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Delayed Urinary Symptoms Induced by Ketamine

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ABSTRACT

One of the side-effects of ketamine abuse is genito-urinary damage. This report describes a case of a former ketamine user who presented with urinary symptoms associated with ketamine years after stopping consumption. This was a 26-year-old male with a history of ketamine abuse. He started treatment for alcohol dependence at age 19. He smoked marijuana daily and denied any other drug use. During the follow-up, urinary symptoms were evidenced (dysuria, frequency, urgency, incontinence, nocturia, hematuria, and suprapubic pain). Urinary symptoms started two years ago and worsened over time. The patient was referred to a urologist. A cystoscopy revealed lesions compatible with interstitial cystitis like the ones that appear in some ketamine abusers. Given the medical history, the urologist asked him about ketamine consumption and the patient declared a daily use of 50 milligrams intranasally from age 15 to age 17. Given these findings, not reported previously in the medical literature, future research should follow up patients who at some point in their life made an abusive consumption of ketamine in order to understand the pathogenesis and to be able to intervene before clinical disease manifests itself.

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Ketamine is a non-competitive antagonist of a N-methyl-d-aspartate (NMDA) receptor first synthesized in 1962 as a safer alternative to phencyclidine (PCP), previously used as a sedative drug in surgical procedures (Sassano-Higgins et al. 2016), but it is known that non-medical use of ketamine has grown in recent decades around the world (Liu et al. 2016; Bokor and Anderson 2014; Chakraborty, Neogi, and Basu 2011; Liu, Lian, and Zhao 2006).

The prevalence of ketamine misuse worldwide is unknown, and is variable from one country to another. According to the latest data from the World Health Organization (2012), ketamine use is common in the U.K., Australia, the U.S., Hong Kong. and Taiwan, putting special emphasis on Asian countries.

Effects pursued by ketamine misusers include a sense of well-being, psychedelic experiences, or increased perceptions (Copeland and Dillon 2010). Nonetheless, there are several complications related to ketamine abuse, including psychological effects (psychotic-like symptoms and mood disturbances) and physical symptoms (brain atrophy, cholestasis, liver fibrosis, or genitourinary damage) (Dalgarno and Shewan 1996; Liao et al. 2011; Martin and Dolengevich 2015).

Ketamine-induced genito-urinary dysfunctions

One of the side-effects of ketamine abuse, and one of the main concerns for physicians, is damage to the genito-urinary system. Depending on the studies, around 20–50% of ketamine users suffer from symptoms at this level (Chen, Huang, and Lin 2014; Muetzelfeldt et al. 2008; Winstock et al. 2012).

The most frequently reported symptoms are dysuria/burning sensation, frequency, urgency, lower abdominal or perineal pain, urinary incontinence, nocturia, or even gross hematuria (Chen et al. 2011; Mason et al. 2010; Shahani et al. 2007; Storr and Quibell 2009; Winstock et al. 2012; Yek et al. 2015). There have also been reported cases of sexual dysfunction associated with ketamine abuse (Jang et al. 2012; Suppiah et al. 2016).

The histopathological examination may show urothelial ulceration with reactive changes, inflammatory cell infiltration and mast cells, granulation tissue, ureter wall thickening, apoptosis signs (Baker et al. 2016; Jhang, Hsu, and Kuo 2015; López-Beltran et al. 2017; Wei et al. 2013), and bladder fibrosis with lower volume in late stages (Tsai, Birder, and Kuo 2016). Patients could even present with vesico-ureteric reflux hydronefrosis and kidney failure, and radical surgical

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procedures may be required (Middela and Pearce 2011; Chu et al. 2008; Selby et al. 2008)

Several hypotheses based on findings try to explain the etiopathogenic mechanism, such as direct toxicity, oxidative stress, microvascular changes, or indirect autoimmune reaction (Baker et al. 2016; Tsai and Kuo 2015; Chu et al. 2008; Jhang, Hsu, and Kuo 2015; Wu et al. 2012)

Frequency of abuse, dose of the drug, and time of consumption seem to be associated with the onset of the symptoms and the evolution of the disease, even though personal variability has been assessed (Cottrell et al. 2009; Winstock et al. 2012). Tissue changes and genito-urinary symptoms could be irreversible (Chung, Wang, and Kuo 2014; Mak et al. 2011; Middela et al. 2011; Winstock et al. 2012), and quality of life could be affected to a severe degree (Wei et al. 2013).

Surgical and pharmacological approaches (cystoplasty, distention, partial cystectomy, opiates, pregabalin, duloxetine, tricyclic antidepressants, anticholinergics, anti-inflammatory drugs) have been tried in order to relieve some symptoms (Chao and Shai 2010; Jhang et al. 2016; Yee et al. 2015; Yek et al. 2015), but until now, the most important solution has been to achieve total abstinence (Winstock et al. 2012; Zeng et al. 2015), so urologists recommend that patients stop using ketamine, but compliance is difficult and continued consumption may lead to a worse evolution of the disease (Chen, Chen, and Huang 2009; Chu et al. 2008; Selby et al. 2008). Around 50% of patients who achieve abstinence reported progressive improvement in urinary symptoms, but a group of patients suffered clinical progression of the disease (Mak et al. 2011; Winstock et al. 2012).

Ketamine damage in the urinary tract is underdiagnosed (Lai et al. 2012), and is almost unknown to many of the professionals who treat addictions. We report a case of a former ketamine user treated in an outpatient drug clinic who presented with urinary symptoms associated with ketamine years after stopping consumption.

Case report

We describe the case of a 26-year-old male with a history of ketamine abuse. The patient was unmarried and without children. He finished compulsory education and started to work as a parking driver, without a driving licence. He was the oldest of four brothers, all of whom were diagnosed with substance use disorders. His father was an alcohol-dependent patient who died from hepatocarcinoma when the patient was six years old, and his mother was alive but had serious injuries due to intravenous heroin use for years (Human Immunodeficiency Virus [HIV], Hepatitis C Virus). He denied drug allergy reactions in the past. When questions about somatic diseases, he reported asthma when he was a child, but now receives no treatment for this disease. Two years ago, he was hospitalized due to an overdose of cocaine and heroin, which did not respond to Naloxone. He was in the hospital for two weeks and was diagnosed with HIV and cirrhosis. He reported no prior psychiatric hospitalizations, suicidal ideation, or attempts.

The patient started an outpatient treatment for his alcohol dependence at the age of 19. He started drinking at 15 with a binge drinking pattern and, when he was 16, he drank two bottles of wine and half a bottle of whisky daily. He smoked marijuana every day (3–4 cigarettes), starting at the age of 16. He denied any other drug use, except cocaine once during a party. When he was 19, he lost his job and his girlfriend, so he decided to start treatment for alcohol dependence. Urine tests, conducted three times a week, were negative for all drugs tested.

When he started treatment, he was anxious and in distress due to relational factors. He had good self-care and he was showing a good physical aspect. His discourse was correct and lineal, and there was no evidence of delusional ideas or disturbances in the flow of thought. He reported feeling a bit depressed, but his humor was appropriate. No emotional lability was observed. He denied suicidal ideations. He didn't show sensoperceptive alterations and his judgment of reality was preserved.

During the follow-up treatment, urinary symptoms were evidenced as dysuria, frequency, urgency and urinary incontinence, nocturia, isolated episodes of gross hematuria, and suprapubic pain. The patient complained about urinary symptomatology which started two years ago in the shape of frequency and urgency, and worsened over time. He denied risky sexual behavior and, after a physical and analytical exploration with serology, sexually transmitted diseases were ruled out.

After excluding venereal diseases and the persistence of the urinary symptomatology, the patient was referred to the Urology Service. The patient was doing up to 6 micturitions per hour. Visual examination with a cystoscope revealed bladder inflammation and biopsies verified that the patient had lesions compatible with interstitial cystitis with areas of denuded mucosa, superficial edema, and abundant vascularization. Neutrophilic leukocyte infiltrates were observed. Ultrasonography study of the upper urinary tract revealed small bladder capacity and unilateral hydronephrosis. Given the medical history, the urologist asked him about ketamine consumption and the patient declared a daily use of 50 milligrams of ketamine intranasally from age 15 to age 17. The patient was diagnosed with ketamine-associated cystitis.

Discussion

Given these findings, not reported previously in the medical literature, future research should follow patients who, at some point in their life, abused ketamine in order to understand the pathogenesis of the disease and to be able to intervene before clinical disease manifests itself. The establishment of symptoms of cystitis without known bacterial or medical causes should raise the concern of cystitis associated with ketamine as a differential diagnosis. For this, it is advisable to take into account the clinical pathway for management of ketamine cystitis patients published by Ma and Chu (2015).

In the present case, urinary symptoms appeared despite the cessation of ketamine consumption. Winstock et al. (2012), in their study of a ketamine-consuming population, reported that 43% of the patients who stopped consuming had the same symptoms and 3.8% presented a progressive deterioration, suggesting that, in some cases, once the disease is established, it could be maintained or even progress. Early diagnosis could prevent or delay the pathology (Mak et al. 2011; Wei et al. 2013; Mason et al. 2010). In this case, the stated hypothesis is the existence of a subclinical but progressive disease whose symptoms could appear years after the cessation of consumption, but this new syndrome requires further animal studies to investigate the underlying pathophysiology (Chu et al. 2008). It would also be interesting to investigate why the effects did not occur during the ketamine consumption, but years after ending it.

Treatment and rehabilitation centers for drug-dependent patients should take into account the possibility of developing collateral damage at the urinary tract in ketamine-consuming patients. During the clinical interview, it is important for the clinician to ask the patient about possible urinary discomfort (dysuria, frequency, suprapubic pain), advise the patient about making a voiding diary, and request an initial analysis for monitoring renal function (Middela et al. 2011; Shahani et al. 2007).

If the symptoms suggest the presence of this pathology, we recommend referring the patient to a urologist. It is also important that the urologist inquires about substance use and is able to refer the patient to a drug-addiction center, given that the cessation of ketamine use is the paradigm of the treatment (Jhang et al. 2016; Jhang, Hsu, and Kuo 2015; Mak et al. 2011; Zeng et al. 2015). However, compliance and cessation of consumption are complicated, especially when withdrawal symptoms appear, such as depression, anxiety, decreased appetite, insomnia, or fatigue (Chao et al. 2010; Chen, Huang, and Lin 2014; Lin, Lane, and Lin 2016).

The prevalence of recreational consumption of ketamine is increasing (Liu et al. 2016; Bokor et al. 2014), and the number of cases of damage to the urinary tract associated with consumption may also increase. A multidisciplinary approach involving psychiatrists, urologists, nurses, social workers, and other health professionals will be necessary to improve the quality of life of these patients and to avoid progression to more severe cases of the disease (Myers, Bluth, and Cheung 2016; Yek et al. 2015; Zhong et al. 2015).

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References

Baker, S. C., S. Shabir, N. T. Georgopoulos, and J. Southgate. 2016. Ketamine-induced apoptosis in normal human urothelial cells: A direct, N-Methyl-d-aspartate receptor-independent pathway characterized by mitochondrial stress. *American Journal Pathology* 186 (5):1267–77. doi:10.1016/j.ajpath.2015.12.014.

Bokor, G., and P. D. Anderson. 2014. Ketamine: An update on its abuse. *Journal of Pharmacy Practice* 27:582–86. doi:10.1177/0897190014525754.

Chakraborty, K., R. Neogi, and D. Basu. 2011. Club drugs: Review of the "rave" with a note of concern for the Indian scenario. *Indian Journal of Medical Research* 133:594–604.

Chao, J. Y., and H. A. Shai. 2010. Duloxetine treatment of long-term ketamine abuse-related lower urinary tract symptoms: A case report. *General Hospital Psychiatry* 32 (6):647. doi:10.1016/j.genhosppsych.2010.06.009.

Chen, C. H., M. H. Lee, Y. C. Chen, and M. F. Lin. 2011. Ketamine-snorting associated cystitis. *Journal of Formosan Medical Association* 110 (12):787–91. doi:10.1016/j.jfma.2011.11.010.

Chen, L. Y., K. P. Chen, and M. C. Huang. 2009. Cystitis associated with chronic ketamine abuse. *Psychiatry and Clinical Neuroscience* 63 (4):591. doi:10.1111/j.1440-1819.2009.01972.x.

Chen, W. Y., M. C. Huang, and S. K. Lin. 2014. Gender differences in subjective discontinuation symptoms associated with ketamine use. *Substance Abuse Treatment, Prevention and Policy* 22:9–39.

Chu, P. S., W. K. Ma, S. C. Wong, R. W. Chu, C. H. Cheng, S. Wong, J. M. Tse, F. L. Lau, M. K. Yiu, and C. W. Man. 2008. The destruction of the lower urinary tract by

ketamine abuse: A new syndrome? *BJU International* 102 (11):1616–22. doi:10.1111/j.1464-410X.2008.07920.x.

Chung, S. D., C. C. Wang, and H. C. Kuo. 2014. Augmentation enterocystoplasty is effective in relieving refractory ketamine-related bladder pain. *Neurourology and Urodynamics* 33 (8):1207–11. doi:10.1002/nau.22477.

Copeland, J., and P. Dillon. 2005. The health and psychosocial consequences of ketamine use. *International Journal of Drug Policy* 16:122–31. doi:10.1016/j.drugpo.2004.12.003.

Cottrell, A., K. Warren, R. Ayres, P. Weinstock, and D. A. Gillatt. 2009. The relationship of chronic recreational ketamine use and severe bladder pathology: Presentation, management of symptoms and public health concerns. *European Urology Supplement* 8:170. doi:10.1016/S1569-9056(09)60202-5.

Dalgarno, P. J., and D. Shewan. 1996. Illicit use of ketamine in Scotland. *Journal of Psychoactive Drugs* 28:191–99. doi:10.1080/02791072.1996.10524391.

Jang, M. Y., C. Y. Long, S. M. Chuang, C. H. Huang, H. Y. Lin, W. J. Wu, and Y. S. Juan. 2012. Sexual dysfunction in women with ketamine cystitis: A case-control study. *BJU International* 110 (3):427–31. doi:10.1111/j.1464-410X.2011.10780.x.

Jhang, J. F., L. A. Birder, M. B. Chancellor, and H. C. Kuo. 2016. Patient characteristics for different therapeutic strategies in the management ketamine cystitis. *Neurourology and Urodynamics* 36 (3):687–91. doi:10.1002/nau.22996.

Jhang, J. F., Y. H. Hsu, and H. C. Kuo. 2015. Possible pathophysiology of ketamine-related cystitis and associated treatment strategies. *International Journal Urology* 22 (9):816–25. doi:10.1111/iju.12841.

Lai, Y., S. Wu, L. Ni, Z. Chen, X. Li, S. Yang, Y. Gui, Z. Guan, Z. Cai, and J. Ye. 2012. Ketamine-associated urinary tract dysfunction: An underrecognized clinical entity. *Urologia Internationalis* 89 (1):93–96. doi:10.1159/000338098.

Liao, Y., J. Tang, P. R. Corlett, X. Wang, M. Yang, H. Chen, and C. Fletcher. 2011. Reduced dorsal prefrontal gray matter after chronic ketamine use. *Biological Psychiatry* 69:42–48. doi:10.1016/j.biopsych.2010.08.030.

Lin, P. C., H. Y. Lane, and C. H. Lin. 2016. Spontaneous remission of ketamine withdrawal-related depression. *Clinical Neuropharmacology* 39 (1):51–52.

Liu, Y., D. Lin, B. Wu, and W. Zhou. 2016. Ketamine abuse potential and use disorder. *Brain Research Bulletin* 126:68–73.

Liu, Z., Z. Lian, and C. Zhao. 2006. Drug use and HIV/AIDS in China. *Drug & Alcohol Review* 25:173–75.

Lopez-Beltran, A., G. P. Paner, R. Montironi, M. R. Raspollini, and L. Cheng. 2017. Iatrogenic changes in the urinary tract. *Histopathology* 70 (1):10–25.

Mak, S. K., M. T. Chan, W. F. Bower, S. K. Yip, S. S. Hou, B. B. Wu, and C. Y. Man. 2011. Lower urinary tract changes in young adults using ketamine. *Journal of Urology* 186 (2):610–14.

Martin Larregola, M., and H. Dolengevich Segal. 2015. Energy drinks o bebidas energéticas. In *Nuevas drogas psicoactivas*, ed. H. Dolengevich Segal. Madrid, Spain: Grupo Editorial Entheos.

Mason, K., A. M. Cottrell, A. G. Corrigan, D. A. Gillatt, and A. E. Mitchelmore. 2010. Ketamine-associated lower urinary tract destruction: A new radiological challenge. *Clinical Radiology* 65 (10):795–800.

Middela, S., and I. Pearce. 2011. Ketamine-induced vesicopathy: A literature review. *International Journal of Clinical Practice* 65 (1):27–30.

Muetzelfeldt, L., S. K. Kamboj, H. Rees, J. Taylor, C. J. Morgan, and H. V. Curran. 2008. Journey through the K-hole: Phenomenological aspects of ketamine use. *Drug and Alcohol Dependence* 95 (3):219–29.

Myers, F. A., Jr, M. H. Bluth, and W. W. Cheung. 2016. Ketamine: A cause of urinary tract dysfunction. *Clinics in Laboratory Medicine* 36 (4):721–44.

Sassano-Higgins, S., D. Baron, G. Juarez, N. Esmaili, and M. Gold. 2016. A review on ketamine abuse and diversion. *Depression and Anxiety* 33:718–27.

Selby, N. M., J. Anderson, P. Bungay, L. J. Chesterton, and N. V. Kolhe. 2008. Obstructive nephropathy and kidney injury associated with ketamine abuse. *Nephrology Dialysis Transplantation Plus* 1 (5):310–12.

Shahani, R., C. Streutker, B. Dickson, and R. J. Stewart. 2007. Ketamine-associated ulcerative cystitis: A new clinical entity. *Urology* 69 (5):810–12.

Storr, T. M., and R. Quibell. 2009. Can ketamine prescribed for pain cause damage to the urinary tract? *Palliative Medicine* 3:670–72.

Suppiah, B., B. Vicknasingam, D. Singh, and S. Narayanan. 2016. Erectile dysfunction among people who use ketamine and poly-drugs. *Journal of Psychoactive Drugs* 48 (2):86–92.

Tsai, Y. C., L. Birder, and H. C. Kuo. 2016. Abnormal sensory protein expression and urothelial dysfunction in ketamine-related cystitis in humans. *International Neurourology Journal* 20 (3):197–202.

Tsai, Y. C., and H. C. Kuo. 2015. Ketamine cistitis: Its urological impact and management. *Urological Science* 25:153–57.

Wai-Kit, M., and C. Peggy. 2015. Burden of ketamine cystitis in Chinese society. *Urological Science* 26:167–73.

Wei, Y. B., J. R. Yang, Z. Yin, Q. Guo, B. L. Liang, and K. Q. Zhou. 2013. Genitourinary toxicity of ketamine. *Hong Kong Medical Journey* 19 (4):341–48.

Winstock, A. R., L. Mitcheson, D. A. Gillatt, and A. M. Cottrell. 2012. The prevalence and natural history of urinary symptoms among recreational ketamine users. *BJU International* 110 (11):1762–66.

World Health Organization (WHO). 2012. Ketamine expert peer review on critical review report. Paper presented at the 35th expert committee on drug dependence, Hammamet, Tunisia, June 4–8 .

Wu, S., Y. Lai, Y. He, X. Li, Z. Guan, and Z. Cai. 2012. Lower urinary tract destruction due to ketamine: A report of 4 cases and review of literature. *Journal of Addiction Medicine* 6 (1):85–88.

Yee, C. H., P. T. Lai, W. M. Lee, Y. H. Tam, and C. F. Ng. 2015. Clinical outcome of a prospective case series of patients with ketamine cystitis who underwent standardized treatment protocol. *Urology* 86 (2):236–43.

Yek, J., P. Sundaram, H. Aydin, T. Kuo, and L. G. Ng. 2015. The clinical presentation and diagnosis of ketamine-associated urinary tract dysfunction in Singapore. *Singapore Medical Journal* 56 (12):660–64.

Zeng, M., L. Huang, Z. Tang, Y. Li, F. Zeng, and R. Xue. 2015. A preliminary study on mechanisms for urinary system disorders before and after ketamine withdrawal in rats. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 40 (3):269–75.

Zhong, D., F. Yu, J. Chen, C. Lin, and H. Luo. 2015. Bladder leiomyosarcoma in a patient with chronic ketamine abuse: A case report. *Canadian Urological Association Journal* 9 (7–8):514–16.