In this issue of *Urological Science*, Ma and Chu have given a timely review on the current knowledge and burden of ketamine cystitis. Since 2007, when the earliest reports appeared on bladder dysfunction and cystitis associated with recreational ketamine use, our understanding of the problem has grown, but not substantially. Several fundamental questions remain unanswered.

One important lesson we have learned from clinical experience is that the disease is not confined to the bladder, but may involve the upper urinary tract. In one study, computed tomography urography revealed that up to 44% of patients had hydronephrosis. Shahani et al first coined the term “ketamine-induced ulcerative cystitis”; however, the simpler term “ketamine cystitis” has gained greater popularity. Neither of these two terms can adequately describe the possible extent of the disease. Another term has also been proposed: “ketamine-induced uropathy.” Thus, a consensus is needed for naming the disease. For the time being, I would think the term “ketamine uropathy” (KU) is simple and appropriate.

Research into KU pathophysiology suggests the involvement of various pathways and mechanisms such as inflammation, nerve dysfunction, epithelial barrier impairment, immunological reaction, microvascular injury, oxidative stress, and apoptosis. However, it is more important to know how the disease begins than how it progresses. The disease process of KU may bear many similarities to other chronic inflammatory or pain disorders, but its etiology should be unique. The toxic effects of ketamine and its metabolites norketamine and hydroxynorketamine have been postulated as the initiating event. However, this assumption has one drawback: if toxicity is the sole cause, how do we explain that only approximately one-quarter of users experience urinary symptoms? Of course, one possible explanation is that there are ketamine dose or duration thresholds that must be achieved for toxic effects to occur. However, such evidence is lacking to date. Therefore, future epidemiology studies should aim to analyze the relationship between various parameters of ketamine usage and the occurrence of KU. We should look with more interest for heavy ketamine users who do not have KU. If indeed such people do exist, we should study them carefully to understand the underlying protective mechanisms.

Another point worth pondering concerning KU etiology is that to date the disease is reported only in relation to recreational use, not clinical use. Long-term ketamine administration is clinically provided to patients with chronic pain or psychological disorders. The adverse effects of ketamine reported in clinical studies include psychedelic effects (e.g., hallucinations, memory defects, panic attacks), nausea or vomiting, somnolence, cardiovascular stimulation and, in a minority of patients, hepatoxicity. No reports of KU have been reported in patients with clinical ketamine use. Street ketamine is not legally manufactured and we are understandably unsure of its composition. There could be some harmful impurities. Therefore, it is imperative to compare the chemical composition of ketamine from different sources. We may otherwise overlook the real culprit.

Advanced cases of KU are difficult to treat because few effective measures are available. Some patients ultimately need urinary diversion or dialysis. By contrast, milder cases are more treatable, provided the patient can stop using ketamine. Quitting may unfortunately be difficult.

One of my patients is a young female sex worker who experiences severe pain during intercourse. My prescriptions did not help; therefore, her only solution has been to use ketamine during her working hours. Some KU patients come to the hospital. However, after they leave, they enter an environment where there is no escape from ketamine. These patients need more than lifestyle modification; they need life modification. Therefore, KU is more than a medical problem; it is also a social problem. It is a good sign that some governments and nongovernmental organizations are taking the initiatives to tackle the problem.

After joining a Christian fellowship, a male patient of mine successfully quit his 14-year ketamine snorting habit. He achieved a dramatic improvement in symptoms. The disease can be and should be terminated. When the abuse stops, the disease stops. We hope KU will someday be just an historical term in our medical literature.

**Conflicts of interests**

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