Is medicinal ketamine associated with urinary dysfunction issues? Assessment of both the European Medicines Agency (EMA) and the UK Yellow Card Scheme pharmacovigilance database-related reports

Nicolo' Schifano[1,2], Stefania Chiappini[3], Fabio Castiglione[4,5,6], Andrea Salonia[1,2], Fabrizio Schifano[3]

[1]Università Vita-Salute San Raffaele, Milan, Italy

[2]Division of Experimental Oncology/Unit of Urology; URI; IRCCS Ospedale San Raffaele, Milan, Italy

[3]Psychopharmacology; Drug Misuse; and Novel Psychoactive Substances Research Unit; School of Life and Medical Sciences, University of Hertfordshire, Hatfield, Herts, UK

[4]Institute of Andrology, Department of Urology, University College London Hospitals NHS Trust

[5]NIHR Biomedical Research Centre University College London Hospital

[6]Division of Surgery and Interventional Science, UCL

RUNNING TITLE: Medicinal ketamine related urological issues

CORRESPONDING AUTHOR:

Stefania Chiappini, MD

ORCID: https://orcid.org/0000-0002-6810-1540

Psychopharmacology, Drug Misuse, and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, Herts, United Kingdom

stefaniachiappini9@gmail.com

ABSTRACT

Objective - A range of associated urinary dysfunction (KIU) issues have been typically described in ketamine misusers. Conversely, more knowledge is needed in terms of medicinal ketamine-related urological disturbances. since ketamine prescribing is being increasingly considered for a range of medical and psychopathological conditions.

Methods - To assess medicinal ketamine-induced uropathy issues, we aimed at analyzing both the 2005-2017 European Medicines Agency (EMA) and the 2006-2018 UK Yellow Card Scheme (YCS) pharmacovigilance databases.

Results - A total number (e.g., all categories) of 11,632 EMA ketamine-related adverse drug reaction (ADR) reports were here identified. Out of these, some 9,971 ADRs (e.g., 85.7% of the total) were judged as 'suspect' and were here analyzed. Some 1,758 ADRs (17.7% of 9,971, corresponding to 194 individual patients) referred to urological issues, relating to either kidney/ureter (922 ADRs) or bladder/urethra (837 ADRs). Ketamine was the sole drug administered in 156/194 (80.4%) cases/patients. Although most cases occurred in the 1 month-1 year time frame following the start of ketamine prescribing, in 30 cases the ADR occurred within 48 hours. Most ADR-related cases resolved, although both sequelae (18 cases) and fatalities (79/1,758; 4.5%) were recorded. Overall, YCS data were consistent with EMA findings, with some 50/217 (23%) ADRs referring to renal/urinary disorders.

Conclusions - Current data may only represent a gross underestimate of the KIU real prevalence issues. It is here suggested that chronic treatment involving higher doses/repeated exposure to ketamine be restricted to the context of controlled trials or clinical audits.

KEY WORDS: drug abuse; ketamine; ketamine uropathy; lower urinary tract dysfunction; LUTS

INTRODUCTION

Ketamine prescribing is on the increase; this molecule is considered for a range of clinical conditions, including: anaesthesia induction/maintenance, chronic pain syndromes with a neuropathic component[1] and treatment-resistant depression[2]. In parallel, a number of recreational ketamine-related adverse effects have been reported[1]. However, of particular concern are the ketamine-induced uropathy (KIU) reports, issues thought to affect over one-half of misusers[3]. The side effects of street ketamine may differ from those identified with prescribed medical ketamine. In clinical settings, ketamine is typically well tolerated. The most commonly reported side effects associated with medical use of ketamine are psychiatric disorders, hypertension, nausea and vomiting[4]. Conversely, specific uropathy issues have been anecdotally reported as adverse effects of ketamine in pain therapy[5], and to the best of our knowledge there are no systematic studies assessing the occurrence of uropathy issues associated with medical ketamine. Ketamine is a dissociative anaesthetic medication typically administered at the dosage of 35-900 mg, depending on the ways of intake (e.g., oral, sublingual, transmucosal, intranasal, intramuscular, intravenous and subcutaneous routes); a dose of 10 mg/kg usually produces 12–25 minutes of surgical anaesthesia[6]. Ketamine works mainly by blocking the N-methyl-D-aspartate (NMDA) receptor and inhibiting serotonin and dopamine reuptake[7]. Ketamine analgesic effects may be explained as well by its action on remaining receptors, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA); kainate; and gamma-aminobutyric acid (GABA-A) receptors[8]. Patients with severe storage phase lower urinary tract symptoms (LUTS), a positive history of ketamine abuse and the absence of any other aetiology should be considered to have KIU. The most typical LUTS in KIU-patients include increased frequency, urgency, nocturia, urge urinary incontinence (UUI), pelvic discomfort/pain during voiding and haematuria[9]. A feature consistent with KIU

diagnosis is indeed reduced functional bladder capacity, with values ranging between 10 and 150mL[9]. Cystoscopic features are similar to those that are associated with interstitial cystitis/bladder pain syndrome (IC/BPS); thus including ulcers, submucosal ecchymosis and bleeding glomerulations[9]. The rate of upper urinary tract involvement, namely hydronephrosis and ureteral wall thickening, varies from 6% to 63%[9]. Hydronephrosis develops secondary to long-term decreased compliance of the bladder or ureteral stenosis. Both vesicoureteral reflux due to trigonal fibrosis and abnormal ureter peristalsis are further possible mechanisms of damage to the upper urinary tract[9]. Chronic kidney failure may develop as a final consequence.

KIU management issues

Most patients with KIU are managed conservatively. The treatment aims at relieving pain and LUTS, together with preventing upper tract deteriorating kidney function. Whilst ketamine abstinence is the first step in KIU management[9] to achieve symptoms recovery, urological issues may persist for up to 1 year after ketamine abstinence[10]. Management of KIU patients is carried out following a three-line treatment approach[9]. The first step includes a trial of anti-inflammatory and anti-cholinergic drugs, with opioids in the case of unsatisfactory response[9]. The second line of treatment includes instillation of intravesical agents such as hyaluronic acid, and intravesical injections of Botulinum toxin A[9]. Bladder hydrodistension was also trialled as a second line treatment approach. Finally, partial cystectomy with enterocystoplasty; total cystectomy along with heterotopic derivation; or orthotopic neobladder formation are surgical options reserved for those with refractory symptoms, contracted bladder, or advanced upper tract involvement[11]. Indeed, partial/total bladder resection may help in reducing the source of inflammation, whilst augmentation enterocystoplasty aims at improving bladder capacity[9]. Finally, preclinical studies have

suggested a future, putative, treatment role for both intravesical liposomal onabotulinumtoxin-A instillation and administration of mesenchymal stem cells into the bladder submucosal layer[9].

KIU pathogenesis issues

The pathogenesis of ketamine-related cystitis may involve many different pathways. Ketamine itself in urine might trigger bladder inflammation, through a direct toxicity mechanism[12]. Additionally, ketamine is supposed to alter the permeability of the urothelium, causing an increased susceptibility to irritants[13]. Microscopically, the urothelium is denuded and infiltrated by inflammatory cells, such as mast cells and eosinophils[14]. Interestingly enough, these pathological features resemble those of eosinophilic cystitis, with a predominance of transmural eosinophilic infiltration in the tunica propria and focal muscle necrosis[15]. Eosinophilic cystitis is a common finding in atopic patients; with the eosinophilic-predominant inflammatory response secondary to the formation of allergen-IgE antibodies' complexes[15]. Accordingly, Jhang et al. showed that KIU patients had higher levels of serum IgE than controls[16]. Microvascular injury and subsequent ischaemia flare up the inflammatory response, causing epithelial-to-mesenchymal transition, which contributes to bladder fibrogenesis[17]. NMDA receptors were found into the vesical blood vessels, thus possibly explaining the detrimental effect of ketamine to the microcirculation[18]. Further toxicity mechanisms have been suggested, including: alteration in chronic wound healing response and collagen accumulation, ultimately facilitating fibrosis progression[19]; and abnormal cell apoptosis[20]. High potassium solutions cause contraction in rat urinary bladder by causing membrane depolarisation, and subsequent influx of calcium through voltage-operated calcium channels (VOCCs)[21]. Ketamine can inhibit potassium-induced contractions by inhibiting VOCC current[22]. How or if the inhibition of bladder contractility relates to long-

term detrusor overactivity (DO) is uncertain[22]. However, Meng et al. reported that mice receiving daily injections of ketamine showed, after 4 weeks, lower baseline detrusor pressure and higher compliance vs controls[23], consistent with the observation that all the essential NMDA receptors (NMDARs) are present in the lower urogenital tract, and NMDAR antagonists such as ketamine induce relaxation of tissue strips. This would allow ketamine and its metabolites to accumulate in the urine whilst increasing the contact time between the drug and the urothelium[24], thus possibly enhancing direct toxicity effects. To assess ketamine-related uropathy issues, we aimed here at analyzing both the European Medicines Agency (EMA) EudraVigilance (EV) and the UK Yellow Card Scheme databases, collecting reports of suspected adverse drug reactions (ADRs) for all medicinal products respectively authorized either in the European Economic Area/EEA (EMA) or in the UK.

MATERIALS AND METHODS

The European Medicines Agency (EMA) is responsible for the safety-monitoring of medicines in the European Union: it operates through EudraVigilance (EV) that analyses information on suspected ADRs to medicines which have been authorized in the European Economic Area (EEA). The EV database, focusing on case-reports submitted during the period August 2005-May 2017 relating to ketamine uropathy ADRs, was here assessed. The ADRs here considered were spontaneous and unsolicited communications reported by both Regulatory Authorities of the Member States where the reaction occurred, and/or by the Marketing Authorization Holders for those ADRs occurring outside the EEA. Data analyzed were available from the EMA upon a drug-specific request to access the EV related dataset (identified as 'EMA request reference ASK-29346'). The data requested were provided within three months through a hyperlink that expired within two months. Data were provided as large Excel files divided into information sections reporting in a standardised format. EV data included Level 2A information, such as: general information on the ADR (sender type; sender organization; type of report; date when the report was first received; primary source country; reporter qualification; seriousness of the case; and medical confirmation of the case); information on the patient (age; sex; and height); type of reaction/event; drug information, including concomitant licit and illicit drugs (the information provided enclosed indicated: type of drug; dosages; administration route; and duration), medical history and comments; outcome of the reaction and any death. ADRs were recorded according to the Medical Dictionary for Regulatory Activities (MedDRA), which is a clinically validated international medical terminology dictionary (and thesaurus) used by regulatory authorities[25]. Within the standardized MedDRA Query (SMQ) for Adverse Drug Reactions, the following adverse reactions, listed as Preferred Term (PT) in the EV database, were here identified: lower

abdominal pain, acute kidney injury, anuria, bladder disorder, bladder dysfunction, bladder pain, chronic kidney disease, contracted bladder, cystitis, haemorrhagic cystitis, non-infective cystitis, dysuria, haematuria, hydronephrosis, hydroureter, hypertonic bladder, lower urinary tract symptoms, nicturia, oliguria, frequent urination, polyuria, proteinuria, renal tubular necrosis, renal infarction, renal impairment, renal failure, suprapubic pain, urethritis, urge incontinence, urinary bladder haemorrhage, urinary tract disorder, urinary tract injury, and vesico-ureteral reflux. ADRs' numbers differed from those referring to case reports, since different reporters/senders could have independently flagged the same ADR to EMA. Each individual patient in the database has a code/EV local number for identification, so that the number of unique/individual patients was unequivocally identified. Patients were analyzed considering a range of parameters, including: socio-demographic characteristic (age and sex), source/reporter country (i.e., from EEA or non-EEA) and reporter qualification (i.e., pharmacist, physician), outcomes (fatal, recovered, resolved), and concomitant drug(s). When possible, medication duration, dosages and polydrug intake issues were here assessed as well. To better assess ketamine-associated issues, we took into account as well the January 2006-February 2018 Drug Analysis Profiles pharmacovigilance data available from the UK-Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card Scheme. MHRA-related data were available without restrictions through interactive Drug Analysis Profiles (iDAPs), selecting the product of interest from all the listed products. MHRA collects reports of ADRs from within the UK, and these data are then consistently forwarded to EMA, hence formally contributing to the EV database implementation.

Ethics' issues

Because of EMA and MHRA protection of privacy and integrity of individuals, certain data elements (e.g., names/identifiers of individuals involved; country specific information,

nationally authorized products, etc.) were here not disclosed. The University of Hertfordshire-UK provided Ethics' approval for this study on 11th June 2018 (Code: aLMS/PGR/UH/03234(1).

RESULTS

A total number of 11,632 case reports, submitted up to May 9th, 2017, to the EMA EV database and where ketamine single ingredient was reported as a suspect or interacting active substance, were here identified. Of 11,632 reports, some 9,971 ADRs (e.g., 85.7% of the total, referring to 210 single cases) were judged as 'suspect' and were here properly analysed. Conversely, those concerning the MedDRA reaction System Organ Class 'Renal and urinary disorders' corresponded to 1,758 ADRs (e.g., 17.7% of 9,971, corresponding to 194 individual patients). Number of ADRs first peaked in 2010 (512 ADRs), and then again in both 2014 (324 ADRs) and 2017 (150 ADRs until April 2017; Figure 1). Most ADRs involved adult females (female/male ratio: 2.06) and were reported either by regulatory authorities (50.3%) or pharmaceutical companies (49.1%) which were typically located in the European Economic Area (53.7%; see Table 1). Out of the total number of 1,758 'Renal and urinary disorders' suspect ADRs (Table 2), those most frequently reported were relating to kidney/ureter issues (922 ADRs) and included: acute kidney injury/renal failure (487; 27.7%); oliguria/anuria (277 ADRs; 15.8%); and hydronephrosis (82; 4.7%). Conversely, most frequent lower urinary tract issues (836 cases) included: frequent urination/dysuria/polyuria (296 ADRs; 16.8%); haematuria/haemorrhagic cystitis (14.2%); suprapubic/bladder pain (145 cases; 8.3%); hypertonic/contracted bladder and cystitis (139 cases; 7.9%; see Table 2). Most typically reported routes of administration were intravenous (93 ADRs) and respiratory/nasal (51 ADRs). Ketamine was the sole drug administered in 156/194 (80.4%) cases/patients; most frequently associated molecules included gabapentin (9 cases) and opiate/opioid analgesics (7 cases). Ketamine dosage was here specified for 116/194 (60%) cases/patients; e.g. it had been administered in the 1-7,500 mg dosage range, including <25 mg in 27 cases and in excess of 1 gram in 70 cases (see Table 2). The time

interval between the beginning of drug administration and the occurrence of the index ADR was made available for 100/194 (52%) cases/patients; this was in the range of 1-31 days for 32 cases/patients (out of these, in 30 cases the ADR occurred within 48 hours); 1 month-1 year in 58 cases; and in excess of 1 year in 10 cases. Following the ADR occurrence, ketamine was reduced/withdrawn in 278 ADRs. The duration of the ADR-related signs and symptoms was infrequently reported; they lasted for 2-7 days in 25/1758 ADR cases and for 14-45 days in 12/1758 ADR cases. In the vast majority of cases, the ADR was either in resolution or already resolved at time of reporting; in some cases however this was either associated with sequelae (18 cases) or no recovery was observed (15 cases). Some 107/1,758 (6.1%) ADRs, referring to issues such as: acute kidney injury; oliguria; renal failure; and haematuria were reported as life-threatening sequelae. Some 79/1,758 (4.5%) cases, relating to issues such as: renal failure; and acute/chronic kidney disease, resulted in death. Finally, 1,205/1,758 (68.5%) ADRs were associated with prolonged hospitalization levels. Yellow Card Scheme (YCS) data were overall consistent with EMA findings; out of a total number of 217 ADR reports, 50/217 (23%) were identified as renal and urinary disorders, with a peak of reporting identified in 2017 (9 reports). Most frequent ADRs, typically affecting males in the 20-39 years-old age frame, referred to bladder disorders (19 cases), whilst urinary tract signs and symptoms/genitourinary tract disorders were identified in 12 cases; ureteral disorders in 10 cases and renal issues (excluding nephropathies) in 8 cases (see Table 3). All cases were reported as serious, but no fatalities were identified.

DISCUSSION

To the best of our knowledge, this is the very first study aimed at systematically identifying a range of urological adverse effects reported over a meaningful timeframe and relating to the medicinal use of ketamine. Present, large-scale data were extracted from a pharmacovigilance database, such as the EMA's EV that, together with the World Health Organization's Drug Monitoring Program, is considered a worldwide reference standard[26]. Moreover, to better understand the relevance of these KIU issues, further UK-based pharmacovigilance data were here assessed as well. Current findings suggest that 17.7% and 23% of those ADRs respectively reported to EMA and UK-YCS databases were relating to urological issues. In considering the increasing interest towards the clinical ketamine use, this may be a reason of concern. Somehow consistent with current data, ketamine misusers' surveys have suggested that urological issues in women are more frequently reported than in men due to higher symptoms' score[27], tentatively suggesting higher levels of susceptibility to ketamine toxicity in females with respect to males. The typical abusing ketamine-related urological literature concerns focus on the lower urinary tract, e.g., on the 'K bladder' [7]. However, present findings (e.g., 52% of ADRs related here to kidney/ureter) are consistent with other suggestions[28]. Even in the UK-based YCS database involvement of the upper urinary tract was reported in 18/50 (36%) cases. Hence, in agreement with Huang et al.[28] one could argue that the upper urinary tract ketamine-related issues may be fairly common.

Although the duration of ketamine medicinal use prior to the occurrence of KIU was reported for some 52% of patients only, consistent with previous literature focusing on ketamine misusers most ADRs where here observed after a chronic (i.e., 1 month-1 year) administration[29]. Conversely, some 30 patients made experience of the urological disturbance within the first 2 days of treatment, consistent with previous anecdotal observations[30].

Although this finding will need to be replicated, this may tentatively suggest that even an acute ketamine administration may be associated with levels of urological risks.

An issue of interest was here the variation overtime in the number of urological ADRs, with the most relevant peak having been identified in 2010, followed by the years 2014 and 2017. Since detailed data of worldwide ketamine prescribing are not available, it may be problematic to provide here a straightforward explanation for this finding. It is of interest, however, that ketamine is a molecule being typically considered as an alternative to opioids for some forms of pain control[31] and hence is often prescribed in chronic pain syndromes[1]. Indeed, consistent with current findings, increasing levels of strong painkillers' prescribing have been reported at the end of this century's first decade[32,33]. Furthermore, recent research focussing on prescribing fentanyl-related ADRs has showed reporting peaks overtime (e.g. 2008; 2014; 2017)[34] very similar to those observed here.

Limitations

Even though pharmacovigilance studies on ADRs can be considered a tool to detect hypotheses of safety issues, the analyses here performed on the ADRs do not allow to conclude for the existence of a causal link/association between a pharmaceutical product and the reaction(s) reported. In fact, even though analyzing data from pharmacovigilance databases should be considered as a valuable starting point for assessing specific drug-related concerns, these reporting systems might have limitations, given their reliance on self-reporting and likelihood of missing data. Furthermore, the worldwide ketamine prescribing rates were not available here and hence the true toxicity risk of the KIU phenomenon may not be calculated. Unfortunately, the EV database did not provide some details of clinical interest, including possible concurrence of urological or medical conditions that may simulate some clinical findings erroneously attributed to ketamine use. Also, as reports are

spontaneously submitted, several ADRs relating to the same patient were here identified. This may have happened because of a range of different sources reporting the same ADR but also because a number of different ADRs may have been reported for the same patient. For this reason, report duplications may occur indeed (e.g., where a healthcare professional reported the same suspected ADR to both the national regulator and the Marketing Authorization Holder, and both eventually reported the index ADR to the EV). Finally, due to the spontaneous nature of reporting, not all data fields were provided for all reports, thus making data interpretation more problematic. In particular, the ketamine duration and dosage levels were here mentioned for only 52% and 60% of patients.

Conclusions

In parallel with recently increasing levels of both medicinal ketamine prescribing and ketamine abuse, data regarding the ketamine impact on the urinary tract is relatively new, so it is likely that a more accurate characterization of long-term effects will become elucidated with time. However, present figures have suggested that between 18 and 23% of ketamine adverse effects, as respectively reported by international and UK-based pharmacovigilance systems, related to KIU issues. Indeed, the occurrence of painful ketamine-associated urinary dysfunction, as here highlighted, can facilitate persistent ketamine intake because of its analgesic properties[7;29]. Current findings are felt here to be specifically relevant for urologists, nephrologists, and general practitioners, who will need to be fully aware of the range of ketamine-related uropathy issues on both the lower and upper urinary tract. Indeed, standard toxicity tests cannot typically identify the vast range of prescribed/non prescribed drugs with a misusing potential, including ketamine and its derivatives[7]. Notwithstanding these toxicological identification issues, ketamine use should be routinely clinically assessed and should be considered within the list of differential diagnoses in any patient presenting

with LUTS in association with haematuria, suspicious upper tract radiographic findings, or indeed any sign of renal impairment.

Physicians should be invited to a responsible prescribing of ketamine, whilst carefully evaluating the possibility for some clients (e.g. those prone to ingest high-/megadosage medications[7]) to be more vulnerable to developing KIU issues. Further focus should be on drafting specific guidelines to better help clinicians in treating and managing the acute and long-term urological consequences of ketamine intake.

It is suggested here that there is a need to improve pharmacovigilance tools, in order to detect and prevent drug-related adverse effects. These findings may have implications for the acute, recurrent, and chronic clinical use of ketamine. Until safety issues are resolved, it is suggested that treatment involving higher doses and repeated exposure to ketamine should be restricted to the context of randomized controlled trials or clinical audits.

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Table 1. Overview of general data relating to the 'Renal and urinary disorders' Adverse Drug Reaction (ADRs) recorded by the European Medicines Agency (EMA)

Total suspect ADRs (2006-Apr 2017)	**1,758**	%
Occurrence country		
EEA	**906**	**51.5%**
Non EEA	812	41.8%
Not specified	40	2.3%
Reporter qualification		
Physician	**908**	**51.7 %**
Other health professional	735	41.8%
Consumer or other non health professional	23	1.3%
Not specified	92	5.2%
Reporter country		
EEA	**944**	**53.7%**
Non-EEA	720	41.0%
Not Specified	94	5.3%
Sender		
Pharmaceutical company	864	49.1%
Regulatory authority	**884**	**50.3%**
Not specified	10	0.6%
Age		
1-9 years	3	0.2%
9-18 years	85	4.8%
>18-64 years	**886**	**50.4%**
>64 years	10	0.6 %
Unknown	774	44.0 %
Gender		
Female	**1157**	**65.8%**
Male	561	31.9%
Not specified	40	2.3%

Keys: ADR: Adverse Drug Reaction; EEA: European Economic Area.

Table 2. Characteristics of the most frequently reported 'Renal and urinary disorders' suspect Adverse Drug Reaction (ADRs) recorded by the European Medicines Agency (EMA)

ADRs according to the PT		Total 1,758	%
Upper urinary tract		Total 922	52.45
	Acute kidney injury/renal impairment/failure	**487**	**27.7%**
	Oliguria/anuria	**277**	**15.8%**
	Hydronephrosis	82	4.7%
	Chronic kidney disease	40	2.3%
	Renal tubular necrosis	21	1.2%
	Proteinuria	9	0.5%
	Renal infarction	1	0.05%
	Hydroureter	4	0.2%
	Urethritis	1	0.05%
	Vesical-ureteral reflux	2	0.1%
Lower urinary tract		Total 836	47.55%
	Irritative LUTS: frequent urination/dysuria/polyuria/nicturia/urge incontinence	**296**	**16.8%**
	Haematuria; haemorrhagic cystitis	**249**	**14.2%**
	Suprapubic/bladder pain	145	8.3%
	Hypertonic/contracted bladder; cystitis	139	7.9%
	Sterile pyuria	4	0.2%
	Urethritis	1	0.05%
Routes of administration (where indicated):			
	Unknown	621	
	IV	**93**	
	Respiratory/nasal	**51**	
	Oral	10	
	Intrathecal	5	
	Subcutaneous	1	
Outcome of the ADR (when indicated)			
	Unknown	809	
	Recovering/recovered	**916**	
	Not recovered/not resolved	15	
	Recovered/resolved with sequelae	18	
Action taken after ADR occurrence (when indicated)			
	Not specified	464	
	Drug reduced/withdrawn	**278**	
	Dose not changed	35	
Time interval between the start of ketamine administration and occurrence of the index ADR (indicated			

for 100/194 patients)			
	1-31 days	32	
	1 month-1 year	**58**	
	>1 year	10	
total		**100**	
Dosages (indicated for 116/194 patients)			
	1-25 mg	27	
	26 mg- 1 gr	19	
	>1 gr	**70**	
total		**116**	
Possible concomitant drugs (where indicated according to a total of 1,758 ADRs corresponding to 194 cases/patients)			
	Ketamine only	**156**	
	Other, non-psychotropic, drugs	16	
	Gabapentin	9	
	Opiates/Opioids (oxycodone, codeine, hydrocodone, fentanyl, morphine, methadone)	7	
	Benzodiazepines	3	
	Antidepressants (escitalopram, duloxetine)	2	
	Cocaine	1	
	Cannabis	1	
	Alcohol	1	

ADR: Adverse Drug Reaction; LUTS: Lower Urinary tract symptoms; IV: intravenous; PT: Preferred Term.

Table 3. Overview of the UK-based Yellow Card Scheme ADRs

ADRs' frequencies (total: 50)		
	Bladder and bladder neck disorders (excluded calculi)	19
	Urinary tract signs and symptoms; genitourinary tract disorders	12
	Ureteric disorders	10
	Renal disorders (excluding pre-existing nephropathies)	8
	Urolithiases	1

ADRs: Adverse Drug Reactions.