Urological Science 26 (2015) 167–173

Contents lists available at ScienceDirect

Urological Science

journal homepage: www.urol-sci.com

Review article

Burden of ketamine cystitis in Chinese society☆

Wai-Kit Ma [a,*], Peggy Sau-Kwan Chu [b]

[a] Urology Division, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong Special Administrative Region
[b] Urology Division, Department of Surgery, Tuen Mun Hospital, Hong Kong Special Administrative Region

ARTICLE INFO

Article history:
Received 23 May 2015
Received in revised form
7 July 2015
Accepted 18 July 2015
Available online 21 August 2015

Keywords:
cystitis
ketamine abuse
uropathy

ABSTRACT

Ketamine cystitis, also referred to as ketamine-induced uropathy, is a new clinical syndrome affecting primarily young to middle-aged ketamine abusers and has become a global phenomenon since its first reported series in 2007. A spectrum of urological destructions ranging from mild cystitis to severely contracted bladder, ureteric stricture, upper tract damage, and irreversible renal failure has been reported. This review considers the scope and burden of ketamine cystitis in the Chinese population in Asia, stating the current status of management pathway, and reviews our current understanding on the pathophysiology of ketamine-induced uropathy.

1. Prevalence of ketamine cystitis among a Chinese population

Since the first report of street ketamine-associated cystitis involving 10 young Chinese patients by the authors' team from Hong Kong in 2007,[1] more cases of the new clinical syndrome of ketamine cystitis were subsequently reported from other Chinese regions: Taiwan and China.[2,3] The first case series in mainland China was from Nanfong Hospital, Guangzhou, China in 2008.[2] As for Taiwan, the first reported case series was from Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan in 2009.[3] Extremely low market price and easy accessibility to the drug have made ketamine the drug of choice among young people.[4] Furthermore, cracking down of ketamine trafficking is particularly difficult, as it is legally produced and shipped for use in both human and veterinary medicines, which can be easily diverted for illicit purposes.[5] This legal availability may help explain why ketamine came to prominence as a recreational drug in the past number of years.

The exact prevalence of ketamine cystitis, however, is difficult to measure numerically, because many drug abusers are poly-substance abusers and most of them will not seek medical advice until they have severe symptoms. In addition, unless physicians have a high index of suspicion to identify ketamine abuse as a possible cause of lower urinary tract symptoms in young patients, the diagnosis will otherwise be missed. A rough estimation of the prevalence of ketamine cystitis among different Chinese populations, however, may be possible from the statistics published from respective government narcotic bureaus.

In Hong Kong, ketamine was first seized in 1999 and has been on top of the list of commonly abused psychotropic substances since 2001.[6] According to the Hong Kong Central Registry of Drug Abuse Sixty-third Report, which gathered information from various reporting agencies including local law enforcement departments, drug treatment and rehabilitation centers, counseling centers for psychotropic substance abusers, centers for drug counseling of nongovernment organizations, youth outreach teams of nongovernment organizations, and substance abuse clinics under the Hospital Authority, ketamine remained the most popular psychotropic substance being abused from 2004 to 2013, with a peak of > 5000 abusers in 2009 (Fig. 1). When stratified by age, the trend was also similar for young abusers under the age 21 years.[7] The actual number of young ketamine abusers in recent years, however, was not decreasing as it seemed to be, as more abusers are “hidden ketamine abusers”—51% of abusers younger than 21 years have admitted to have abused ketamine at home or at friend's home in 2013, which is a substantial increase from 13% in 2006.[8]

Regarding the proportion of ketamine abusers presenting with lower urinary tract symptoms, a small scale survey conducted by a psychotropic substance rehabilitation center in Hong Kong

* Corresponding author. Department of Surgery, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong Special Administrative Region.
E-mail address: kitkitma@yahoo.com (W.-K. Ma).

☆ There are 3 CME questions based on this article.

http://dx.doi.org/10.1016/j.urols.2015.07.007

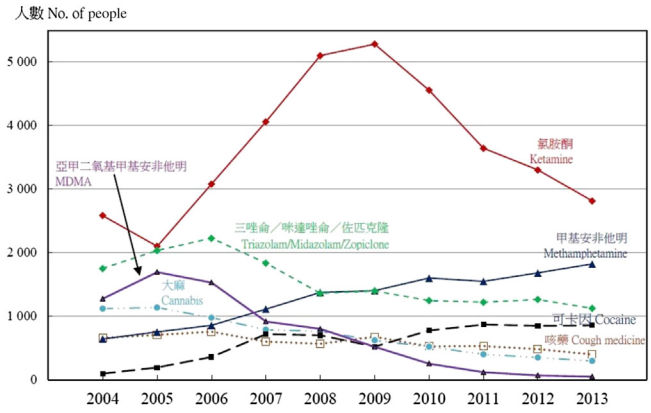

Fig. 1. Reported drug abusers of major types of psychotropic substances in Hong Kong.[7] MDMA = methylenedioxylmethamphetamine.

reported that ~30% of ketamine abusers had lower urinary tract symptoms.[9]

As for Taiwan, according to the National Bureau of Controlled Drugs, the 2014 International Narcotics Central Report, and local Taiwan Bureau, ketamine abuse has been a growing problem in Taiwan since 2008 and remains to be a popular party drug among teenagers because of its low potential for addiction and absence of criminal penalties for possession of a small amount (< 20 g). China is the source of ~76% of the ketamine seized or sold in Taiwan.[10–12]

According to China's National Narcotics Control Commission 2014 Annual Report on Drug Control in China, ketamine is the second most abused drug in China with seizures of 9.7 metric tons of ketamine in 2013, compared to 4.7 metric tons in 2012.[13]

All in all, if 30% of the ketamine abusers in China, Taiwan, and Hong Kong suffer from clinical manifestations of ketamine cystitis, not only does this greatly impair the health conditions of the affected individuals, but also imposes a huge burden on the public health system with increasing numbers of hospital admissions and dialysis requirements for possible upper tract damages.

2. Management of ketamine uropathy in Hong Kong Chinese population

2.1. Investigation pathway

A comprehensive clinical pathway has been established in some urology centers pioneering in the study of this syndrome in the region[9] (Fig. 2). This includes detailed documentation of symptomatology and quantification by questionnaires, blood tests (routine renal and liver function tests), urine tests (culture and toxicology), urinary system ultrasonography, uroflowmetry, flexible cystoscopy, video urodynamic study, and computed tomography for severe cases with possible upper tract involvement.

While pain symptoms can be represented by the widely used visual analog scale (VAS) of 1–10, more comprehensive quantification of the symptoms are documented using standardized frequency/voiding charts and the Pelvic Pain and Urgency/Frequency (PUF) symptom scale. Developed by Parsons et al,[14] the PUF symptom scale questionnaire has been validated and used in screening and diagnosing patients with interstitial cystitis. It comprises seven questions concerning day- and night-time frequency, pelvic/urological pain and its severity, and urgency and its degree of severity. A symptom score and a bother score are included, totaling a maximum of 35 points. In view of the clinical and histopathological resemblance between interstitial cystitis and ketamine cystitis,[15] centers in Hong Kong adopted the PUF symptom scale as an assessment tool for symptom quantification in these patients. A Chinese version of the PUF symptom scale (Fig. 3) has been validated, and correlations with the symptomatology and investigation results were evaluated.[16] In the series comprising 50 patients with a mean age of 24 years and a mean duration of ketamine abuse of 4.7 ± 2.8 years, the prevalence of urinary symptoms was as follows: urinary urgency (46 patients, 92%), frequency (42 patients, 84%), nocturia (44 patients, 88%), dysuria (43 patients, 86%), and hematuria (34 patients, 68%).[16] The same study suggested that higher mean PUF total scores were noted in patients with positive cystoscopic, urodynamic, and ultrasonographic investigation results, and a higher PUF score was associated with smaller bladder capacity. The cutoff value of 17 is suggestive of more serious urological sequelae: endoscopically confirmed cystitis (83% vs. 47%), detrusor instability (48% vs. 0%), vesicoureteric reflux (14% vs. 0%), poor bladder compliance (48% vs. 0%), and hydronephrosis (37% vs. 0%).

In a more recent series from the region involving 318 ketamine abusers with a mean duration of 81 months of ketamine use, the mean voided volume was 111 mL and the mean bladder capacity was 152 mL, with a mean bladder emptying efficiency of 73%.[17] In more severe patients, the typical voided volume can be < 50 mL, and these patients are napkin dependent because of severe urge incontinence. In our earlier series, in which video cystometrogram had been performed in 47 patients, the mean cystometric bladder capacity was 154.5 mL (range 14–600 mL), with 51% ($n = 24$) of the patients having a bladder capacity of ≤ 100 mL.[9] Most of the patients showed decreased bladder compliance and/or detrusor overactivity of different magnitudes at a very low bladder infusion volume (as low as 14 mL). Of the patients, 13% showed vesicoureteral reflux as a secondary event to the severely contracted bladder with high detrusor pressure. This finding correlated well with the symptoms of these patients, in that both functional and cystometric bladder capacities were markedly decreased, causing them to have very frequent small voids.

Cystoscopy examination aims to reveal if there are any inflammatory and cystitis changes and the cause of hematuria, if any. However, because of the small, painful bladder, this procedure is not well tolerated by patients with severe symptoms if performed under local anesthesia. To date, the largest series on cystoscopic findings on ketamine abusers from the region involved 42 patients, in which 30 patients had cystoscopy under local anesthesia, while the others had cystoscopy and transurethral resection biopsy under regional or general anesthesia.[9] All patients showed various degrees of epithelial inflammation of the bladder and neovascularization. Severe cases showed petechial hemorrhages, as classically described in patients with interstitial cystitis. Histologically, there is mucosal ulceration, striking urothelial reactive atypia, lamina propria inflammation with predominant lymphocyte infiltration, and a variable number of eosinophils. Ultrastructural examination by electron microscopy showed querciphylloid muscle cells (vacuoles at the periphery of muscle cells; Fig. 4). This feature has also been found in interstitial cystitis. In another UK series involving 17 patients in whom cystoscopy and bladder biopsies were performed, urothelial atypia with features mimicking carcinoma *in situ* was noted in a significant number of patients.[18] Marked urothelial atypia was seen in the biopsy specimens of 12 patients with nuclear enlargement and loss of polarity. Immunohistochemistry for CK20, p53, and Ki67 was performed in 10 cases, in which high expression of p53 was present in nine cases and that of Ki67 was present in six cases. However, none of the biopsy specimens showed expression of CK20 in the atypical urothelium, which would be against carcinoma *in situ*. In addition, squamous metaplasia, nephrogenic metaplasia, and calcification have been

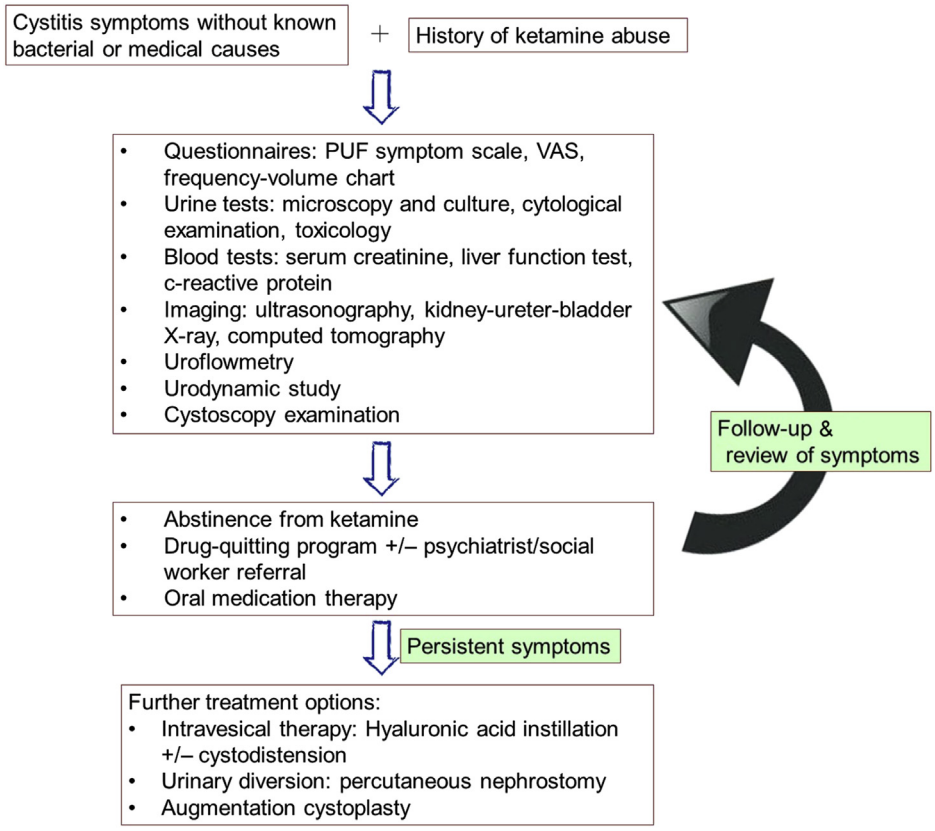

Fig. 2. Clinical pathway for management of ketamine cystitis patients. PUF = Pelvic pain and Urgency/Frequency; VAS = visual analog scale.

described.[19] Histopathological findings have great implications for its underlying pathophysiology, as the mechanism of chronic interstitial inflammation by ketamine metabolites is the main area of on-going research based on current histology findings.

2.2. Management options

2.2.1. Abstinence from ketamine use

The single most important step in the management of ketamine uropathy or cystitis is obvious: cessation of ketamine abuse. While a dose–symptom relationship between ketamine use and symptomatology occurrence has been established,[20] abstinence from ketamine abuse is essential in protecting the urological system from further damage. Medication therapy, intravesical instillations, urinary diversion, and surgical treatment options have all been suggested,[1–3,9,21–24] but management of the condition remains a great challenge to urologists. The difficulty in management is attributed not only to the relatively unclear pathophysiology, but also to complex psychosocial factors. Although cessation of the use of soft drugs such as ketamine and phencyclidine would not lead to physical withdrawal symptoms, many ketamine abusers are poly-drug abusers, and it is difficult to eliminate their psychological dependence on the drugs by their own efforts.[25–27] A multidisciplinary approach, preferably by a team of related professionals, would increase the success rate in following up and dealing with the complex psychosocial as well as physical problems in these abusers. In 2009, an outreach team of volunteers comprising psychiatrists, urologists, physiotherapists, nurses, and social workers performed a screening evaluation of ketamine abusers outside the setting of a hospital at night time and were able to get in touch with 66 young adults socializing in community centers in Hong Kong.[28] Evaluation of these abusers revealed that for individuals after 1 year of abstinence, the PUF scores were significantly lower and voided volumes were higher than those for active abusers. Good rapport building with abusers is the key to success in treating the condition.

2.2.2. Medication therapy

Different medications have been advocated in treating ketamine cystitis, including oral antibiotics, nonsteroidal anti-inflammatory drugs, anticholinergics, steroids, amitryptiline, hydroxyzine, and pentosan polysulfate.[1–3,9,21–23] However, most of the oral medications fail to achieve good symptomatic relief in patients, and even if they do, the effect is transient; none of these medications can reverse the detrimental effects of ketamine use on the bladder once fibrosis has taken place. Pentosan polysulfate has been shown to have more sustaining symptomatic relief in some patients who failed steroid and antibiotic therapies.[21] It is postulated that this drug can help replenish the denuded urothelial layer of the bladder mucosa, as in patients with interstitial cystitis/bladder pain syndrome. However, it is unclear whether the relief was resulted from ketamine abstinence, use of pentosan polysulfate, or a combination of both. No comparative studies were available to further prove the efficacy of individual medication therapy.

2.2.3. Intravesical instillation/hydrodistension therapy

With the small, contracted bladder as a common finding in ketamine cystitis patients, intravesical instillation of medications and/or hydrodistension therapy has been suggested for directly improving the damaged glycosaminoglycan layer in the bladder mucosa and increasing the bladder capacity, as in interstitial cystitis.[29,30] Rescue instillations with diluted lignocaine followed by hydrodistension with normal saline, or intravesical instillation of sodium hyaluronic acid, have been studied and showed

姓名：_____ 日期：_____

盆腔痛楚及尿急／尿頻
病人症狀尺度

		0	1	2	3	4	症狀分數	困擾分數
1	你在日間上廁所多少次？	3–6	7–10	11–14	15–19	20+		
2	a. 你在夜間上廁所多少次？	0	1	2	3	4+		
	b. 若你在夜間起床排尿，這情況困擾你嗎？	從不	間中	時常	經常			
3	a. 你現在/以往曾否在性行為時或之後感到痛楚/不適？	從不	間中	時常	經常			
	b. 你曾否因為痛楚或尿急不適而避免性行為？	從不	間中	時常	經常			
4	你有沒有膀胱或盆腔（陰道、陰唇、下腹、會陰、睪丸、或陰囊位置）的痛楚？	從不	間中	時常	經常			
5	a. 若你有此痛楚，程度是：		輕微	中度	嚴重			
	b. 這些痛楚困擾你嗎？	從不	間中	時常	經常			
6	你排尿後還有尿急的感覺嗎？	從不	間中	時常	經常			
7	a. 你有尿急嗎？若有，程度是：		輕微	中度	嚴重			
	b. 尿急的情況困擾你嗎？	從不	間中	時常	經常			
8	你有恒常的性行為嗎？	有/沒有						

症狀分數 (1, 2a, 3a, 4, 5a, 6, 7a) = _____

困擾分數 (2b, 3b, 5b, 7b) = _____

總分（症狀分數＋困擾分數）= _____

Fig. 3. Validated Chinese version of the Pelvic Pain and Urgency/Frequency symptom scale.

symptomatic relief in some patients.[3] A small-scale pilot study on sodium hyaluronic acid instillation, conducted in Hong Kong among 12 ketamine abusers with severe symptomatology (mean PUF score = 28.7 out of 35, mean VAS score = 6.7 out of 10) and very small bladder capacity (mean cystometric bladder capacity = 64.8 mL), with weekly intravesical instillation of sodium hyaluronic acid for at least 6 weeks, has shown significant improvement in all the studied parameters (mean PUF 21.2, mean VAS 4.9, and mean cystometric bladder capacity 125.8 mL) and that the effects have been sustained on the mean follow-up of > 2 years.[31] Although it would be difficult to ascertain that the results were not contributed by ketamine abstinence alone, this treatment option has been shown to be safe and can be tolerated in ketamine abusers.

2.2.4. Urinary diversion and upper tract protection

Hydronephrosis occurs in a significant proportion of chronic ketamine cystitis patients, ranging from 13% to 50%.[9,32–34] The proposed mechanisms include ureteric reflux secondary to detrusor overactivity and/or a poor compliance bladder, and ureteric stricture related to ketamine use. Interventions such as percutaneous nephrostomy for renal impairment were required in ~5% of the presenting patients.[9] Every effort has to be paid in protecting the upper tract damage, although the young adults have poor acceptance and compliance to percutaneous nephrostomy drainage, and the blockage or dislodgement rate is high. Antegrade or retrograde stenting was an alternative treatment for hydronephrosis and renal impairment secondary to reflux, although the stent tip may irritate the bladder and, in turn, cause more irritative urinary symptoms or hematuria.[35] Long-term metallic ureteric stenting has also been recently reported.[36]

In our experience, endourological procedures in treating ureteric strictures (if any) in these patients have been difficult, as most of them suffer from long and tight strictures because of chronic inflammation and fibrosis. The choice of definitive reconstruction surgery in these patients is often limited by the concomitant small contracted bladder. More sinister disease course has been observed in a handful of ketamine abusers in the region, who developed end-stage renal failure and required dialysis. This has indeed a significant influence on the burden in the health care system and the society.

2.2.5. Augmentation cystoplasty/neobladder reconstruction

Reconstruction of the fibrotic, small bladder with augmentation cystoplasty has been performed in nine patients in three different centers in Hong Kong, with the initial four cases being published previously.[24] Their outcomes varied. Although the patients abstained from ketamine usage prior to surgery, many of them resumed usage at different stages after surgery. Four of them developed serious complications, including renal failure, convulsion, and ureteric strictures. One of the possible causes for the rapid development of complications was recirculation of ketamine and

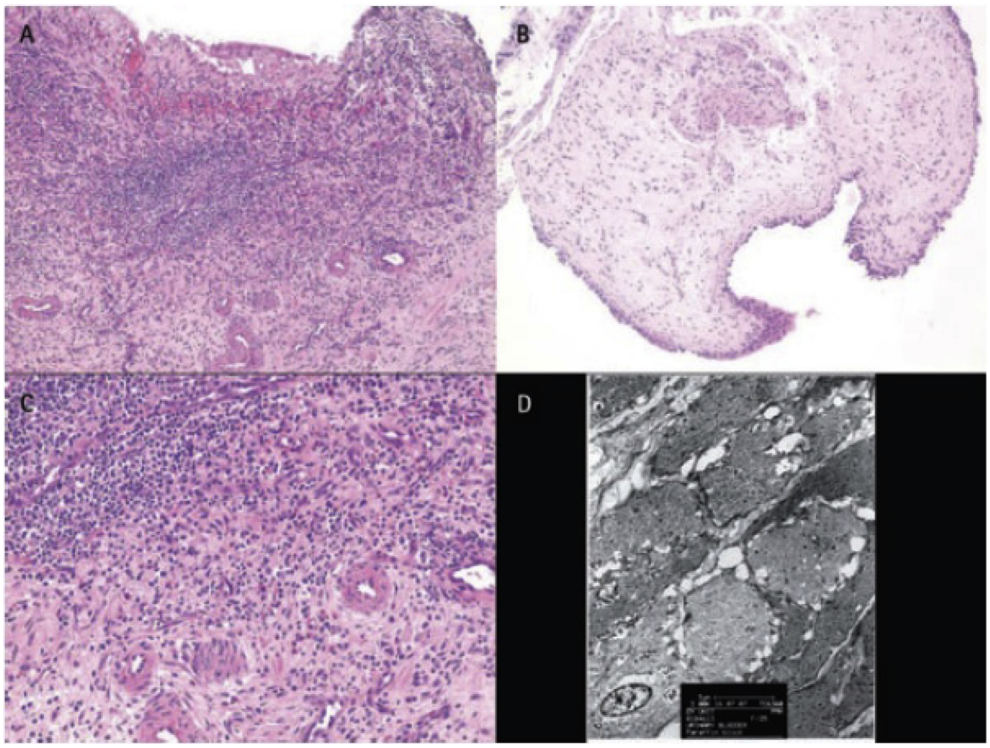

Fig. 4. (A,B) Ketamine-associated cystitis shows a variable degree of inflammation. (C) The infiltrates comprise predominantly lymphocytes and a variable number of eosinophils. (D) Ultrastructural examination shows querciphylloid muscle cells. *Note*. From "The destruction of the lower urinary tract by ketamine abuse: a new syndrome?" by P.S. Chu, W.K. Ma, S.C. Wong, R.W. Chu, C.H. Cheng, S. Wong S, et al, 2008; *BJU International*, *102*, p. 1616–22. Copyright 2008/ W.-K. Ma and P.S.-K. Chu. Adapted with permission.

its metabolites in the body in relation to the intestine used for augmentation. Therefore, careful selection of patients and repeated emphasis on the maintenance of abstinence are important steps prior to surgery.

While preservation of part of the bladder would potentially retain the bladder pain symptoms, some propose removal of the whole bladder with cystectomy, followed by neobladder reconstruction.[37] Detailed counseling regarding, as well as assessment of, the patient's compliance to postoperative care and dignity on ketamine cessation after surgery is necessary in order to avoid poor outcomes of the ultramajor procedure.

3. Understanding the pathophysiology of ketamine cystitis

The exact pathophysiology of ketamine uropathy is still unknown, despite the efforts made in gathering clinical, biochemical, and histological evidences together with laboratory and animal studies. Our current knowledge is that ketamine or its metabolites, being primarily excreted in urine, induce an initial acute inflammatory reaction of the urothelium, which starts a chain reaction that eventually results in bladder damage, such as epithelium denudation, ulceration, submucosal inflammation, and fibrosis. A recent Taiwan study has revealed elevated serum immunoglobulin E levels in ketamine cystitis patients compared with interstitial cystitis patients, bacterial cystitis patients, and controls.[38] This suggests that hypersensitivity may play an important role in the pathogenesis of ketamine uropathy.

3.1. *In vitro studies*

Two *in vitro* cell line studies from Taiwan and mainland China have demonstrated the detrimental effect of ketamine in inducing apoptosis in a dose- and time-dependent manner.[39] Ketamine arrested the cells in G1 phase and increased the sub-G1 population, which could be the mechanism of urothelium damage, increasing barrier permeability to other toxic substances. The cytotoxicity of ketamine has indeed also been reported in neuroblastoma,[40,41] lymphoma Jurkat cells,[41] and hepatoma.[42]

3.2. *In vivo studies*

Five animal *in vivo* studies have been reported to date on the topic with three mouse and two rat models.[39,43–46] Summarizing the key findings from these studies, it has been shown that ketamine can induce the following changes: (1) submucosal infiltration of mononuclear inflammatory cells; (2) thinning of urothelium and a reduction in the number of nerve fibers; (3) a decrease in the mouse body weight growth rate and bladder capacity; (4) an increase of adenosine triphosphate-evoked detrusor contraction and P2X1 receptor protein; (5) increase of phosphorylated transgelin of bladder smooth muscle; (6) induction of cyclooxygenase-2 and inducible nitric oxide synthase gene expression; and (7) down-regulation of a total of 52% of keratin family genes, particularly keratin 6a, 13, and 14. All these changes give further insights for us to understand the pathophysiology of ketamine uropathy, although human bladder physiology is much more complex and multiple mechanisms may come into play after chronic ketamine exposure.

4. Resources and direction on lowering the burden

In Hong Kong, since the publication of the first report of 10 patients with ketamine cystitis in 2007,[1] the Government of the Hong Kong Special Administrative Region has provided tremendous financial support to antiketamine abuse research on clinical and basic laboratory science, projects on raising community and school awareness, and rehabilitation.[47] Besides, enhanced law

enforcement by the Hong Kong Judicial Bureau on drug trafficking of ketamine since 2008 had helped reduce ketamine supply in the territory (Table 1).[48,49]

The burden on the society arising from ketamine abuse is a vicious cycle: it starts as a social problem when young people begin to abuse ketamine, who are then complicated by urological consequences that may be irreversible and, in turn, create more social and economic problems.

One of the clinical projects supported by the Beat Drugs Fund in Hong Kong is a prospective longitudinal study on the outcomes of various treatment modalities under a standardized protocol in patients suffering from ketamine-induced voiding dysfunction.[50] This study concluded that both anti-inflammatory drugs and analgesics could effectively alleviate symptoms of ketamine cystitis. However, abstinence from ketamine usage and the amount of ketamine consumed remained two important factors determining the response to treatment as well as symptom relief.

Another large-scale project supported by the Beat Drugs Fund was establishment of the Youth Urological Treatment Centre in 2011.[51] This center involves a multidisciplinary team with experts from all fields: social workers, pediatricians, clinical psychologists, psychiatrists, urologists, occupational therapists, and more importantly patients' family members. The mission is to provide early urological assessment and treatment to young patients suffering from ketamine-associated uropathy, and to formulate a practical and cost-effective management protocol by concentrating the experience in a single center. The center had benefitted over 300 patients in 2 years.[17]

Among the many community projects supported financially by the Beat Drugs Fund, the project named “A community study of uro-psycho-physical changes in young adults using ketamine” led by urologists, with coinvestigators involving other paramedical health personals, provided data on community-based prevalence of ketamine cystitis.[20,28,52]

Several basic laboratory scientific research projects funded by the Beat Drugs Fund were mostly animal model studies of ketamine abuse, which aimed at explaining the pathophysiology of damaging effects of ketamine on the urinary system.[53]

All in all, the future direction of resource allocation and studies will most likely be multinational, multidisciplinary clinical and/or basic scientific studies, hoping to provide understanding on the pathophysiology of ketamine cystitis and also to formulate a Chinese or an Asian guideline on diagnostic, investigation, and treatment protocols. By providing effective clinical treatment, and cooperating with other specialties (psychiatrists, social workers, occupational therapists, and nurse counselors), urologists will be able to offer rehabilitation opportunities to these patients with the aim of reintegrating them into the society. To achieve this, the government of every region should play the paramount role of coordinating different bureaus (such as education, police, and judicial departments), counseling centers for psychotropic substance abusers, antidrug volunteer groups, and family support groups in combating drug abuse.

Table 1
Change in HKSAR's sentence tariffs for traffickers in ketamine before and after June 2008.[48]

Years of imprisonment	Before June 2008 (g)	After June 2008 (g)
Within sentencer's discretion	≤ 25	≤ 1
2–4	25–400	1–10
4–6		10–50
4–8	400–800	
6–9		50–300
≥ 8	> 800	
9–12		300–600
12–14		600–1000
≥ 14		> 1000

HKSAR = Hong Kong Special Administrative Region.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

Sources of funding

The authors received a one-off grant from the Beat Drugs Fund, Narcotics Division, Security Bureau, the Government of the Hong Kong Special Administrative Region (BDF 080050), in 2008/2009 for conducting the project “Research on Urological Sequelae of Ketamine Abuse.” Some of the results quoted in this paper were extracted from studies funded by the project.

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