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LETTERS TO THE EDITOR

Reduced functional bladder capacity associated with ketamine use

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Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is a dissociative anesthetic with sedative and analgesic effects that was developed in the 1960s for human and veterinary medicine. More recently, ketamine has been used to treat severe, refractory depression when pharmacotherapy and electroconvulsive therapy are not effective.[1,2] In addition, ketamine is also consumed as drug of abuse, potentially leading to serious and irreversible complications.

Deleterious effects of ketamine on the lower urinary tract were first described in 2007. Since then, urinary, neuropsychiatric, hepatobiliary, and gastrointestinal side effects of ketamine misuse have been reported.[3-5] In the present article, we describe a case of chronic ketamine abuse with irreversible reduction in bladder capacity.

A 32-year-old white male was referred to our service after 4 years of treatment for multiple addictive disorders (cocaine, marijuana, and alcohol). After that treatment, he continued with habitual use of alcohol and occasional use of ecstasy (MDMA). He was introduced to ketamine by friends who described the substance as not properly a drug, since it was freely sold in veterinary pharmacies. He liked the psychopharmacological effects of ketamine, which was quickly elected as his drug of choice. He turned the liquid anesthetic into powder and snorted it, consuming up to 3 vials a day.

Painful urination developed following daily use of ketamine. During the last year before treatment at our service, urinary symptoms progressed gradually into lumbar and supra-pubic pain, polyuria, urinary urgency, nocturia, and episodes of macroscopic hematuria. A voiding diary confirmed a functional capacity of 74.88 mL, with intervals of less than 1 hour between urinations. Urinalysis demonstrated hematuria and pyuria with no bacterial growth. Polymerase chain reaction (PCR) and culture for *Mycobacterium tuberculosis* were negative. Ultrasound revealed thickening of the bladder wall and trabeculation with bilateral ureteropyeloectasia. Magnetic resonance imaging (MRI) demonstrated intra and extrahepatic biliary ectasia and moderate bilateral hydronephrosis with bladder wall thickening.

Urodynamic assessment was prevented by pain. Cystoscopy revealed reduced bladder capacity, signs of fibrosis, and bladder mucosal inflammation. On pathology, chronic inflammatory exudate containing fibrin and neutrophils as well as PAS- positive macrophages was detected. Acid-fast positive organisms and mast cells were not identified in the specimen. Despite medical warnings, the patient was unable to abstain from ketamine and did not respond to antimuscarinics. Cyclosporine (2 mg/kg/day for 6 months) was prescribed to reduce the immune inflammatory/fibrotic response. The patient was admitted to a specialized service to treat the chemical dependence. In the second week of hospitalization, hematuria declined, but the reduced functional capacity of the bladder persisted.

Urinary tract symptoms are estimated to affect more than 20% of people who use ketamine for recreational purposes.[4] A possible explanatory mechanism is an inflammatory response triggered by chemical irritation in the urothelium caused by ketamine and its metabolites. The most frequent signs and symptoms are dysuria, supra-pubic pain, increased urinary frequency, urinary urgency, nocturia, and hematuria. With prolonged exposure to the drug, a decrease in bladder capacity may also occur, with vesicoureteral reflux and unilateral or bilateral hydronephrosis, leading to irreversible renal damage. Urodynamic studies demonstrate high pressure and low bladder capacity with cystoscopic findings of ulcerative cystitis with inflammation and epithelial denudation. Histopathological examination shows ulceration of the urothelium, chronic inflammatory infiltration, granulation tissue, and thickening of the ureteral and bladder wall.[4,5]

Many health care professionals are still unaware of this new clinical entity, i.e., reduced functional bladder capacity. Psychiatrists should be alert to the devastating potential of ketamine for the urinary tract. Gastroenterologists should consider ketamine abuse in a setting of biliary ectasia without an obstructive cause. Urologists and nephrologists should consider this hypothesis in patients with a history of drug abuse and lower urinary tract symptoms in the absence of another etiology. In the present patient, the impaired storage capacity of the bladder and the resulting hydronephrosis indicate the necessity of bladder augmentation (enterocystoplasty). Although other treatments may relieve the symptoms, drug withdrawal is pivotal.

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Disclosure

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Long-term response to cathodal transcranial direct current stimulation of temporoparietal junction in a patient with refractory auditory hallucinations of schizophrenia

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Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that alters the neuronal membrane resting potential by sending a continuous electric current between two electrodes (cathode and anode) placed over the scalp, leading to changes in motor-cortical excitability.[1] Given the neuromodulatory effects of tDCS, the applicability of this technique has been tested for different clinical entities, such as ultra-treatment resistant hallucinations in schizophrenia.[2,3]

The main mechanisms of tDCS modulation have been linked to the action of N-methyl-D-aspartate (NMDA) receptors, especially with regard to post-stimulation effects, which may also be influenced by neuromodulators such as serotonin, dopamine, adrenaline, GABA, and acetylcholine. Furthermore, it is believed that the NMDA receptor plays a central role in the induction of neuroplasticity, and that NMDA modulation by tDCS produces remission of long-term symptoms.[4]

In our research, we search for a long-term effect of tDCS on auditory hallucinations, which if confirmed could suggest long-term modulation of NMDA receptors. Thus, the present case report describes the use of a stimulation protocol as adjuvant treatment for an ultra-treatment resistant schizophrenic patient.

A 28-year-old white man with a 22-year DSM-V diagnosis of schizophrenia was admitted to a psychiatric inpatient unit with auditory hallucinations, persecutory delusions, and severe psychomotor agitation. The initial prescription included haloperidol tapered up to 20 mg/day, and up to 6 mg/day of risperidone in multiple daily doses (twice in a day). Unfortunately, the use of both medications led to neuroleptic malignant syndrome. After recovery from this clinical condition, the patient was switched to clozapine up to 400 mg/day. Because the auditory hallucinations persisted, a course of 12 electroconvulsive sessions was indicated, with no response.

Because the residual symptoms of auditory hallucinations strongly impacted the patient's overall functioning, he made the decision to try an off-label tDCS protocol. The protocol consisted of two 20-minute stimulation

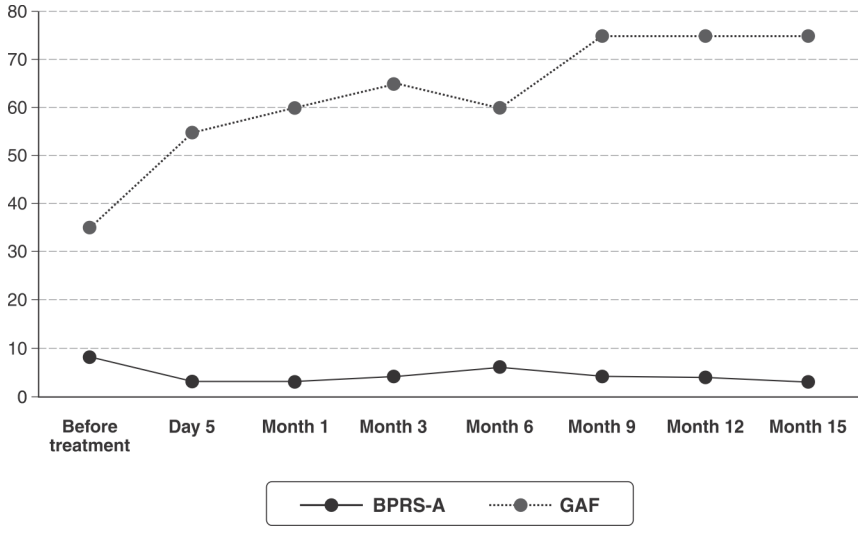

Figure 1 Clinical progress measured by BPRS-A and evaluation of overall functioning measured by GAF. Note the robust post-intervention response in both psychometric scales; the effect was maintained during the 15 months of follow-up. BPRS-A = Brief Psychiatric Rating Scale-Anchored; GAF = Global Assessment of Functioning.