

# Ketamine

## A Cause of Urinary Tract Dysfunction



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### KEYWORDS

• Ketamine • Urology • Urinary Tract Dysfunction • Inflammation • Bladder • Illicit

### KEY POINTS

- Lower urinary tract symptoms such as urgency, frequency, dysuria, and hematuria are common urologic complaints in men and women and the differential remains broad.
- Illicit ketamine abuse is a growing problem and can lead to a cystitis symptom complex that mimics common genitourinary complaints.
- Ketamine abuse induces complex changes to the environment of the urinary tract, specifically the bladder, that can be observed clinically and at the molecular level.
- Currently, there is no standard for diagnosing and treating ketamine induced cystitis, however, treatment currently involves symptom management.
- More investigations should be done to develop standard and/or individually targeted diagnostic and treatment protocols for this emerging cause of cystitis.

### INTRODUCTION

According to the 2014 national survey on drug use and health, approximately hundreds of thousands of people in the United States aged 12 and over have used illicit substances of varying types.<sup>1</sup> Drug addiction is a chronic relapsing disorder, and people who suffer with it tend to demonstrate binge use, intoxication, withdrawal associated with a negative emotional state, and anticipation of substance use that modifies the brain reward and stress systems.<sup>2</sup> The association between reward and stress has been demonstrated previously. For example, using a mouse model, Piazza and colleagues<sup>3</sup> found that when mice were injected with corticosterone, self-administration frequency increased, particularly at higher doses. Interestingly, in

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this study, the investigators also found that different animals had different propensities to self-administer the steroids based on their individual sensitivities to drugs of abuse.

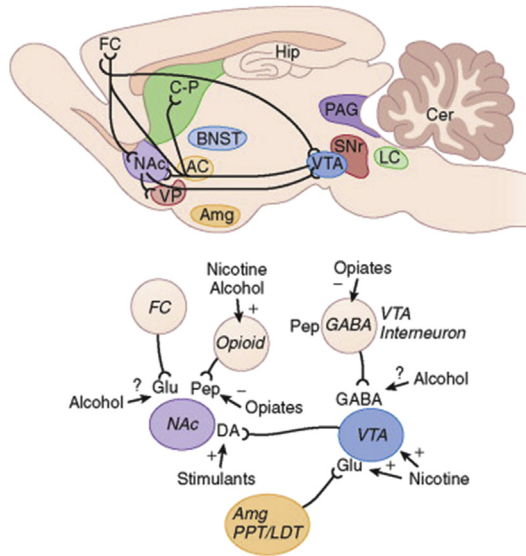
The neurobiological basis of addiction involves a complex array of circuitry and brain structures, and a detailed discussion of this topic is beyond the scope of this work. In brief, the mesocorticolimbic dopamine system involves forebrain structures like the nucleus accumbens, the midbrain's ventral tegmental area, and the amygdala, and is critical in modulating the reinforcing actions of many drugs of abuse (Fig. 1).

Aside from dopamine, other molecules like glutamate, dynorphin, corticotrophin-releasing factor, neuropeptide Y, and endocannabinoid also appear to be involved.<sup>2,4-6</sup>

It is estimated that the lifetime prevalence for any prescription opiate use disorder in treated patients with chronic pain is approximately 42%.<sup>7</sup> Other substances are also abused. For example, in a sample of 921 patients with prescriptions for opiates, a portion of these patients had promethazine- and benzodiazepine-positive urine. Of these individuals, only 50% had prescriptions for promethazine. In addition, the finding of benzodiazepine-positive urine without a prescription for it was associated with illicit promethazine use.<sup>8</sup> Because of these kinds of findings, clinicians must be conscious of the abuse of other classes of medications.

In the urologic setting, a commonly abused drug that is becoming more of a problem worldwide is ketamine (Fig. 2).

Ketamine is important to the urologist because it can adversely impact the lower urinary tract. In addition, the clinical and objective findings can mimic a commonly



**Fig. 1.** Substances of abuse and complex interactions of brain neurocircuits. AC, anterior commissure; Amg, amygdala; BNST, bed nucleus stria terminalis; Cer, cerebellum; C-P, caudate-putamen; DA, dopamine; FC, cerebrofrontal cortex; Glu, glutamate; Hip, hippocampus; LC, locus ceruleus; NAc, nucleus accumbens; PAG, periaqueductal gray; Pep, opioid peptides; PPT/LDT, peduncular pontine tegmentum/lateral dorsal tegmentum; SNr, substantia nigra pars reticulata; VP, ventral pallidum; VTA, ventral tegmental area. (From Choi DS, Karpayak VM, Frye MA, et al. Drug addiction. In: Waldman SA, editor. Pharmacology and therapeutics: principles to practice. Philadelphia: Elsevier Saunders; 2009. p. 821; with permission.)



**Fig. 2.** Ketamine prescription. (From AccessMedicine Drug Monographs Online Database. Available at: [www.accessmedicine.mhmedical.com/drugs.aspx](http://www.accessmedicine.mhmedical.com/drugs.aspx). Accessed June 5, 2016; with permission.)

encountered urologic chronic pain syndrome called bladder pain syndrome/interstitial cystitis (BPS/IC). This presents a unique dilemma for the urologist or any clinician managing these kinds of urologic problems, which tend to be chronic in nature. In this work, the toxicology of ketamine, primarily from a urologic frame of reference, is discussed.

## KETAMINE

Ketamine, also called “K,” “Special K,” “Vitamin K,” or “Kiddy Smack” to name a few pseudonyms, is an *N*-methyl-D-aspartate (NMDA) receptor antagonist (Fig. 3).<sup>9–13</sup>



**Fig. 3.** Ketamine.

In the central nervous system (CNS), NMDA receptors reside on cation-gated channels that respond to the excitatory neurotransmitter glutamate, rendering these channels permeable to calcium and causing depolarization of neurons (Fig. 4).<sup>11,14</sup>

Other excitatory amino acids, such as glycine, are also thought to interact with the NMDA receptor. It is thought that NMDA receptors responding to glutamate influence some of these other neuronal circuits through GABAergic neurons and inhibit them.<sup>11,12,15</sup>

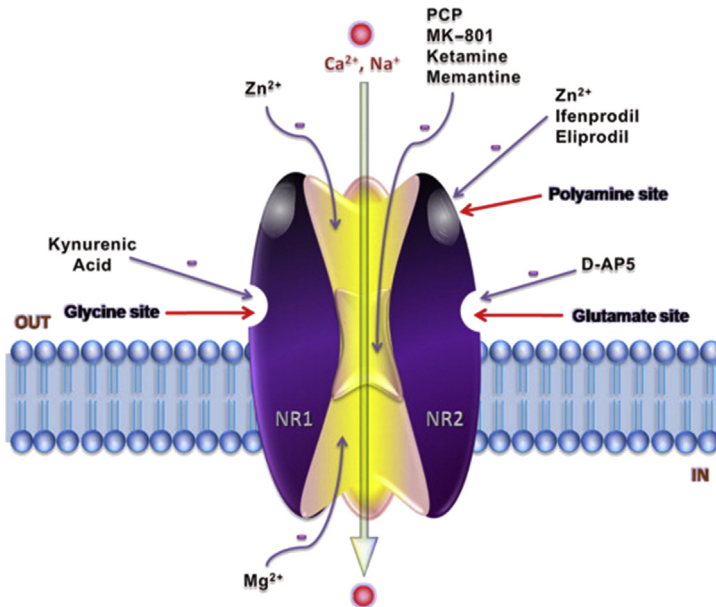
### **N-METHYL-D-ASPARTATE RECEPTORS AND KETAMINE**

NMDA receptors are present throughout the CNS, including the cerebral cortex, cerebellum, brain stem, and spinal cord, and appear to be crucial in the processing of complex communication at the neuronal level. The limbic system, for example, is important in regulating memory, emotion, and subsequent integration with sensory input and becomes affected by the administration of ketamine.<sup>11</sup>

### **KETAMINE AS AN ILLICIT SUBSTANCE**

According to the World Health Organization (WHO) in 2012, approximately 1.1% of the Australian population had abused ketamine at some point in their life and less than 2% of youths in Denmark had used ketamine. At that time, 19 countries worldwide reported illicit activities related to ketamine, with the United States and China reporting the largest seizures of the substance.<sup>16</sup> That same year, up to 1.5% of US high school students reported ketamine use.<sup>17</sup> Interestingly, as per the WHO, in some African countries, there were no reports of ketamine abuse.<sup>16</sup>

As per the US Drug Enforcement Agency (DEA), drugs, or chemicals used to make drugs, are classified into 5 categories (or schedules) depending on medical uses for the drug and the drug's potential for abuse or dependency. Essentially, the higher the schedule, the lower the potential for abuse.<sup>18</sup> Ketamine has been a schedule III drug in the United States since 1999 and has been associated with recreational drug abuse for more than 30 years.<sup>17,19</sup>



**Fig. 4.** NMDA receptor and binding sites of various neurotransmitters including glutamate.  $Mg^{2+}$ , MK-801, ketamine, PCP, and memantine act as noncompetitive antagonists whose binding sites are within the ion channel pore region. (From Ghasemi M, Schachter SC. The NMDA receptor complex as a therapeutic target in epilepsy: a review. *Epilepsy Behav* 2011;22(4):618; with permission.)

In certain Asian cities and countries, ketamine has had a huge impact. In Hong Kong for example, ketamine has become a common drug of abuse, surpassing opiates, which were formerly responsible for most of the problems associated with illegal drugs in that city.<sup>20</sup> In Taiwan, ketamine use is popular among high school students and is part of a popular drug sequence called “Trinity,” which includes the use of MDMA/ecstasy, followed by ketamine and then marijuana.<sup>21</sup> Although several investigators have reported on ketamine abuse in Asian populations,<sup>10,22–26</sup> it is important to note that ketamine abuse is also seen in non-Asian populations. In a US cohort of 23 patients who reported chronic ketamine use, 57% were Caucasian/White, 22% were Latino/Hispanic, and 17% were biracial, compared with only 4% who were Asian.<sup>27</sup> This finding suggests that a ketamine use may not follow any ethnic predilections.

In nonclinical settings, ketamine has been obtained illegally typically from medical offices and has been sold in 10-mL bottles for as much as \$200.<sup>28</sup> Ketamine can be snorted, mixed in drinks, injected, smoked, or inhaled as a powder; however, intramuscular (IM), rectal, and oral (PO) formulations also exist, and in these forms, the drug is absorbed relatively quickly.<sup>9–11,17,28–32</sup> Lankenau and Clatts<sup>27</sup> interviewed 40 young injection drug users from New York City, assessing their injection practices, and found that the route of administration varies with the individual.

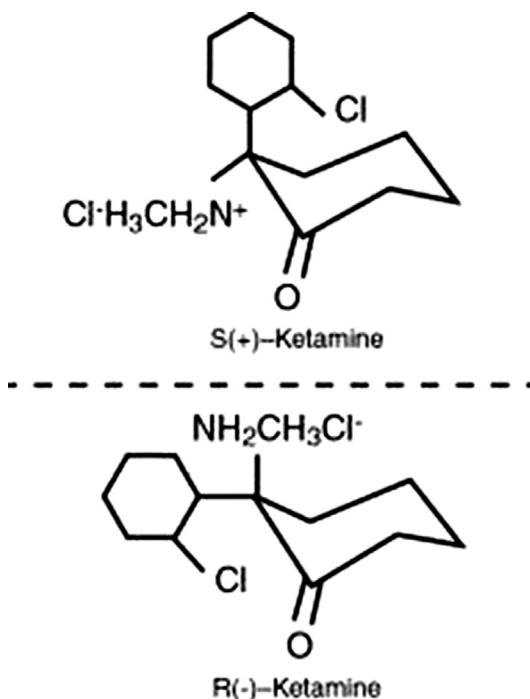
When used in a recreational setting, the ketamine doses vary. According to the US National Highway Traffic Safety Administration, dosages for the IM, intranasal, and PO routes are 25 to 50 mg, 30 to 75 mg, and 75 to 300 mg, respectively.<sup>31</sup> According to the DEA, an average street dose is 100 mg.<sup>17</sup> In one case report, a 35-year-old woman reported 2 to 3 mL IM per day and gradually progressed to 10 to 20 mL IM per day.<sup>33</sup>

For illicit production of ketamine, which has a reputation of being laborious, the substances cyclohexanone, methylamine and chlorobenzene, o-chlorobenzonitrile, and cyclopentyl bromide are thought to be a few precursors with several other solvents used in the synthesis process.<sup>20</sup> The purity of “street” ketamine is questionable, and at least 2 analogues have been found on the black market with effects lasting longer than ketamine itself.<sup>31,34</sup>

### KETAMINE PHARMOKINETICS AND METABOLISM: CONTROLLED SETTING

Although up to 30% is bound to plasma proteins, ketamine itself is highly lipid soluble and can quickly cross the blood-brain barrier to redistribute throughout body tissues.<sup>13,29,35,36</sup> Ketamine has a  $pK_a$  of 7.5, and under normal circumstances, can be administered as a racemic mixture, the active S isomer and inactive R isomer. The R isomer can inhibit the S isomer, and as such, formulations with only the S isomer exist (Fig. 5).<sup>34,37</sup>

The liver and the kidneys are sights of ketamine metabolism, and concurrent use of medications that rely on the same pathways impact ketamine processing.<sup>11,13,37,38</sup> For example, Lo and Cumming<sup>38</sup> demonstrated that the ketamine-induced sleep time in patients that were premedicated with diazepam, hydroxyzine, and secobarbital, all metabolized by liver, were approximately  $137 \pm 3.8$  minutes,  $138 \pm 9.2$  minutes, and  $128 \pm 4.7$  minutes, respectively, in comparison to  $98.5 \pm 4.4$  minutes in those not premedicated ( $P < .05$ ). The plasma half-life of ketamine



**Fig. 5.** Ketamine enantiomers (The molecular formula of ketamine hydrochloride, C<sub>13</sub>H<sub>16</sub>ClNOHCl). (From Blaise GA. Ketamine. In: Murray MJ, editor. *Faust's anesthesiology review*. Philadelphia: Elsevier Saunders; 2015. p. 166; with permission.)

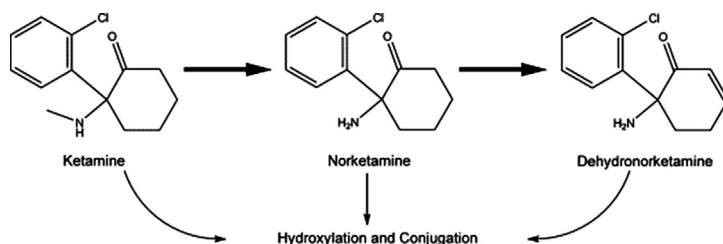
was also increased in a statistically significant manner when coadministered with these same medications.

Approximately 80% of ketamine is metabolized to norketamine by microsomal enzymes. Norketamine is of particular importance, because this metabolite has been shown to have about 35% the biologic activity of ketamine itself. In addition, after intravenous (IV) administration, norketamine appears in blood approximately 2 to 3 minutes after administration and reaches peak concentrations in about half an hour. Other ketamine metabolites formed (to lesser degrees) include 4-OH-ketamine and 5-OH-ketamine.<sup>37</sup> These metabolites can be biologically active and contribute to lower urinary tract abnormality (Fig. 6).<sup>39–41</sup>

When used in the clinical setting, ketamine administration routes include IV, IM, rectal, PO, and intranasal.<sup>11,35,37</sup> Intranasal administrations can be dosed from 3 to 8 mg/kg/dose depending on age; rectal administration can be dosed 4 to 10 mg/kg/dose, and PO forms can be dosed at 6 to 8 mg/kg/dose. Of note, PO, rectal, and intranasal routes are commonly used in younger patients. For IV and IM formulations, dosages from 1 to 4.5 mg/kg and 5 to 13 mg/kg, respectively, have been used. Onsets of action for intranasal, PO, IM, and IV formulations are 5 to 8 minutes, within 30 minutes, 3 to 25 minutes, and immediate to 10 minutes, respectively. The bioavailability for ketamine for the IM route is about 93% with peak plasma concentration obtained in about 5 minutes. Because of hepatic metabolism, bioavailability for the PO route is around 20% to 30% with a plasma concentration peak in up to 30 minutes. Intrarectal ketamine administration demonstrates bioavailability of about 25% with peak concentrations achieved at about 45 minutes, and intranasal bioavailability is about 25% with peak concentrations in 20 minutes. The half-life of ketamine can be up to 3 hours depending on route.<sup>35,37</sup>

## LABORATORY DETECTION OF KETAMINE

Ketamine and some of its derivatives have been detected in hair, urine, and blood,<sup>29,42,43</sup> however primarily in urine and blood. Ketamine and norketamine have been detected in urine for 5 and 6 days, respectively. Dehydronorketamine, another metabolite, has been detected for up to 10 days.<sup>41</sup> Examples of detection methods include gas and liquid chromatography and mass spectrometry (MS).<sup>39,44</sup> In a recent report by Moreno and colleagues<sup>42</sup> using gas chromatography-tandem mass spectrometry (GS-MS), the investigators were able to identify ketamine and norketamine in artificial laboratory-produced samples of 0.25 mL with high recoveries of the compounds. The investigators extracted the target compounds using a technique referred



**Fig. 6.** Molecular structure of ketamine and its metabolites. (From Bairros AV, Lanaro R, Almeida RM, et al. Determination of ketamine, norketamine and dehydronorketamine in urine by hollow-fiber liquid-phase microextraction using an essential oil as supported liquid membrane. *Forensic Sci Int* 2014;243:48; with permission.)

to as microextraction by packed sorbent (MEPS). Of note, the researchers applied these same methods to samples of suspected ketamine abusers, and ketamine and norketamine were not detected. The investigators thought that the likely reason that these metabolites were not detected was because they were no longer present in the body at the time of sampling. The researchers then administered ketamine intraperitoneally at 50 mg/mg to one rat and obtained plasma and urine samples 1 hour following administration. The metabolites were identified in both samples and the investigators concluded that their method provides a quick and effective approach to detect ketamine and norketamine in biological fluid samples, with specific usefulness in the field of forensic toxicology.

## EFFECTS

Along with phencyclidine, or PCP, which is commonly called “angel dust,”<sup>23,30</sup> ketamine belongs to a class of drugs called arylcyclohexylamines and is typically used as a dissociative anesthetic.<sup>11,30,34,45,46</sup> Several synthetic agents have emerged within this same drug class. Some of these agents include methoxetamine, 3-methoxy-PCP, 4-Meo-PCP, Diphendine, and methoxyphenidine and provide similar dissociative effects as PCP and ketamine.<sup>46</sup>

Ketamine also exhibits analgesic properties by binding mu opioid receptors and has proven beneficial in palliative care patients for analgesia.<sup>11,17,47</sup> Ketamine has agonist activity at  $\alpha$  and  $\beta$  receptors, antagonist activity at muscarinic receptors in the CNS, and has been shown to prevent the uptake of catecholemines.<sup>11,12</sup> Research has also shown that ketamine may also have antidepressant properties; however, this indication has been questioned.<sup>30</sup>

Many potential side effects of ketamine have been described, including cardiopulmonary, neuropsychological, and neuromuscular symptoms.<sup>11,15,30,48–50</sup> Following ketamine infusions, elevated systolic and diastolic blood pressures and increased heart rate can be seen.<sup>30,48</sup> There has also been suggestion that ketamine causes arrhythmias; however, the evidence is somewhat controversial. Some investigators have proposed that the reason for the hemodynamic changes following ketamine administration may be secondary to a centrally acting mechanism, specifically, ketamine’s demonstrated ability to block the reuptake of catecholemines.<sup>11</sup>

Ketamine appears to have respiratory effects as well.<sup>11,49</sup> Hamza and colleagues<sup>49</sup> demonstrated a statistically significant decrease in the CO<sub>2</sub> response curves (minute ventilation/end-tidal CO<sub>2</sub>) of 9 children ages 6 to 10 years undergoing lower abdominal or minor reconstructive procedures treated with an IV bolus of ketamine followed by a continuous infusion compared with controls. The investigators state that the respiratory depressant effects of ketamine appear to be similar in their cohort of children as has been shown in adults. Care should also be taken when ketamine is coadministered with other agents because synergistic effects have been reported.<sup>11,51</sup>

Psychotropic effects, such as intense euphoria and dissociation, can be experienced with ketamine and are some of the most well-known side effects of the drug.<sup>30</sup> At lower doses, hallucinations can be experienced; however, at higher doses of greater than 150 mg, a severe dissociative state called the “K Hole” occurs.<sup>9,50</sup> The “K Hole” experience can be dampened with administration of certain medications like benzodiazepenes.<sup>52</sup>

As stated earlier, glutamate, acting through  $\gamma$ -aminobutyric acid (GABA)ergic NMDA receptors throughout the CNS, maintain the tonic inhibition of multiple excitatory neuronal circuits. It is thought that in certain individuals with hypofunctioning glutamate-mediated NMDA receptors, there is an inability to inhibit activity of neurons

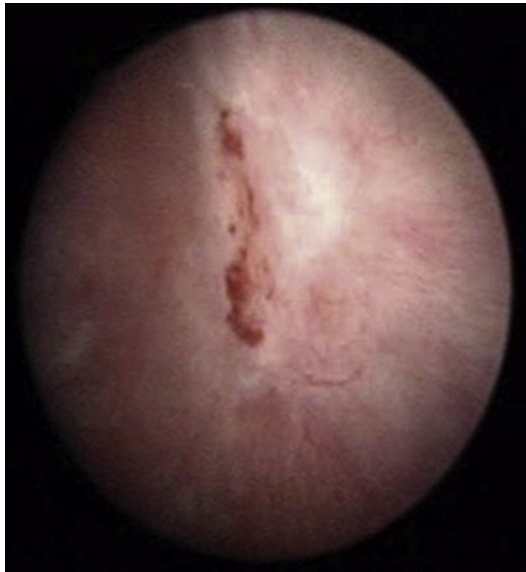


in the corticolimbic system, leading to psychosis. Olney and Farber<sup>15</sup> suggest that NMDA receptor antagonists like ketamine produce a similar situation. Furthermore, the investigators suggest that structural changes in the brains of rats with hypofunctioning NMDA receptors demonstrated structural changes similar to those with schizophrenia. In a separate review, Li and colleagues<sup>50</sup> state that the brains of chronic ketamine users demonstrate a reduced volume of gray matter in the frontal cortex bilaterally, similar to those with schizophrenia. These findings explain the psychosis-like effects of ketamine by highlighting similarities with a condition characterized by similar symptoms.

### KETAMINE AND BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

Aside from the cardiopulmonary and neurologic effects, ketamine can cause genitourinary dysfunction, especially urothelial dysfunction. This dysfunction can mimic a common urologic condition known as BPS/IC (**Fig. 7**).<sup>22</sup>

BPS/IC has been defined as an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks' duration, in the absence of infection or other identifiable causes.<sup>53</sup> BPS/IC can be associated with flares that have a physical and emotional impact on the patient. Different definitions have been used over the years for clinical and research purposes; however, depending on the definition used, one can see prevalence from 1% to almost 3%. Women tend to be affected more than men. Some studies quote incidence as high as almost 7% in women.<sup>54</sup> Those with a lower socioeconomic status are more impacted compared with their counterparts.<sup>55</sup>



**Fig. 7.** Bladder pain syndrome/Interstitial cystitis cystoscopic appearance. (From Quillin RB, Erickson DR. Management of interstitial cystitis/bladder pain syndrome: a urology perspective. *Urol Clin N Am* 2012;39(3):391. © 2011, American Urological Association Education and Research, Inc; with permission.)

## UROTHELIUM

The urothelium is usually composed of at least 3 to 6 layers of cells at different stages of differentiation.<sup>56,57</sup> From basal to superficial, these layers include basal cells, intermediate cells, and “umbrella” cells. The umbrella cells on the apical surface of the urothelium prevent the penetration of ions and toxins from the urine through bladder tissue with the aid of tight junction proteins and a cytoskeleton acting as scaffolding (Fig. 8).<sup>58</sup>

Some of these proteins include the cytoplasmic zonula occludens-1 and membrane proteins called claudins and occludins, which can also be decreased in bladders exposed to noxious substances like ketamine.<sup>59–61</sup> The superficial umbrella cells themselves are composed of proteins called uroplakins.<sup>57,61,62</sup>

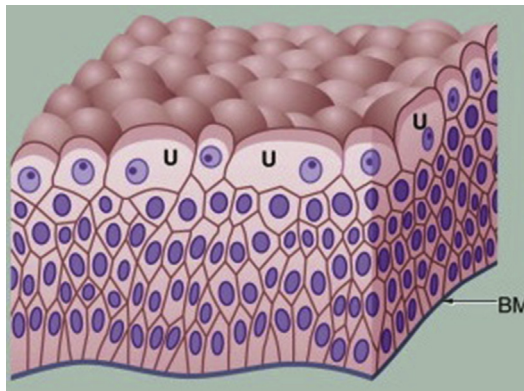
Although relatively impermeable, normal urothelium is highly flexible, accommodating large changes in volume.<sup>62,63</sup> The urothelium as a whole contains a significant amount of glycosylation, with the luminal surface containing a matrix of sugars and proteins called glycocalyx.<sup>57</sup> Glycocalyx also contributes to its barrier function.

Exterior to the urothelium, the layers of the bladder include the lamina propria, muscularis mucosa, muscularis propria, and serosa.<sup>58,64,65</sup> The term “mucosa” generally refers to urothelium, lamina propria, and muscularis mucosa and contains both sensory and motor nerves within it that respond to various neurotransmitters.<sup>56,64–67</sup> It is thought that these nerve fibers work in conjunction with a nonselective ion channel called transient receptor potential vanilloid subfamily 1 (TRPV1), which has been shown to mediate noxious bladder stimuli and high-frequency bladder contractions occurring during pathologic conditions using an animal model (Fig. 9).<sup>68</sup>

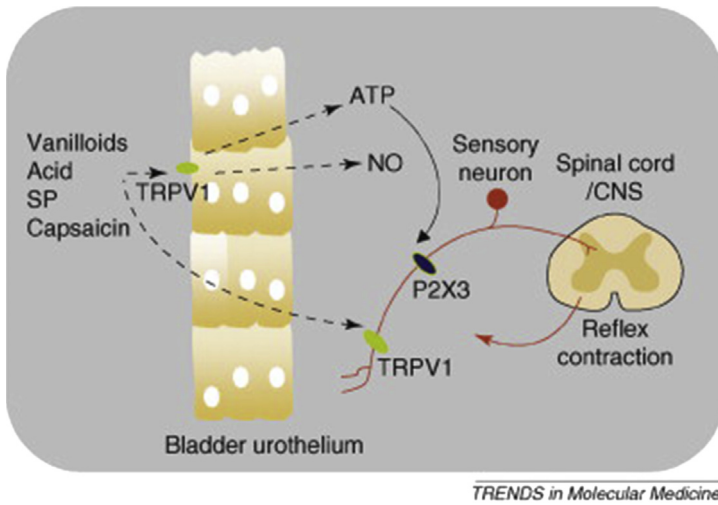
## KETAMINE AND THE LOWER URINARY TRACT

The impact of ketamine on the genitourinary tract has been documented clinically, and with objective measures like voiding diaries, imaging, histologic examinations, cystoscopy, video urodynamics, and even semen analyses (Figs. 10–12).<sup>10,19,22–24,26,32,61,69–77</sup>

Shahani and colleagues<sup>36</sup> provided what is thought to be one of the earliest descriptions of ketamine-associated lower urinary tract dysfunction in 2007. The investigators described the associated genitourinary symptoms of 9 ketamine users. Each patient had similar findings on cystoscopy, which typically demonstrated erythematous

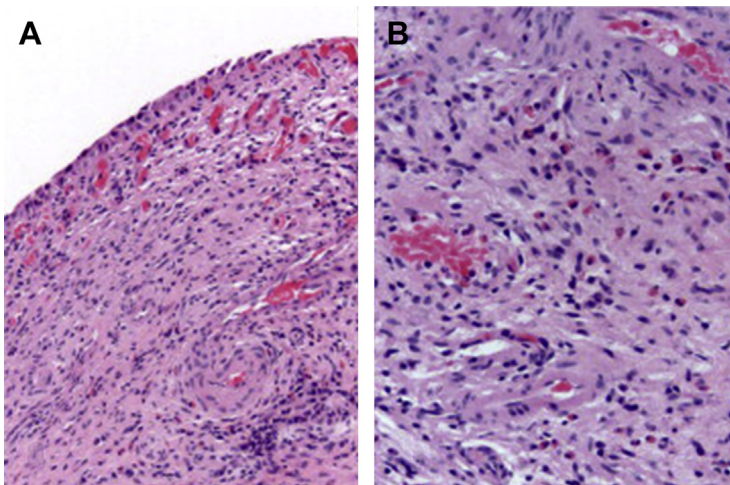


**Fig. 8.** Urothelium. U, umbrella cells; BM, basement membrane. (From Young B, O'Dowd G, Woodford P. Epithelial tissues. In: Wheater's functional histology. Elsevier Churchill Livingstone; 2014. p. 82–100; with permission.)

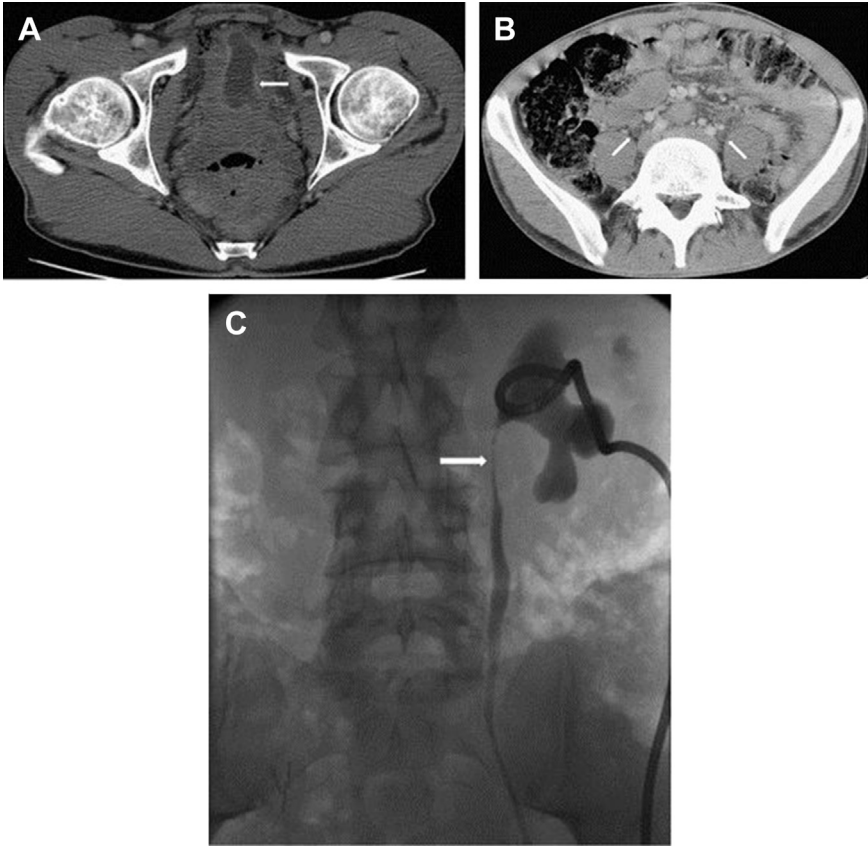


**Fig. 9.** TRPV1 receptor and neurogenic bladder. NO, nitric oxide; P2X3, a type of purine receptor; SP, substance P. (From Khairatkar-Joshi N, Szallasi A. TRPV1 antagonists: the challenges for therapeutic targeting. *Trends Mol Med* 2009;15(1):17; with permission.)

ulcerated patches. Four of the patients underwent bladder biopsies. In all of the specimens, the urothelial mucosa appeared to be denuded with evidence of a thin layer of reactive epithelium. With respect to the lamina propria, the superficial aspect was edematous with an abundance of inflammatory cells and granulation tissue. The deeper aspect of the lamina propria was fibrotic. In the stroma, many eosinophils were noted along with mast cells.



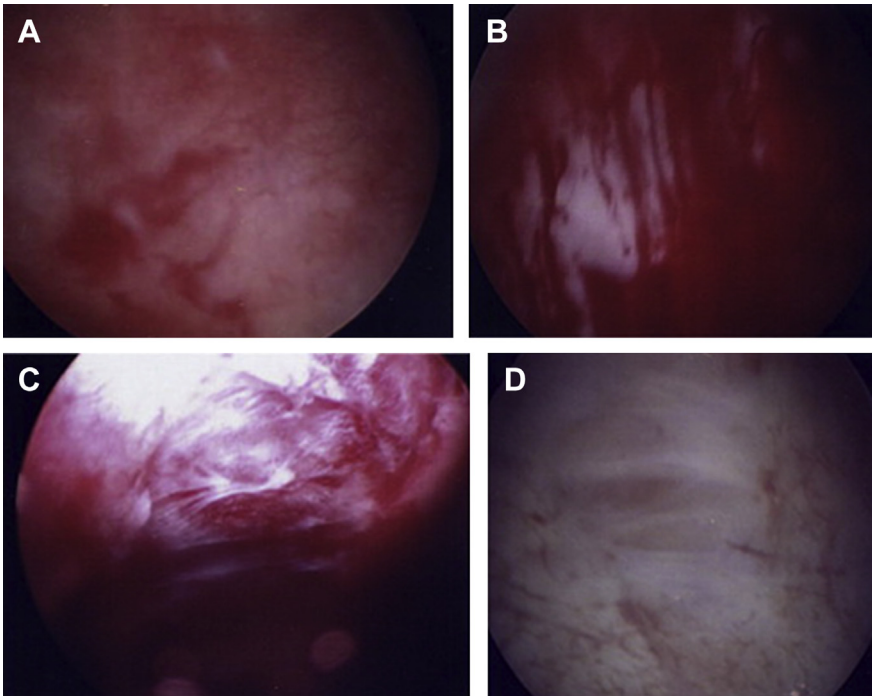
**Fig. 10.** (A) Denuded urothelium, regenerating epithelial cells, ulcerations, granulation tissue, and inflammatory cells (hematoxylin-eosin, original magnification  $\times 10$ ). (B) Stroma showing eosinophils, mast cells, and lymphocytes (hematoxylin-eosin, original magnification  $\times 100$ ).



**Fig. 11.** Contrast-enhanced CT and nephrostogram of a 27-year-old male chronic ketamine abuser with (A) thickened bladder wall, (B) dilated ureters bilaterally, (C) nephrostogram demonstrating narrowing of proximal ureter and dilation of collecting system. Please see corresponding arrows. (From Mason K, Cottrell AM, Corrigan AG, et al. Ketamine-associated lower urinary tract destruction: a new radiological challenge. *Clin Radiol* 2010;65(10):799; with permission.)

All patients demonstrated some degree of irritative urinary symptoms and painful hematuria. Improvement with cessation of ketamine use was noted in only some subjects. Computed tomographic (CT) scans of the abdomen and pelvis demonstrated thickened and contracted bladders.

In a cohort of 10 patients from Hong Kong who abused ketamine chronically (1–4 years), urgency with and without incontinence, dysuria, frequency, and hematuria were noted in all patients. Each patient, aged 20 to 30 years, had total bladder capacities of 30 to 100 mL, and 7 patients had documented detrusor over activity on urodynamic studies.<sup>10</sup> In 2008, the same lead author retrospectively looked at 59 patients with moderate to severe lower urinary tract symptoms. They found that 71% of the cohort had cystoscopic examinations showing many different degrees of epithelial inflammation and neovascularization. Biopsies were performed on 12 patients, and histologic examinations generally revealed denuded epithelium and a lamina propria with granulation tissue and infiltrates of eosinophils and lymphocytes. The average bladder capacity was approximately 150 mL; however, 51% of the 59 patients had



**Fig. 12.** Cystoscopic evaluation of a 23-year-old woman with 1 year of ketamine abuse: (A) erythematous lesions, (B) diffuse hemorrhage postdistention, (C) ulcerated mucosa, (D) bladder perforation. (From Chen CH, Lee MH, Chen YC, et al. Ketamine-snorting associated cystitis. *J Formos Med Assoc* 2011;110(12):788; with permission.)

bladder capacities less than 150 mL. The investigators noted that most of the participants had reduced bladder compliance and detrusor over activity at volumes as low as 14 mL. Approximately 50% of the study subjects had either unilateral or bilateral hydronephrosis on renal ultrasound; 7% had radiologic features suggestive of papillary necrosis, and 8 patients had elevated serum creatinine levels. The specific causes of ketamine-induced lower urinary tract dysfunction remain unknown. The investigators go on to surmise possible theories that could account for the lower urinary tract damage sustained from ketamine exposure. First, they state that ketamine's impact on the lower urinary tract may be secondary to direct toxic effects, causing significant edema and an inflammatory response, leading to some of the clinical and histopathological effects noted. Second, they suggested that ketamine exposure causes changes in the microvascular of the bladder and kidney, leading to endothelial cell dysfunction and compromised circulation. The findings of neovascularity and papillary necrosis support this idea. The investigators also suggest that the presence of ketamine or its metabolites in the urine may induce an autoimmune response and induce some of the findings noted in bladders exposed to ketamine.<sup>22</sup> Lai and colleagues<sup>23</sup> also demonstrated similar lower urinary tract symptoms and reduced bladder capacities, in addition to hydronephrosis.

Using a mouse model, Song and colleagues<sup>75</sup> also demonstrated ketamine's deleterious impact on the lower urinary tract. Forty-two rats were evenly distributed into 6 groups, 5 with increasing concentrations of IV ketamine chloride at 1, 5, 10, 25, and 50 mg/kg and one control group, wherein phosphate-buffered saline was used. The



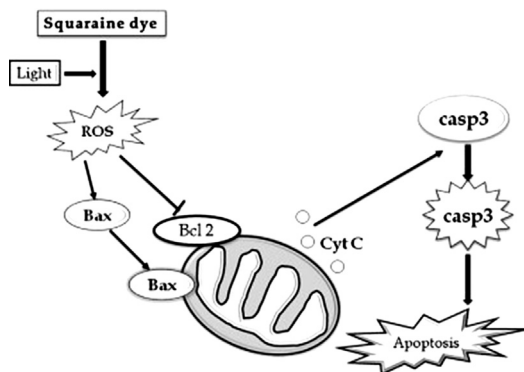
investigators compared various cystometric parameters, histology, and apoptotic changes 2 weeks following administration. With respect to cystometric parameters, the investigators found that the voiding intervals and the bladder capacities tended to decrease in a statistically significant manner as the ketamine concentration increased compared with the control group. Bladder compliance, maximum micturition pressure, and residual urine volume did not significantly differ between groups. Histologically, the thickness of fibrosis in the urothelium increased significantly directly proportional to the amount of ketamine that each mouse was exposed to. When staining for cytokeratin, an epithelium-specific protein, the bladders exposed to ketamine demonstrated less.

## APOPTOSIS

Ketamine impacts the urothelium's ability to make new cells and has been shown to induce apoptosis. Apoptosis, a complex interplay of cellular functions that leads to programmed cell death, is typically mediated by a cascade of proteases called caspases.<sup>78,79</sup> Cytochrome C, a mitochondrial protein involved in the respiratory chain located on inner mitochondrial membrane,<sup>61,80</sup> is released and triggers some of these caspases.<sup>78</sup> On the contrary, the bcl-2 protein, located on the outer membrane of the mitochondria, has been implicated in the prevention of apoptosis through an unknown mechanism (Fig. 13).<sup>81,82</sup>

Several studies have demonstrated ketamine's ability to induce apoptosis of urothelial cells by demonstrating high levels of caspase activity, decreased expression of bcl-2, by demonstrating reduced urothelial cell counts in bladders exposed to ketamine at different concentrations and for varying periods of time, and/or with special staining techniques.<sup>61,73,75,83-85</sup>

Using a human tissue engineered bladder model and cultured urothelial cells, Bureau and colleagues<sup>85</sup> examined the impact of ketamine on the bladder urothelium. Bladders were exposed to ketamine-soaked filter paper at increasing concentrations and incubated for 48 hours before being compared with controls. The investigators assessed the amount of caspase-3, a marker for apoptosis, using a fluorescence assay kit for the same single layer of urothelial cells. The concentrations of ketamine used were 1.5, 5, and 10 mM. Increasing amounts of caspase activity at higher



**Fig. 13.** Regulation of apoptosis. BAX, BCL2 associated X protein; BCL2, B-cell lymphoma 2; casp 3, caspase-3; Cyt c, cytochrome c; ROS, reactive oxygen species. (From Devi DG, Cibin TR, Abraham A. Bis(3,5-diiodo-2,4,6-trihydroxyphenyl) squaraine photodynamic therapy induces in vivo tumor ablation by triggering cytochrome c dependent mitochondria mediated apoptosis. *Photodiagnosis Photodyn Ther* 2013;10(4):516; with permission.)

concentrations of ketamine were noted. Of note, there was no difference in caspase activity at the highest concentration of ketamine used in the study, 10 mM. The investigators also noted a reduced amount of urothelial cells at higher ketamine concentrations with what appeared to be apoptotic bodies within the cells.

In their study, Song and colleagues<sup>75</sup> used terminal dUTP nick end-labeling staining to assess the level of apoptosis in ketamine-exposed bladders. The amount of apoptotic cells were increased compared with controls. The investigators also found that the BAX protein, indicative of apoptosis, and tumor necrosis factor- $\alpha$ , a marker for inflammation, were both upregulated in the bladders of the groups exposed to ketamine, and these findings were statistically significant.

Liu and colleagues<sup>61</sup> also demonstrated similar findings, in the urothelium, the detrusor muscle itself, and the bladder interstitium in subjects chronically exposed to ketamine. In their study, 48 rats were randomized to a control group that received either 0.5 mL normal saline intraperitoneally for either 2 or 4 weeks or study groups receiving 25 mg/kg/d of ketamine for either 2 or 4 weeks. Mitochondrial and endoplasmic reticulum (ER) –mediated apoptotic pathways were involved with the clinical findings associated with chronic ketamine use. Similar to the findings by Bureau and colleagues,<sup>85</sup> apoptotic urothelial cells in the groups exposed to ketamine were also noted using special staining techniques. The proapoptosis proteins cytochrome c and caspases 3, 8, and 9 were present at significantly higher concentrations in those study subjects exposed to ketamine for longer periods of time compared with controls. Furthermore, the ER chaperone protein Glucose Regulated Protein 78 (GRP78) and the ER protein C/EBP Homologous Protein (CHOP), associated with apoptosis, were significantly increased in those exposed to ketamine compared with controls.<sup>61</sup> GRP78 is an ER protein that regulates this organelle's ability to combat cell stress, such as the abnormal processing of misfolded proteins, in an adaptive process called the "Unfolded Protein Response." Although this mechanism is meant to promote cell survival, prolonged stress can lead to apoptosis through the CHOP protein.<sup>86</sup> The investigators also found that the antiapoptotic protein bcl-2 was significantly decreased in study subjects compared with controls.

## NEUROPATHOLOGY

Pathologic neuroanatomy within the urothelium itself results from ketamine exposure. In 21 patients with ketamine-induced cystitis, prominent nerve fibers were noted within the lamina propria.<sup>87</sup> Approximately 95% of subjects had nerve fibers that stained positive for neurofilament protein compared with 3 of 21 patients in other BPSs. Peripheral nerve fascicle hyperplasia was also noted in 20 of 21 subjects with ketamine-induced cystitis compared with their counterparts. Jhang and colleagues<sup>32</sup> also demonstrated increased nerve tissue in bladder urothelium exposed to ketamine.

## OXIDATION

It has been suggested that oxidation may play a prime role in several types of bladder abnormalities. In a study by Abraham and colleagues,<sup>88</sup> rats treated with cyclophosphamide, a cause of hemorrhagic cystitis, demonstrated decreased activity of several antioxidant enzymes compared with those pretreated with the antioxidant aminoguanidin. As another example, with partial bladder obstruction, the levels of protein carbonylation and nitrotyrosine, both markers for oxidative stress, increase as these bladders move toward decompensation. It has also been shown that symptoms associated with hyperactive detrusor can be dampened with administration of reactive

oxygen species scavengers.<sup>89</sup> The study by Liu and colleagues<sup>61</sup> addressed this idea and examined the impact that ketamine has on oxidative stress markers and mitochondrial reactive oxidative species in relation to the bladder's urothelium. In this study, the oxidative stress markers nitrotyrosine and 2,4-dinitrophenol were significantly higher in study subjects treated with ketamine. Of note, nitrotyrosine levels were seen even after shorter exposure times. The antioxidants superoxide dismutase (SOD), which catalyzes superoxide to peroxide, and catalase, which forms oxygen and water from peroxide after its generation by SOD, were decreased in bladders of the study participants after assessing messenger RNA (mRNA) expressions and polymerase chain reactions. In fact, expression levels of some of the antioxidants were as low as 40% less in those treated with ketamine for 1 month compared with controls. The investigators even reported significantly increased expressions of certain mitochondrial respiratory enzyme complexes that contribute to the generation of reactive oxygen species in those treated with ketamine, suggesting a potential role of the generation of these toxic molecules secondary to ketamine use.

## INFLAMMATION

Treating ketamine's destruction of the lower urinary tract tends to be empiric and is usually similar to BPS/IC,<sup>25,90,91</sup> although some potential strategies do exist. For example, interest in anti-inflammatory therapies has surfaced given the inflammatory histologic and cystoscopic findings. In a retrospective study, Lin and colleagues<sup>24</sup> performed urothelial biopsies on 23 Taiwanese patients with a self-reported history of ketamine abuse and confirmed cystitis. The samples were then immunostained to assess for cyclo-oxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), matrix metalloproteinase-9, mammalian target of rapamycin, and phosphorylated 40s ribosomal protein S6 (Phos-S6). The investigators stratified the degree of inflammation as mild, moderate, or severe. The immunostains were all positive. The investigators also noted immunopositive stains in vessel walls and smooth muscle. Of note, the amount of COX-2 differed significantly between the different levels of inflammation, with the amount of COX-2 proportional to the degree of inflammation. The amount of iNOS staining differed significantly between the different degrees of inflammation in smooth muscle tissue only. There was also a positive correlation between the amount of inflammation and Phos-S6 ( $P = .001$ ). Juan and colleagues<sup>90</sup> also found that COX-2 is upregulated in the tissue of lower urinary tracts exposed to ketamine and one of its metabolites norketamine, facilitated by the transcription factor nuclear factor kappa light chain enhancer of activated B cells (NF- $\kappa$ B). The investigators divided 36 rats into 3 groups, receiving saline, ketamine with the COX-2 inhibitor parecoxib, or ketamine alone, all intraperitoneally. The investigators found that in the group treated with ketamine alone, detrusor hyperactivity, reduced bladder capacity, and increased interstitial fibrosis, as well as increased mRNA and protein levels of NF- $\kappa$ B and COX-2, were higher compared with controls. These effects were not as pronounced in the group receiving ketamine with the COX-2 inhibitor. Because of the above findings, these investigators and others<sup>22</sup> have questioned the role that anti-inflammatory drugs may play in ketamine cystitis.

## TREATMENT AND ABSTINENCE

Formal approaches to treatment (including abstinence<sup>76</sup>) of ketamine-associated lower urinary tract dysfunction have been explored in an attempt to halt or reverse the detrimental impact that ketamine has on the urinary tract. Yee and colleagues<sup>25</sup> examined a 4-tier treatment approach in 463 patients with ketamine lower urinary tract



dysfunction who presented to their institution between December 2011 and June 2014. Follow-up data were present for approximately 68.9%. First-line therapy included nonsteroidal anti-inflammatory drugs (NSAIDs) and anticholinergics. Phenytoin and paracetamol were used for analgesia in this tier. Opiates and pregabalin were second-line treatments. Eight weeks of intravesical therapy with sodium hyaluronate was considered third-line therapy. If symptoms were still severe and patients could maintain ketamine abstinence for 6 months, surgical therapy to include hydrodistention or augmentation cystoplasty was considered the last line of therapy. On the first visit, serum creatinine, uroflowmetry, and urinalysis and culture were performed. Functional bladder capacity (FBC) was also calculated. The investigators assessed patient symptoms using the pelvic pain and urgency or frequency score (PUF) and EuroQol visual analog scale (EQ VAS). Ultrasonography of the urinary tract was used to assess for obstructive uropathy. The patients were further subdivided into 3 groups based on abstinence. Group 1 became abstinent before attending the clinic; group 2 patients became abstinent after attending the clinic, and patients in group 3 were active ketamine users at last follow-up. Mean follow-up was  $10.7 \pm 8.5$  months. Two hundred ninety patients underwent first-line therapy, and 42 patients had second-line therapy with significant improvements in PUF, EQ VAS, and FBC. The amount of ketamine used and abstinence status were significant predictors of first-line treatment failure on multivariate analysis. A total of 17 patients required third-line therapy; however, only 8 completed the treatment. Of these patients, 5 were able to decrease the amount of PO medications taken. One patient underwent hydrodistention and another had an augmentation cystoplasty. Overall, the investigators reported 109 adverse effects, primarily secondary to anticholinergics. The investigators conclude that NSAIDs and anticholinergics in conjunction with abstinence from ketamine could potentially be an effective treatment for ketamine-associated urinary dysfunction.

## STAGING

Some investigators have even postulated a clinical staging system to classify patients with ketamine-associated dysfunction of the urinary tract with implications for treatment. Wu and colleagues<sup>91</sup> retrospectively examined 81 hospitalized patients with ketamine-associated urinary dysfunction from January 2008 to June 2014. Patients were stratified into 3 stages based on history of ketamine use, approximate amount, renal and liver function, bladder wall thickening, decreased bladder capacity, ureteral wall thickening, ureteral dilation, and hydronephrosis. The 3 stages included I, inflammatory stimulation; II, initial bladder fibrosis; and III, end-stage bladder fibrosis and contracture. Voided volume, micturition interval, nocturnal void frequency, and symptom assessment scores were evaluated after treatment. Stage I patients received behavioral modification treatment to include cessation of ketamine, dietary restrictions, and bladder training. Medical therapy for patients in this stage included antibiotics, glucocorticoids, antihistamines, antioxidants, and anticholinergics. Stage II patients received intravesical hydrodistention with heparin, lidocaine, and sodium bicarbonate. Stage III patients received augmentation cystoplasty or cystectomy with urinary diversion if medical therapies and/or hydrodistention failed. Of note, stage II and III patients with ureteral strictures and hydronephrosis received ureteral stents. In total, there were 24, 47, and 10 patients in stages I, II, and III, respectively. All patients in each stage demonstrated statistically significant improvements in void volume, micturition interval, nocturnal void frequency, and symptom scores. The investigators conclude that their staging system may serve as a tool for assessing progression of ketamine-associated urinary tract

dysfunction progression and stage-based treatment that could avoid inappropriate interventions.

### **PROPOSED INITIAL ASSESSMENT/LABORATORY ASSESSMENT OF KETAMINE**

Although no specific algorithm for the assessment and management of ketamine abusers exists, the authors would like to propose a reasonable strategy based on the literature presented in this work. As with other medical conditions, management should start with a history and physical examination. With respect to the history, a thorough substance use and abuse history and psychiatric assessment should be obtained in a nonjudgmental manner. Clinicians should ascertain the formulation of ketamine used, duration of use, frequency, and any use of other illicit substances. Any lower urinary tract symptoms such as hematuria, dysuria, frequency, urgency, incomplete emptying, or other obstructive symptoms should be noted. Any abnormal weight loss or other constitutional symptoms, especially in the setting of a tobacco use history, should be part of the assessment because urothelial cancer may also present with similar lower urinary tract symptoms. A validated symptom assessment may be helpful in characterizing the patient's symptoms. For the physical examination, a thorough skin assessment to identify any needle tracks, a focused abdominal examination (to assess suprapubic tenderness and distention and costovertebral tenderness) and genitourinary examination should be performed.

Clinicians should also obtain serum and urine studies to include comprehensive metabolic panel, human immunodeficiency virus testing (with patient consent), urinalysis with microscopy, and urine culture, and should strongly consider urine cytology. In addition, detecting ketamine or its metabolites in biologic fluid specimens can be an important part of the workup, especially in facilities with the capabilities to do so and with patients who endorse recent use. Many techniques for detection of ketamine and its metabolites have been used; however, they can be expensive, labor intense, and time consuming. These techniques also require organic solvents that can have an adverse impact on the environment. Moreno and colleagues<sup>42</sup> provide a validated, accurate, and precise method of detection using a combination of MEPS and GS-MS to detect ketamine and norketamine in blood and urine from small quantities with high recoveries. The methods outlined in their paper can serve as a method for the detection of ketamine and/or its metabolite(s) in suspected users. Please refer to the referenced paper for specific details of the procedure.

Mid and upper tract imaging is likely to be helpful, so the treating health care provider can consider obtaining an imaging study when no recent one is available (renal/bladder ultrasound or CT scan, preferably a CT urogram, especially if the patient has gross hematuria or >3 red blood cells per high power field on urinalysis; if patient has an iodinated contrast allergy or other contraindication to obtaining a CT scan, an MR urogram can be considered). Once the above steps are taken, the patient should then be referred to a urologist for a cystoscopic evaluation and urodynamics evaluation (to include uroflowmetry).

If the patient has any evidence of chronic kidney disease, clinicians should consider involving a nephrologist. Mental health counseling should be considered for addiction and substance abuse, and patients should be offered abstinence resources. A pain specialist may also play a role in the management of these patients. For symptomatic relief, clinicians can consider oxybutynin or mirabegron (consider prescribing after urodynamics evaluation), pain control with NSAIDs, COX-2 inhibitors, pregabalin, phenazopyridine, and/or opiates assuming no contraindications. For more refractory cases, urologists can consider intravesical therapies such as lidocaine and

hydrodistention (similar to that recommended for BPS as per the American Urological Association guidelines). In rare cases, the urologist can consider augmentation cystoplasty.

## SUMMARY

In conclusion, the abuse of the anesthetic ketamine is becoming more prevalent recreationally. The inappropriate use of ketamine presents a great dilemma to the urologist because of its negative impact on the urinary tract. From a clinical standpoint, the symptoms produced as a result of ketamine-associated lower urinary tract dysfunction mimic the common chronic pain syndrome called BPS/IC. BPS/IC is a very complex disease, and ketamine abuse is also complex. As a result, the treating physician must effectively integrate multiple aspects of the patient to ensure that the patient is being appropriately treated. Ketamine causes severe destruction to the urinary tract, specifically the bladder, ureters, and kidneys. Most patients are young and go on to develop debilitating changes to the urinary tract that can be demonstrated clinically through symptom score instruments, radiographically, and on cystoscopic and video-urodynamic studies. Inflammatory and apoptotic changes can also be seen histologically. End-stage renal disease from upper tract obstruction is another very real threat to chronic ketamine users.

The literature regarding ketamine's 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, and although unfortunate, as illicit ketamine use increases. One would presume that fibrosis is generally a permanent anatomic and functional alteration; however, ketamine abstinence does seem to have promising results with respect to prevention of progressive dysfunction. Whether abstinence can induce total reversal of the signs and symptoms of ketamine-associated lower urinary tract changes remains to be seen. What is clear is that ketamine use should be assessed and remain on the list of differential diagnoses in any patient presenting with lower urinary tract symptoms, cystometric findings suggestive of bladder dysfunction, and suspicious mid and upper tract radiographic findings.

Ketamine's deleterious impact of the urinary tract is a serious matter with an end result of poor quality of life, chronic pain, and even end-stage renal disease. By keeping this entity at the forefront of clinical suspicion in the appropriate situation, ketamine-associated urinary tract dysfunction can be identified, and it is hoped, halted in its tracks. Ketamine abuse as a cause of urinary dysfunction requires a multidisciplinary effort, because the psychosocial aspects of drug abuse and addiction need to be addressed along with the urologic aspects. More work needs to be done to better understand the natural history of the lower urinary tract dysfunction, progression, treatment, and prevention of ketamine-induced cystitis.

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