ORIGINAL ARTICLE

Urinary symptoms and impaired quality of life in female ketamine users: persistence after cessation of use

CME

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Objective To compare the urinary symptoms and quality of life in ex–ketamine abusers and controls.

Design Prospective observational study.

Setting A hospital in Hong Kong.

Patients Female ex–ketamine abusers admitted to a local drug rehabilitation centre and age-matched controls attending a general gynaecology clinic between December 2009 and April 2010.

Main outcome measures Evaluation of urinary symptoms based on a 3-day bladder diary, and responses to the Urogenital Distress Inventory Short Form (UDI-6) and the Incontinence Impact Questionnaire Short Form (IIQ-7). The study group had repeat measurements 3 months later.

Results Overall, 90% of ex–ketamine abusers had active urinary symptoms. On average, they had increased 24-hour urinary frequency (10.0 vs 5.8; P=0.001) and lower maximum voided volume (253.3 mL vs 401.9 mL; P<0.001) compared to controls. Correspondingly, the median functional bladder capacity was smaller (195.3 mL vs 261.2 mL; P=0.011) and the mean UDI-6 and IIQ-7 scores were higher (P<0.001). Among those who abused ketamine for 2 years or more, the mean UDI-6 and IIQ-7 scores were higher (P=0.03, P=0.02 respectively). When they stopped abusing ketamine for 3 months or more, their mean 24-hour urinary frequency had decreased (P=0.03), the maximum voided volume had increased (P=0.03) and the mean UDI-6 and IIQ-7 scores had decreased (P=0.04, P=0.02 respectively), although they were still higher than in controls. After 3 more months, in the ex–ketamine abusers there had been a further decrease in 24-hour urinary frequency (P=0.01) and a further improvement in quality of life based on mean UDI-6 scores (P=0.04) but nevertheless poorer than the control group (P<0.01).

Conclusion Female ex–ketamine abusers had significant urinary symptoms affecting their quality of life when studied at a mean of 8 (range, 0.5-48) months after cessation of use. The symptom severity was inversely correlated with the duration of cessation; though they improved with time, some still persisted.

New knowledge added by this study

- Urinary symptoms are common in ex–ketamine users and affected up to 90% of persons we studied.
- Subjects who had stopped ketamine use for 3 months or more had significantly fewer urinary symptoms than those who had stopped for less than 3 months; persons who had abused ketamine abuse for 2 years or more and ceased for less than 3 months endured significantly poorer quality of life (QoL).
- Both urinary symptoms and QoL of the study group had improved 3 months after the first consultation, but continued to be inferior to those of controls.

Implications for clinical practice or policy

- A history of ketamine abuse should be explored in patients with lower urinary tract symptoms.
- Early cessation of ketamine is the key to improving the associated urinary symptoms and the QoL.
- Although complete recovery as compared to the controls was not evident even 6 months after cessation of ketamine abuse, significant progressive improvement was demonstrated.

Key words
Female urogenital diseases; Ketamine; Quality of life; Substance-related disorders; Urinary incontinence

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氯胺酮女性濫用者停止濫藥後的排尿症狀及生活質量持續受損的情況

目的 比較曾是氯胺酮濫用者及對照組於排尿症狀及生活質量的情況。

設計 前瞻性觀察研究。

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患者 研究對象為2009年12月至2010年4月期間入住本地一所戒毒康復中心的氯胺酮前濫用者，而對照組則是同期於一婦科診所求診的病人。

主要結果測量 根據為期三天的小便日誌而評估的排尿症狀，以及參與者填寫的生殖困擾量表簡易版（UDI-6）及尿失禁影響問卷簡易版（IIQ-7）的結果。氯胺酮前濫用者於三個月後再次進行量度。

結果 九成的氯胺酮前濫用者持續出現排尿症狀。與對照組比較，氯胺酮前濫用者有較高的24小時尿頻率（10.0比5.8；P=0.001）及較低的最大排尿容量（253.3 mL比401.9 mL；P<0.001）；她們的功能性膀胱容量中位數相對較少（195.3 mL比261.2 mL；P=0.011），UDI-6及IIQ-7平均分數亦相對較高（P<0.001）。曾濫用氯胺酮兩年或以上的女性，其UDI-6（P=0.03）及IIQ-7（P=0.02）平均分數較高。當停止服用氯胺酮三個月或以上，她們的24小時尿頻率減少（P=0.03），最大排尿容量增加（P=0.03），而UDI-6（P=0.04）及IIQ-7（P=0.02）平均分數也減少；可是與對照組比較，氯胺酮前濫用者的讀數仍然偏高。再過三個月後，她們的24小時尿頻率進一步減少（P=0.01），其UDI-6分數亦顯示她們的生活質量進一步改善（P=0.04），但結果仍然較對照組差（P<0.01）。

結論 氯胺酮女性濫用者在停止濫藥平均8個月後（介乎0.5-48個月），其排尿症狀明顯地持續影響她們的生活質量。症狀嚴重程度與停止濫藥時間的長短呈負相關。雖然停止濫藥後，排尿症狀有所改善，可是部分症狀仍然會持續出現。

Introduction

Ketamine is a non-competitive glutamate N-methyl-d-aspartate receptor antagonist with well-documented safety in medical and veterinary settings. The recreational use of ketamine was first reported in 1971 in North America, and since then has gained in popularity; in Hong Kong it overtook ecstasy in 2001 to become the commonest abused psychotropic drug.[1] Abusers of the drug consider it to be a short-acting psychotropic agent with a wide margin of safety and low potential for dependence and minimal long-term side-effect. The major concern about ketamine intake was its immediate acute effect,[2] while most reports of long-term morbidity have focused on neurological sequealae.[3] However, severe lower urinary tract symptoms including urinary frequency, urgency, and dysuria have been reported to ensue in active ketamine abusers. Active ketamine use has also been associated with cystitis and contracted bladders and even been implicated in irreversible secondary renal damage (hydronephrosis and deranged renal function).[4,5] However, to what extent if any of these adverse effects were reversible after cessation of the drug was unclear. The association between the dosage and duration of previous ketamine use and such symptoms was also poorly understood. Furthermore, the impact of these symptoms on the quality of life (QoL) of the abusers has not been well evaluated.

The objective of our study therefore was to determine the effect of ex–ketamine abuse on urinary symptoms and QoL. The relationship of the symptom severity and the amount and duration of previous ketamine used were also evaluated. Using a bladder diary and health-related QoL questionnaires, these symptoms were also compared with those of an age-matched group of controls.

Methods

This prospective observational study was conducted in the gynaecology clinic of a tertiary referral centre. A local drug rehabilitation centre referred all women who had a history of ketamine abuse and had stopped using the drug to our subspecialty urogynaecology clinic. Corresponding ex–ketamine abusers and age-matched control seen in our clinic between December 2009 and April 2010 were asked to participate in this study. Written consent was obtained from all participants, and ethics approval for the entire study was granted by our institution (Reference No. CRE-2009.453). A research assistant first invited subjects to complete the validated Chinese version of Urogenital Distress Inventory Short Form (UDI-6) and the Incontinence Impact Questionnaire Short Form (IIQ-7) independently, which are two widely used comprehensive health-related quality of life (HRQoL) questionnaires specific to lower urinary tract dysfunction.[6] The total and subscale scores of their short forms UDI-6 and IIQ-7 correlate well with their long-form versions.[7] The UDI-6 consists of six items that assess the life impact of urinary symptoms. They were irritative symptoms of urgency and urge incontinence, stress incontinence symptoms, obstructive symptoms, difficulty completely emptying the bladder, and pain or discomfort over the lower abdomen. The IIQ-7 consists of seven items designed to assess different domains of QoL, including physical, travel, social, and emotional aspects.

Following completion of the HRQoL questionnaires in a confidential setting, the subjects filled in a specially designed 47-item questionnaire concerning their history of ketamine

use. Questions included the age when they started their illicit ketamine use, duration and dosage of their use, duration of cessation of use, and relevant demographic data.

The gynaecologist, who subsequently conducted the individual consultations and assessments, was blinded to the results obtained from the above questionnaires. Clinical details of urinary symptoms—including urinary frequency, urgency, voiding difficulty, dysuria, stress or urge incontinence—were assessed.[8] If any urinary symptom was present, mid-stream urine was sent for culture to exclude urinary tract infection. Urine samples were collected to confirm discontinuation of ketamine. Blood tests to assess renal function were performed together with transabdominal ultrasonography to evaluate possible hydronephrosis.

To provide information on the actual drinking and voiding patterns, a 3-day bladder diary was completed by all the subjects. Two standard measuring cups were provided for each subject. The number of voiding in the daytime, at bedtime, and the total in 24 hours were respectively recorded as daytime urinary frequency, nocturia, and 24-hour frequency. The volume voided at each micturition was recorded. The maximum volume voided was defined as the maximum voided volume and the median functional bladder capacity was defined as the median of all the voided volumes.

Subjects were confirmed ceased ketamine abuse and completed a second set of UDI-6 and IIQ-7 and the 3-day bladder diary 3 months after their first consultation to review their urinary symptoms without any active treatment. Urine samples were collected again to confirm cessation of ketamine use.

An age-matched control group who had never taken any ketamine was selected from the general gynaecological clinic of the same unit. Two-staged sampling was used for the patients attending the general gynaecological clinic, as they were stratified according to their age (13-18, 19-24, and 25-30 years old) and then selected by systematic sampling. The UDI-6 and IIQ-7 and the 3-day bladder diary were completed by the controls. Their urinary symptoms were also assessed and mid-stream urine was cultured if urinary symptoms were present.

Statistics

Statistical analysis was performed using the Statistical Package for the Social Sciences (Windows version 17.0; SPSS Inc, Chicago [IL], US). Descriptive statistics were used for frequency of urinary symptoms. Chi squared or Wilcoxon signed rank test were used for non-parametric data; and paired *t* test for parametric data of the paired samples; and the independent sample *t* test and the Mann-Whitney *U* test for comparison between groups. Any P value of less than 0.05 was considered statistically significant.

Results

From December 2009 to April 2010, 44 female ex-ketamine abusers were referred to us, four declined and finally 40 (91%) of them consented to be studied. In all, 40 women were recruited as controls, all of whom had presented with a menstrual disorder (70% for oligomenorrhoea and 30% for dysfunctional uterine bleeding). The mean age of the study group was 20 (range, 13-29; standard deviation [SD], 4) years, while in the controls the respective values were 20 (range, 15-30; SD, 4) years. The mean body mass index (BMI) of the study and control groups were 22 kg/m^2 (range, 17-31; SD, 3 kg/m^2) and 23 kg/m^2 (range, 17-35; SD, 4 kg/m^2), respectively. There was no statistically significant difference between the groups with respect to age and BMI.

In the study group, eight (20%) of them started abusing ketamine before 13 years of age; the youngest started when she was 9 years old; 26 (65%) had their first ketamine experience aged 13 to 16 years. None of the subjects was pure ketamine abusers; 34 (85%) of them had abused three or more kinds of drugs. In all, 15% had used ketamine for less than a year, while 63% had used it for 3 years or more. The mean duration of ketamine abuse was 53 (range, 6-132) months and the mean duration since ceasing ketamine abuse was 8 (range, 1-48) months. In all, 18 (45%), 20 (50%) and 2 (5%) of the subjects had stopped their use for <6 months, ≥6-24 months, and ≥24 months, respectively.

In the study group, 36 (90%) had active urinary symptoms, with 21 (53%) had urinary frequency, 24 (60%) urinary urgency, 12 (30%) urge incontinence, 22 (55%) dysuria, and 15 (38%) had sense of incomplete bladder emptying. The controls did not report any urinary symptoms. None of the subjects had urinary cultures that yielded positive results, abnormal renal function, or hydronephrosis.

Overall, 36 (90%) of the study subjects and all 40 controls completed the 3-day bladder diary; four study subjects did not return their bladder diary and hence no data for them were available for analysis. In the study subjects, their daytime, night-time, and total voiding frequencies were significantly increased, while their maximum voided volumes and median functional bladder capacity were both reduced (Table 1). Two (5%) subjects reported urinary incontinence. The QoL of the study group subjects was significantly impaired as indicated by the significantly higher subscale and total scores of the both UDI-6 and IIQ-7 (Table 1).

The age of the first ketamine abuse was not associated with worse urinary symptoms or UDI-6 or

TABLE 1. Results of a 3-day bladder diary and Urogenital Distress Inventory Short Form (UDI-6) and the Incontinence Impact Questionnaire Short Form (IIQ-7) scores in study group and control group

	Mean (standard deviation)		P value
	Study group	Control group	
Bladder diary	(n=36)	(n=40)	
Daytime urinary frequency	8.9 (5.4)	5.7 (1.7)	0.004
Nocturia	1.0 (0.9)	0.2 (0.8)	<0.001
24-Hour frequency	10.0 (6.9)	5.8 (1.8)	0.001
Maximum voided volume (mL)	253.3 (121.0)	401.9 (126.4)	<0.001
Median functional bladder capacity (mL)	195.3 (93.6)	261.2 (98.5)	0.011
UDI-6	(n=40)	(n=40)	
Irritative subscale	26.6 (19.4)	5.0 (7.8)	<0.001
Stress subscale	11.6 (14.8)	2.5 (5.1)	0.002
Obstructive/discomfort subscale	27.6 (23.6)	2.5 (6.0)	<0.001
Total score	65.6 (50.7)	10.0 (13.7)	<0.001
IIQ-7			
Physical activity subscale	20.0 (27.3)	1.1 (4.2)	0.001
Travel subscale	30.4 (30.6)	1.1 (4.2)	<0.001
Social subscale	28.3 (34.2)	1.1 (6.1)	0.001
Emotional subscale	26.3 (29.4)	0	<0.001
Total score	105.0 (109.9)	3.3 (13.4)	<0.001

TABLE 2. Results of a 3-day bladder diary after different durations of ketamine abuse and its cessation

	Ketamine abuse duration Mean (standard deviation)		P value	Cessation of ketamine Mean (standard deviation)		P value
	<2 Years (n=7)	≥2 Years (n=29)		<3 Months (n=6)	≥3 Months (n=30)	
Daytime urinary frequency	6.7 (2.6)	9.43 (5.8)	0.33	15.5 (8.8)	7.6 (3.3)	0.04
Nocturia	0.3 (0.6)	1.2 (2.1)	0.13	2.6 (4.2)	0.7 (0.9)	0.19
24-Hour frequency	6.5 (2.6)	10.7 (7.3)	0.16	18.1 (11.8)	8.3 (4.0)	0.03
Maximum voided volume (mL)	255.7 (66.2)	252.7 (131.7)	0.88	147.8 (122.9)	274.4 (110.9)	0.03
Median functional bladder capacity (mL)	175.3 (75.0)	200.2 (98.1)	0.70	142.6 (136.0)	205.9 (81.9)	0.06

TABLE 3. Scores of Urogenital Distress Inventory Short Form (UDI-6) and the Incontinence Impact Questionnaire Short Form (IIQ-7) after different duration of ketamine abuse and its cessation

	Ketamine abuse duration Mean (standard deviation)		P value	Cessation of ketamine Mean (standard deviation)		P value
	<2 Years (n=9)	≥2 Years (n=31)		<3 Months (n=8)	≥3 Months (n=32)	
UDI-6						
Irritative subscale	12.5 (8.8)	30.6 (19.9)	0.09	37.5 (20.0)	23.8 (18.6)	0.09
Stress subscale	6.9 (9.1)	12.9 (16.0)	0.48	18.8 (18.9)	9.8 (13.4)	0.24
Obstructive/discomfort subscale	15.3 (16.3)	31.2 (24.4)	0.09	44.4 (22.8)	23.4 (22.2)	0.03
Total score	34.7 (30.5)	74.6 (52.2)	0.03	100.6 (54.5)	56.9 (46.5)	0.04
IIQ-7						
Physical activity subscale	9.3 (14.7)	23.1 (29.4)	0.26	45.7 (38.6)	13.6 (19.6)	0.03
Travel subscale	9.3 (14.7)	36.6 (31.4)	0.02	52.1 (37.2)	25.0 (26.8)	0.07
Social subscale	0	36.6 (34.8)	<0.01	58.3 (42.7)	20.8 (27.8)	0.03
Emotional subscale	9.3 (14.7)	31.2 (31.0)	0.05	50.0 (32.1)	20.3 (26.0)	0.02
Total score	27.8 (32.3)	127.4 (114.5)	0.02	206.3 (136.2)	79.7 (87.8)	0.02

TABLE 4. Comparison of results in the 3-day bladder diary and scores of Urogenital Distress Inventory Short Form (UDI-6) and the Incontinence Impact Questionnaire Short Form (IIQ-7) in controls versus the study group after cessation of ketamine use of 3 months or more

	Mean (standard deviation)		P value
	Control group	Cessation of ketamine ≥3 months	
Bladder diary	(n=40)	(n=30)	
Daytime urinary frequency	5.7 (1.7)	7.6 (3.3)	0.001
Nocturia	0.2 (0.8)	0.7 (0.9)	0.004
24-Hour frequency	5.8 (1.8)	8.3 (4.0)	0.001
Maximum voided volume (mL)	401.9 (126.4)	274.4 (110.9)	0.001
Median functional bladder capacity (mL)	261.2 (98.5)	205.9 (81.9)	0.019
UDI-6	(n=40)	(n=32)	
Irritative subscale	5.0 (7.8)	23.8 (18.6)	<0.001
Stress subscale	2.5 (5.1)	9.8 (13.4)	0.010
Obstructive/discomfort subscale	2.5 (6.0)	23.4 (22.2)	0.001
Total score	10.0 (13.7)	56.9 (46.5)	<0.001
IIQ-7			
Physical activity subscale	1.1 (4.2)	13.6 (19.6)	0.002
Travel subscale	1.1 (4.2)	25.0 (26.8)	0.001
Social subscale	1.1 (6.1)	20.8 (27.8)	0.002
Emotional subscale	0	20.3 (26.0)	0.001
Total score	3.3 (13.4)	79.7 (87.8)	<0.001

IIQ-7 scores. Study subjects who had stopped using ketamine for 3 months or more had significantly reduced daytime voiding frequencies and higher maximum voiding volumes than those who had stopped for less than 3 months. The median functional bladder capacity was also higher but the difference did not reach statistical significance (Table 2). Higher voiding frequency was probably associated with the history of ketamine abuse for 2 years or more, though this was not statistically significant.

Ketamine abuse for 2 years or more and cessation of less than 3 months were associated with significantly higher total UDI-6 and IIQ-7 scores (Table 3). When comparing findings of ex–ketamine abusers who had stopped abuse for 3 months or more with controls, significant differences were evident for bladder diary results and all the UDI-6 and IIQ-7 subscales (Table 4).

In the study group, keeping of a bladder diary and responding to the UDI-6 and IIQ-7 questionnaires were repeated 3 months after the first consultation. In all, 20 (50%) and 27 (68%) of the 40 subjects had completed the 3-day bladder diary and questionnaires, respectively. All of them were confirmed to have no recent consumption of ketamine, by the absence of ketamine metabolites in their urine samples. We also confirmed with the subjects and their respective rehabilitation centres that they had not received any active treatment during this follow-up period. There was no significant difference in the age, first bladder diary result and UDI-6 and IIQ-7 scores in those who had or had not completed the second set of results. Their mean daytime urinary frequency (9 vs 8; P=0.014) was significantly reduced, as were their 24-hour urinary frequencies (10 vs 9; P=0.012). All the mean subscale and total scores in UDI-6 and IIQ-7 had improved after 3 months, and with the improvement in the stress subscale (12 vs 8; P=0.038) and the total scores in the UDI-6 (66 vs 53; P=0.037) reached statistical significance. Comparing the second set of data from study subjects (obtained 3 months after the first consultation) with the control group results showed that they continued to have more nocturia (1.0 vs 0.2, P=0.006), and the maximum voided volume and the median functional bladder capacity remained significantly lower (315 vs 402 mL, P=0.001 and 175 vs 261 mL, P=0.037, respectively). Respective mean total scores for UDI-6 and IIQ-7 were also higher (53 vs 10, P=0.002 and 89 vs 3, P=0.002). In summary, both urinary symptoms and QoL of the study group had improved 3 months after the first consultation, but continued to be inferior to those of the controls.

Data on the amount of ketamine used and the extent of urinary symptoms were not available for

analysis as the dosage units of ketamine consumption differed widely between subjects.

Discussion

Ketamine has been increasingly abused by youngsters over the past 10 years. Its low cost and fast onset of action have resulted in it becoming a commonly abused drug around the world in all age-groups, particularly in 2007 to 2009.[9] Drug abusers believed that ketamine has low additive potential and little long-standing harm, and falsely have the view that any adverse physical effects resolve after they stop the abuse. Among its reported adverse effects are reduced functional bladder capacity, detrusor overactivity, ulcerative cystitis, decreased bladder compliance, and vesico-ureteric reflux.[10-12] Whether documented urinary side-effects eventually cease after cessation of use remains unclear. The persistence of urinary symptoms in the ex–ketamine abusers was therefore investigated in this study, with a focus on their impact on QoL.

Urinary symptoms are influenced by age and BMI, therefore having age-matched controls with similar BMIs to the current study was important to reflect the significance of urinary symptoms in ex–ketamine abusers.[13,14] A 3-day bladder diary can generally provide a better reflection of usual voiding patterns and provide especially valuable data from such young subjects.[7] High compliance in completing the bladder diary in both groups also yielded valuable data to studying the urinary problems in this special group.

Urinary symptom scores of ex–ketamine abusers remained significantly increased when compared with controls. All subscales scored in the UDI-6 were higher in the study group. This echoed the findings of moderate-to-severe lower urinary tract symptoms in active ketamine abusers described in previous case series.[2] Even after cessation of use, their QoL remained impaired owing to various urinary symptoms.

This study confirmed that ketamine abuse for 2 years or more was associated with a more impaired QoL than those had taken and abused it for less than 2 years. Besides the duration of ketamine use, the longer the interval after cessation, the greater is the return to normality in terms of QoL. This was supported by our findings in the ex–ketamine abusers who had stopped for 3 months or more. Results from the second set of data (collected 3 months later) also agreed with this conclusion.

The pathophysiology of the urinary symptoms in ketamine abusers remains unclear. Ketamine has numerous central nervous system actions, and possibly includes neuroinflammation in the urinary tract, similar to what occurs in interstitial cystitis.[15,16] No effective treatment has been identified for this group of patients however.[17,18] Intravesical instillation of hyaluronan solution has been used and apparently reduced urinary symptoms in some ketamine abusers with haemorrhagic cystitis who had ceased taking the drug.[19] From our study, cessation of drug and the intervening time proved to be the keys to reversing the symptoms before more severe damage ensued and more aggressive intervention resorted to. In our subjects, although complete recovery as compared to the controls was not evident even after 6 months, significant progressive improvement was demonstrated. Further research is needed to follow up symptoms after a longer period of cessation. In which case, we may be able to work out whether complete resolution of urinary side-effects can occur as well as the time required for this to happen.

Our study was limited in that only female ketamine abusers were referred and recruited to our study, so its results and conclusions are only valid for young female abusers. Whether they are applicable to male abusers is not clear. Other studies in male abusers are therefore warranted.

Another limitation was the small sample size in our study. However, most ketamine abusers are in their teens and very reluctant to reveal their urinary problems to medical personnel. Either they avoid being labelled as drug abuser or they prefer tolerating the symptoms and believe the symptoms will resolve spontaneously. Concerning our subjects, they were all referred from a local drug rehabilitation centre and most had used multiple drugs, not only ketamine. However, no significant associated urinary symptoms have been reported with other commonly used illicit drug. Again our results obtained 3 months after first consultation were limited by the high default rate; only 50% kept a bladder diary, and 68% responded to the questionnaires. Recall bias should be considered in relation to our finding as all information concerning ketamine usage was given by the subjects.

For the control group, the family background, social class, and education level were not investigated. This too may give rise to difference in voiding patterns and could introduce a recall bias about ketamine use. We failed to study the relationship between the dosage of ketamine used and urinary symptoms, because it was not possible to have an accurate estimate of dosage owing to different measure units for quantifying street ketamine as well as the presence of impurities.

In conclusion, ex–ketamine abusers in our study were experiencing significant urinary symptoms as compared with the controls. Their urinary symptoms had also impaired their QoL significantly.

Ketamine abused for 2 years or more was associated with greater degrees of QoL impairment. Urinary symptoms persisted and QoL was impaired, though with reduced severity after cessation of ketamine use for 3 months or more. We urge further studies to provide longer-term follow-up for this group of patients, but a high default rate and difficulties following up such subjects should be expected.

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