration (ng/mL)	Determined Concentration Range (ng/mL)	Determined Concentration Average (ng/mL)	Average % Recovery
500	494.5 – 523.6	506.9	101.4 %
450	470.1 – 492.2	480.8	106.8 %
400	436.7 – 469.2	449.7	112.4 %
350	380.8 – 399.0	390.8	111.7 %
300	318.1 – 345.4	330.3	110.1 %
250	240.5 – 256.8	247.4	99.0 %
200	206.9 – 212.7	210.1	105.0 %
150	157.0 – 162.0	159.9	106.6 %
100	96.4 – 102.0	98.3	98.3 %
50	47.3 – 54.3	48.9	97.8 %
7.5	6.4 – 9.1	8.2	108.9 %
0	0.4 – 3.9	2.2	N/A

Specificity: Various potentially interfering substances were tested for cross-reactivity with the assay. Test compounds were spiked into a drug-free urine pool to various concentrations and evaluated with the assay's calibration curve in both qualitative and semi-quantitative modes. The following table lists the concentration of each test compound that gave a response approximately equivalent to that of the cutoff calibrator (as positive) or the maximal concentration of the compound tested that gave a response below the response of the cutoff calibrator (as negative). Compounds tested at high concentration (100000 ng/mL) with results below the cutoff value were listed as Not Detected (ND). Compounds tested below the high concentration (100000 ng/mL) that gave a result below the cutoff value were given a "< %" value.

Ketamine and Metabolites:

Cross-reactant	Concentration (ng/mL)	% Cross-reactivity
Norketamine	50	100.00 %
Ketamine	25	200.00 %
Dehydronorketamine	2000	2.50 %
Hydronorketamine	100000	ND

Structurally Related Compounds:

Cross-reactant	Concentration (ng/mL)	% Cross-reactivity
Deschloroketamine	1600	3.13 %
Methoxetamine	100000	0.05 %
Phencyclidine	100000	0.50 %

Structurally Unrelated Compounds:

Cross-reactant	Spiked [] (ng/mL)	Spiked Norketamine Concentration		
		0 ng/mL	37.5 ng/mL	62.5 ng/mL
6-Acetylmorphine	100000	ND	Neg	Pos
Acetaminophen	100000	ND	Neg	Pos
Acetylsalicylic Acid	100000	ND	Neg	Pos
Amitriptyline	50000	<0.08%	Neg	Pos
Amlodipine Besylate	100000	ND	Neg	Pos
Amoxicillin	100000	ND	Neg	Pos
d-Amphetamine	100000	ND	Neg	Pos
Atorvastatin	100000	ND	Neg	Pos
Benzoyllecgonine	100000	ND	Neg	Pos
Buprenorphine	50000	<0.10%	Neg	Pos
Bupropion	100000	ND	Neg	Pos
Caffeine	100000	ND	Neg	Pos
Carbamazepine	10000	<0.50%	Neg	Pos
Carbamazepine-10,11-epoxide	10000	<0.50%	Neg	Pos
Cetirizine	100000	ND	Neg	Pos
Chlorpheniramine	100000	ND	Neg	Pos
Chlorpromazine	10000	<0.50%	Neg	Pos
Clomipramine	100000	ND	Neg	Pos
Codeine	100000	ND	Neg	Pos
Desipramine	100000	ND	Pos	Pos
(±)-10,11-Dihydro-10-Hydroxycarbamazepine	10000	<0.50%	Neg	Pos
Diphenhydramine	100000	ND	Neg	Pos
Duloxetine	100000	ND	Neg	Pos
Fentanyl (citrate)	10000	<0.50%	Neg	Pos
Fluoxetine	100000	ND	Neg	Pos
Fluphenazine	100000	ND	Neg	Pos
Gabapentin	100000	ND	Neg	Pos
Hydrocodone	100000	ND	Neg	Pos
Hydromorphone	100000	ND	Neg	Pos
Ibuprofen	100000	ND	Neg	Pos
Imipramine	60000	<0.08%	Pos	Pos
Lisinopril	100000	ND	Neg	Pos
Losartan	100000	ND	Neg	Pos
Loratadine	100000	ND	Neg	Pos
MDA (3,4-methylenedioxymphetamine)	100000	ND	Neg	Pos
MDEA (N-methyl diethanolamine)	100000	ND	Neg	Pos
MDMA (3,4-methylenedioxy-methamphetamine)	100000	ND	Neg	Pos
Meperidine	100000	ND	Pos	Pos
Metformin	100000	ND	Neg	Pos
Metoprolol	100000	ND	Neg	Pos
Methadone	100000	ND	Neg	Pos
d-Methamphetamine	100000	ND	Neg	Pos
Morphine	100000	ND	Neg	Pos
Nalmefene	100000	ND	Neg	Pos
Nicotine	100000	ND	Neg	Pos
Norfentanyl	10000	<0.50 %	Neg	Pos
Nortriptyline	100000	ND	Neg	Pos
Oneprazole	100000	ND	Neg	Pos
Oxazepam	100000	ND	Neg	Pos
Oxycodone	100000	ND	Neg	Pos
Oxymorphone	100000	ND	Neg	Pos
Phenobarbital	100000	ND	Neg	Pos
Promethazine	15000	<0.33%	Pos	Pos
(1S,2S)-(+)-Pseudoephedrine	100000	ND	Neg	Pos
Quetiapine	50000	<0.10 %	Neg	Pos
Ranitidine	100000	ND	Neg	Pos
Salbutamol (Albuterol)	100000	ND	Neg	Pos
Sertraline	100000	ND	Neg	Pos
THC-COOH (11-Nor-Δ-9-THC-9-carboxylic acid)	100000	ND	Neg	Pos
l-Thyroxine	100000	ND	Neg	Pos
Tramadol	100000	ND	Neg	Pos
Zolpidem	10000	<0.50 %	Neg	Pos

It is possible that other substances and/or factors not listed above may interfere with the test and cause false positive results.

The following compounds which showed interference at ±25 % of cutoff concentrations were then spiked into negative urine and at ±50 % of cutoff concentrations (25 ng/mL and 75 ng/mL) for the assay. Results are summarized in the following table:

Cross-reactant	Spiked [] (ng/mL)	Spiked Norketamine Concentration		
		0 ng/mL	25 ng/mL	75 ng/mL
Desipramine	100000	ND	Neg	Pos
Imipramine	60000	<0.08%	Neg	Pos
Meperidine	100000	ND	Neg	Pos
Quetiapine	50000	<0.10%	Neg	Pos
Promethazine	15000	<0.33%	Neg	Pos
Carbamazepine	10000	<0.50%	Neg	Pos

Endogenous and Preservatives Compound Interference Study:

Various potentially interfering endogenous and preservative substances were tested for interference with the assay. Test compounds were split into three portions each and either left un-spiked or spiked to a norketamine concentration of either 37.5 or 62.5 ng/mL (the negative and positive control concentrations, respectively). These samples were then evaluated in semi-quantitative and qualitative modes. Only the preservative Boric Acid (1 % w/v) was found to cause interference with the assay.

Endogenous or Preservative Substance	Spiked [] (mg/dL)	Spiked Norketamine Concentration		
		0 ng/mL	37.5 ng/mL	62.5 ng/mL
Acetone	1000	Neg	Neg	Pos
Ascorbic Acid	1500	Neg	Neg	Pos
Bilirubin	2	Neg	Neg	Pos
Boric Acid	1000	Neg	Neg	Neg
Calcium Chloride (CaCl2)	300	Neg	Neg	Pos
Citric Acid (pH 3)	800	Neg	Neg	Pos
Creatinine	500	Neg	Neg	Pos
Ethanol	1000	Neg	Neg	Pos
Galactose	10	Neg	Neg	Pos
γ-Globulin	500	Neg	Neg	Pos
Glucose	3000	Neg	Neg	Pos
Hemoglobin	300	Neg	Neg	Pos
β-hydroxybutyric Acid	100	Neg	Neg	Pos
Human Serum Albumin	500	Neg	Neg	Pos
Oxalic Acid	100	Neg	Neg	Pos
Potassium Chloride	3000	Neg	Neg	Pos
Riboflavin	7.5	Neg	Neg	Pos
Sodium Azide	1000	Neg	Neg	Pos
Sodium Chloride	3000	Neg	Neg	Pos
Sodium Fluoride	1000	Neg	Neg	Pos
Sodium Phosphate	300	Neg	Neg	Pos
Urea	6000	Neg	Neg	Pos
Uric Acid	10	Neg	Neg	Pos

The following compound which showed interference at ±25 % of cutoff concentrations were then spiked into negative urine and at ±50 % of cutoff concentrations (25 ng/mL and 75 ng/mL) for the assay. Interference was still observed with Boric Acid. Results are summarized in the following table:

Endogenous or Preservative Substance	Spiked [] (mg/dL)	Spiked Norketamine Concentration		
		0 ng/mL	25 ng/mL	75 ng/mL
Boric Acid	1000	Neg	Neg	Neg

pH Interference Study:

pH 3 to pH 11 was tested for interference with the assay. Each pH level was split into three portions each and either left un-spiked or spiked to a norketamine concentration of either 37.5 ng/mL or 62.5 ng/mL (the negative and positive control concentrations, respectively). These samples were then evaluated in semi-quantitative and qualitative modes. No pH interference was observed.

pH	Spiked Norketamine Concentration		
	0 ng/mL	37.5 ng/mL	62.5 ng/mL
pH 3	Neg	Neg	Pos
pH 4	Neg	Neg	Pos
pH 5	Neg	Neg	Pos
pH 6	Neg	Neg	Pos
pH 7	Neg	Neg	Pos
pH 8	Neg	Neg	Pos
pH 9	Neg	Neg	Pos
pH 10	Neg	Neg	Pos
pH 11	Neg	Neg	Pos

Specific Gravity: Samples ranging in specific gravity from 1.000 to 1.025 were split into three portions each and either left un-spiked or spiked to a norketamine concentration of either 37.5 or 62.5 ng/mL (the negative and positive control concentrations, respectively). These samples were then evaluated in semi-quantitative and qualitative modes. No interference was observed.

Specific Gravity	Spiked Norketamine Concentration		
	0 ng/mL	37.5 ng/mL	62.5 ng/mL
1.0030	Neg	Neg	Pos
1.0050	Neg	Neg	Pos
1.0080	Neg	Neg	Pos
1.0100	Neg	Neg	Pos
1.0150	Neg	Neg	Pos
1.0180	Neg	Neg	Pos
1.0200	Neg	Neg	Pos
1.0220	Neg	Neg	Pos
1.0250	Neg	Neg	Pos

Symbols Used

	Authorized Representative		Manufacturer
	Biological Risks		R1, Antibody/ Substrate Reagent
	CE Mark		R2, Enzyme-Drug Conjugate Reagent
	Consult Instructions for Use		Reference Number
	Contents		Safety Data Sheet
	Country of Origin		Temperature Limits
	In Vitro Diagnostic medical device		Use-by Date
	Lot Number		

Bibliography

- Urine Testing for Drug of Abuse, National Institute on Drug Abuse (NIDA) Research Monograph 73, 1986.
- Mandatory Guidelines for Federal Workplace Drug Testing Program, National Institute on Drug Abuse, Federal Register, **23**(82):7920-7970 (2017).
- Bergman, S.A., Ketamine: review of its pharmacology and its use in pediatric anesthesia. *Anesth Prog* **46**:10-20 (1999).
- Brau, M.E., Sander, F., Vogel, W., and Hempelmann, G., Blocking mechanisms of ketamine and its enantiomers in enzymatically demyelinated peripheral nerve as revealed by single-channel experiments. *Anesthesiology*. **86**(2):394-404 (1997).
- Reich, D.L. and Silvay, G., Ketamine: an update on the first twenty-five years of clinical experience. *Can J Anaesth* **36**:186-97 (1989).
- White, J.M. and Ryan, C.F., Pharmacological properties of ketamine. *Drug Alc Review* **15**:145-155 (1996).
- World Health Organization, 37th Expert Committee on Drug Dependence, ECDD Agenda Item 6.1 (2015).
- Berman, R.M., Cappiello, A., Anand, A., Oren, D.A., Heninger, G.R., Charney, D.S., et al. Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry*. **47**(4):351-4 (2000).
- Zarate Jr, C.A., Singh, J.B., Carlson, P.J., et al. A randomized trial of an n-methyl-d-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry*. **63**(8):856-64 (2006).
- Jansen, K.L. and Darracot-Cankovic, R. The nonmedical use of ketamine, part two: A review of problem use and dependence. *J Psychoactive Drugs*. **33**:151-158 (2001).
- Moore, K.A., Kilbane, E.M., and Jones, R. Tissue distribution of ketamine in a mixed drug fatality. *J. Forensic Sci.* **42**(6): 1183-1185 (2007).
- Moreton, J.E., Meisch, R.A., Stark, K., et al. Ketamine self-administration by the rhesus monkey. *J. Pharmacol. Exp. Ther.* **203**: 303-309 (1977).
- Lua, A.C., Lin, H.R., Tseng, Y.T., Hu, A.R., and Yeh, P.C. Profiles of urine samples from participants at rave party in Taiwan: prevalence of ketamine and MDMA abuse. *Forensic Sci. Int.* **36**: 47-51 (2003).
- Curran, H.V. and Morgan, C. Cognitive, dissociative and psychogenic effects of ketamine in recreational users on the night of drug use and 3 days later. *Addiction* **95**(4):575-590 (2000).
- Degenhardt, L., Copeland, J., and Dillon, P. Recent trends in the use of "club drugs": an Australian review. *Subst Use Misuse*. **40**(9-10): 1241-1256 (2005).
- Hijazi, Y. and Bolieu, R.. Contribution of CYP3A4, CYP2B6 and CYP2C9 isoforms to N-methylation of ketamine in human liver microsomes. *Drug Metab. Dispos.* **30**: 853-858 (2002).
- Leung, L.Y. and Baillie, T.A. Comparative pharmacology in the rat of ketamine and its two principal metabolites, norketamine and (Z)-6-hydroxynorketamine. *J. Med. Chem.* **29**:2396-2399 (1986)
- Wieber, J., Gugler, R., Hengstmann, J.H., and Dengler, H.J. Pharmacokinetics of ketamine in man. *Anaesthetist* **24**:260-263 (1975).
- Harun, N., Anderson, R.A., and Miller, E.I. Validation of an Enzyme-Linked Immunosorbent Assay Screening Method and a Liquid Chromatography-Tandem Mass Spectrometry Confirmation Method for the Identification and Quantification of Ketamine and Norketamine in Urine Samples from Malaysia. *J Anal Toxicol.* **33**:310-321 (2009).

Bibliography, continued

- Karch, S.B. and Drummer, O.H. Karch's pathology of drug abuse. 5th ed. Boca Raton (FL): CRC Press, Taylor & Francis Group (2016).
- Adamowicz, P. and Kala, M. Urinary excretion rates of ketamine and norketamine following therapeutic ketamine administration: method and detection window considerations. *J Anal Toxicol.***29**:376-382 (2005).
- Zhen, L. Effects of filtration sterilization on the stability of ketamine, selected benzodiazepines and metabolites in female urine. Boston University Theses & Dissertations (2017). OpenBU: <https://open.bu.edu/handle/2144/20791>
- Rubenstein, K.E., Schneider, R.S., and Ullman, E.F., Homogeneous Enzyme Immunoassay: A New Immunochemical Technique, *Biochem Biophys Res Commun*, **47**:46 (1972).
- Sodium Azide National Institute for Occupational Safety (NIOSH). Pocket Guide to Chemical Hazards. Third Printing, September 2007. Available online at: <https://www.cdc.gov/niosh/npg/default.html>.

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