Impact of synthetic cannabinoids on the duration of opioid withdrawal and craving among patients of Kazakhstan addiction clinics: a prospective case-control study

Abstract

Introduction: Synthetic cannabinoids (SCs) are among the most common classes of novel psychoactive substances. SCs can modulate toxic effects and clinical outcomes related to other types of drugs, especially of opioids. The aim of the present study was to prospectively assess if the regular use of SCs can affect the duration of opioid-related withdrawal and craving symptoms in patients undergoing specific drug detoxification treatments.

Methods: We studied a sample of patients with opioid withdrawal syndrome made of 47 patients who regularly used SCs (cases) and 146 patients who did not use SCs (controls). All participants underwent specific detoxification therapies. The two groups were matched in sex, age, ethnicity, current severity of opioid dependence and grade of opioid withdrawal severity at baseline. The Clinical Opiate Withdrawal Scale (COWS) and visual analogue scale (VAS) were used to assessed opioid withdrawal and craving symptoms correspondingly. By means of survival analyses, the use of SCs was examined as a factor of prolongation of opioid withdrawal and craving.

Results: SCs subjects compared to controls had significantly longer duration of withdrawal ($p<0.001$) and craving symptoms ($p<0.001$). SCs-use significantly decreased the probability of withdrawal ending within 14 days - HR 0.17 (95% CI: 0.098, 0.31; $p<0.001$) and craving ending within 20 days - HR 0.34 (95% CI: 0.23, 0.5; $p<0.001$). The number of SC intakes in the last 30 days ($p=0.045$) and time since the last SC intake ($p=0.033$) were predictors of prolonged withdrawal duration. Longer duration of SCs use and higher dosage of SCs ($p<0.001$) were associated with longer duration of opioid craving.

Discussion: This is the first study to assess the impact of SCs on the course of opioid withdrawal syndrome and craving symptoms while additionally detecting novel patterns of use of SCs. The results (i) suggest that patients with opioid addiction in combination with regular use of SCs exhibit a significantly longer duration of opioid withdrawal and craving symptoms, (ii) add to the accumulating evidence showing clinical and molecular cross-talks between cannabinoids and opioids, and (iii) underline novel harmful effects of SCs

1. INTRODUCTION

The widespread growth in popularity of novel psychoactive substances (NPSs) represents a significant threat for the global public health. By July 2016, 102 countries and territories have reported over 540 NPSs to the United Nations Office on Drugs and Crime (UNODC) - Global Synthetics Monitoring: Analysis, Reporting and Trends (SMART) program, far exceeding the 234 substances currently under the International Drug Control Conventions (United Nations Office on Drugs and Crime (UNODC), 2016).

The NPSs (i) are increasingly used, while the use of International Controlled Drugs (ICDs) seems to have stabilized over the past decades, (ii) have world-wide diffusion via the Internet (Martinotti *et al.,* 2014), and (iii) attract new users due to strong psychoactive effects and lack of detectability in routine urine tests (Schifano *et al.,* 2015). Among the most common classes of NPSs, synthetic cannabinoids (SCs), synthetic cathinones, phenylethylamines, piperazines and tryptamines are often detected.

Among the different types of NPSs, SCs have the largest diffusion and represent the largest group of substances monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). 134 SCs have been discovered in Europe with the EMCDDA Early Warning System by 2015 (EMCDDA, 2015). The rising number of SCs seizures mirrors the popularity of this group of NPSs. Specifically, in 2013 the seizures of SCs comprised 40% of those for all NPSs, and in 2014 they accounted for over 60% of total NPS seizures (EMCDDA, 2016).

The use of SCs is associated with diverse clinical symptoms of acute, subacute and chronic toxicity (Castaneto *et al.,* 2014; Shalit N*et al.*, 2016) including the possibility of dependence with withdrawal syndrome (Nacca *et al.,*2013; Zimmermann *et al.*, 2009). The history of other drugs use plays a relevant role as a predictor of SCs consumption. According to the study of Bonar et al, the patients of residential drug addiction treatment programs were more likely to report use of SCs (i) in association with heroin, methadone, prescription opioids, prescription sedatives, amphetamines, ecstasy, cannabis, hallucinogens, inhalants and tobacco, (ii) to avoid the routine urine test in the hospitals, and (iii) to enhance the effects or treat withdrawal symptoms related to other substances (Bonar *et al.,* 2014). Intake of SCs in subjects with substance use disorders is associated with lower age, shorter duration of substance use, higher amount of legal problems and more frequent relapses and dropouts (Nurmedov *et al.,* 2015). Injection drug users who take SCs and/or other NPSs as substitutes of traditional drugs represent a population at particularly elevated risk of developing

adverse health effects related to synthetic drugs (EMCDDA, 2013; Wagner et al., 2014). This poly-drug use represents an important concern for health care specialists as (i) it can increases health risks and harms (EMCDDA, 2013)., (ii) it can worsen treatment outcomes, and (iii) it can create the so-called phenomenon of "*garbage head syndrome"* (Iudici *et al.,* 2015).

Despite these preliminary data, a clear picture of the co-occurrence of SCs and traditional drugs use has not been presented in the literature, and there is a lack of studies assessing the role of SCs in affecting the course addiction-related symptoms of traditional drugs. The aim of the present study was to assess if the regular use of SCs can affect the duration of opioid withdrawal and craving symptoms in patients undergoing specific drug detoxification treatments. Our hypothesis is that SCs use can worsen clinical course of primary opioid addiction.

2. METHODS

2.1 Study design

We conducted a prospective naturalistic case-control study between November and May 2015. The study protocol was approved by the Ethics Committee of the Semey State Medical University on October 2015 (No.4). The subjects of the study were inpatients with opioid withdrawal syndrome diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (American Psychiatric Association, 2013). The informed consents were obtained for all subjects of our study. Participants received no compensation for their participation. A total of 453 participants who met the criteria in DSM-V were recruited consecutively by eight senior psychiatrists in two hospitals specialized in addiction treatment in north and south Kazakhstan (Pavlodar and Almaty). After admittance, all patients underwent specific detoxification treatments for at least 20 days in specific detoxification units (DU) (details are given in section 2.3) . In addition to the diagnosis of opioid withdrawal, the inclusion criteria for participants were: (i) age of 18-45 years, (ii) the last opioid intake 12-36 hours before the admission, (iii) positive opioid urine test at the time of admission, (iv) negative urine tests for others illicit drugs at the time of admission, (v) the absence of acute symptoms of somatic diseases, and (vi) availability of drug history data from the last year.

In Kazakhstan the longitudinal surveillance of people with addiction disorders is conducted by trained psychiatrists in at least monthly visits in specialized outpatient clinics. During the medical examinations, the physical conditions, the course and the severity of dependence as well as the intake of other psychoactive substances are monitored. To test full remission, urine tests are performed.

One of the two study groups (i.e. the SCs group) was made of 47 patients with the diagnosis of opioid withdrawal who regularly used SCs. Regular SCs consumption was defined as no less than 3-4 times per month minimum for half of the year preceding the beginning of the study. Use of SCs (i.e. JWH-18 and JWH-73) was confirmed with repeated positive urine tests. The other group (i.e. the control group) was made of 146 patients with the diagnosis of opioid withdrawal who did not use SCs. A 1:3 case-control ratio was used to increase the statistical power of the analyses. The two groups were matched in sex, age, ethnicity, current severity of opioid dependence and grade of opioid withdrawal severity at baseline. The procedure of the participants' enrollment is summarized in Figure 1. The symptoms of opioid withdrawal and craving were assessed daily in a period of 20 days since admission.

2.2 Assessments

A 42-item recording form was designed and used by the three investigators. The form is based on three domains of the Addiction Severity Index (UNODC, 2009), namely: (i) general demographic data, (ii) history of drug consumption, and (iii) physical conditions. The SCs intake history, the course of opioid withdrawal and craving symptoms as well as the treatment information were assessed. The opioid dependence was diagnosed in all cases according to criteria of International Statistical Classification of Diseases and Related Health Problems 10th Revision. For the opioid withdrawal assessment, the Clinical Opiate Withdrawal Scale (COWS) was used. (Wesson and Ling, 2003). We summarized the degree of opioid withdrawal symptoms in four levels, according to the COWS, namely mild (5-12 points), moderate (13-24 points), moderately severe (25-36 points) and severe (more than 36 points). The absolute values of withdrawal scores were also taken into consideration. We assessed the changes in craving symptoms daily using the visual analogue scale (VAS). This instrument ranks the scores from 0 to 10 for intensity of craving and provides a reliable subjective symptom's assessment (Mottola, 1993). The study baseline was defined as the moment between the admittance to DU and the beginning of pharmacological therapies (1-1.5 hours). Clinical and sociodemographic data were measured at baseline. In the follow-up visits, the objective and subjective symptoms of the opioid-related withdrawal and craving symptoms were assessed. The severity of withdrawal and craving symptoms were assessed on days 1, 5, 10, 15 and 20.

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2.3 Detoxification treatment

The design of the study had a naturalistic approach, i.e. it intended to assess the clinical symptoms during the standard therapy without any new experimental treatment/intervention. The opioid withdrawal symptoms were treated with α2-adrenergic agonist (clonidine 0.6-0.9 mg/die), anxiety and insomnia were treated with benzodiazepines (diazepam 30-50 mg/die) and antipsychotics (quetiapine 200 mg/die). After clinically significant improvements of withdrawal symptoms relief, usually starting from the seventh - ninth day of treatment, patients started cognitive-behavioral therapy in addition to pharmacotherapy.

2.4 Use of opioids and SCs

For what concerns opioids, we assessed the duration of intake, the onset of withdrawal symptoms, the average duration of the withdrawal periods, the type of opioids (e.g. heroin, acetylated poppy, prescribed opioids and dezomorphine) (Zabransky, 2012), the dosages, the routes of administration and the combination with other drugs often used to reduce withdrawal symptoms (including codeine, tropicamide, phenazepam, zopiclone and trihexyphenidyl (Bersani *et a*l, 2015).

For what concerns SCs, we assessed the history of intake, the street–names of the substances, the ways of drug purchasing, the lifetime motives for SCs use, the dosages, the frequency the routes of administration, the age of first use and the time since the last intake

2.5 Statistical Analysis

Data analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) for Windows. All parameters are presented as mean ± standard deviation (SD). Considering the nonparametric distribution of some variables, we used Friedman F-test to compare continuous variables and chi-square test ($\chi 2$) to compare categorical variables at baseline. The duration of the withdrawal syndrome that was equated to statistical survival period was analyzed with Kaplan-Meier method (Goel *et a*l, 2010) from the baseline until the moment of cessation of clinician-rated opioid symptoms (COWS points ≤ 5 points) or reduction of craving symptoms (VAS≤ 2 points) (McMillan and Gilmore-Thomas, 1996). The follow-up period we defined as 20 days for both dependent variables.
The differences in duration of withdrawal periods and craving between two groups were assessed using the log-rank test. The Cox-analysis was conducted to explore whether regular consumption of SCs including their dosage, duration of consumption, routes of administration and number of the last

30-days intake's could impact the prolongation of both opioid withdrawal and craving after controlling the main demographic and clinical confounders (Bradburn *et a*l, 2003). We also controlled the strength of intercorrelation links among above-mentioned characteristics of SCs use with Pearson correlation coefficient (r). As dependent variables we defined withdrawal symptom sending (according to the COWS 5 points and less) and the craving symptoms decreasing (according to the VAS 2 points and less). The follow-up period was 14 days for withdrawal syndrome and 20 days for craving. The univariate Cox regression analyses were addressed for each dependent variable consecutively considering the insufficient sample size (n=190 cases). The Cox multiple factors regression analysis method was used for the above statistically significant variables. The hazardous risks (HR) of the events were calculated with 95% confidence interval (95% CI). $p < 0.05$ was considered statistically significant.

3. RESULTS

3.1 Participants socio-demographic characteristics

Forty-seven patients with regular SCs consumption and 146 controls were evaluated. Details on their demographic and clinical characteristics are given in Table 1. The majority of participants were males, unemployed, single and of Asian ethnicity; the age ranged between 18 and 38 years.

3.2 Opioid use

The age of first opioid use ranged between 15 and 34 years, the duration of opioid consumption between 3 months and 12 years. Most of participants used heroin intravenously. The patients in the two groups did not present significant differences in 30-days prevalence of non-prescribed medications intake. Tropicamide was mostly used as an alternative to heroin, whereas phenazepam and zopiclone were mostly taken to mitigate opioid withdrawal symptoms and trihexyphenidyl was mostly taken to potentiate the effects of opioid intoxication. Baseline measures showed similar levels of severity of opioid withdrawal symptoms, craving and opioid dependence in the two groups. Despite the matching in sociodemographic and clinical variables, there were significant between-group differences in the number of previous hospitalizations due to opioid dependence. The participants of the SCs group reported 3.57±1.61 hospitalizations, while the control group reported 1.66±1.11 hospitalizations ($p=0.002$). The number of the last year hospitalizations was higher in the SCs-group versus those ones in the control group (1.96±1.04 times and 0.74 ±0.69 times respectively; $F=13.29$, $p=0.01$). Patients of SCs-group demonstrated higher rate of drop-outs during the treatment courses than patients in the control group (i.e. 26 patients - 55.3% - of the SCs-group versus 53 patients - 36.3% - of the control

group; $\chi 2$ =5.32, p=0.02). Involvement in psychosocial rehabilitation programs in the previous year was more often observed in the controls than in subjects of SCs-group (i.e. 19 patients - 40.4% - of SCs-group and 88 patients - 60.3% - of controls; $\chi 2$ =5.67, p=0.017). Details are given in table 1.

3.3 Synthetic cannabinoids use

The evaluation of the main features of SCs use was conducted in the SCs-group exclusively. The reported street labels of SCs included some of the most popular names of NPSs in Kazakhstan, i.e. *spices, JWH, blue weeds, white weeds, chamomile, emint* and *Chinese dust*. Twenty-nine (61.7%) patients purchased SCs via social networks and on-line trading platforms, 12 (25.53%) patients purchased SCs from drug dealers, and the rest of patients received the substances from relatives and friends. The reasons underlying SCs use included curiosity (42 patients - 89.36%), availability of the substance (31 patients - 65.96%), possibility of avoiding identification in urine express-tests (23 patients - 48.93%) and attempts to potentiate opioids' effects (17 patients - 36.17%). Daily dosages of SCs had wide variations, ranging from 0.5 g to 3 g (mean: 1.79±0.73 g/die). The duration of regular SCs use ranged between 6 and 20 months (mean: 13.62±3.97 months). The mean number of SCs intakes in the last 30 days was 15.0±3.48. All cases reported to have inhaled the SCs, with the most popular method being bongs, vaporizers or the so called "*bombaster"* (in 30 patients - 63.8%) followed by cigarettes smoking (in 17 patients - 36.2%). The use of smoking devices in our samples was associated with intake of JWH-powder mixed with tobacco, medicinal plants and parsley. The vaporizer use mainly followed the cigarette smoking after 2-3 months of SCs use onset. The time of the last SCs intake before the study admittance was 21.47±10.27 hours. Twenty-six patients (55.32%) combined SCs and natural cannabis. Twenty-three patients (48.94%) ceased marihuana smoking preferring SCs. Six patients (12.77%) experienced SCs-induced psychosis and had been hospitalized in medical emergency departments at least once in the previous year.

3.4 Opioid Withdrawal Course

The opioid withdrawal duration in SCs and non-SCs groups was calculated using the Kaplan-Meier method. We evaluated the opioid withdrawal changes according to the COWS and the VAS scores (Figure 2). The mean duration of the objective symptoms addressed by the COWS score was 14.66 ± 0.27 days in SCs group versus 12.21± 0.13 days in non-SCs group. The log-rank test confirmed the significant relationship between the duration withdrawal symptoms and SCs consumption ($p<0.001$). The craving symptoms had a longer duration in SCs group (17.98 ± 0.33) days than in the non-SCs group (14.97±0.22 days). The median time was 19 (95% CI: 18.08; 19.92) days versus 15 (95% CI:

14.64; 15.36) days. The statistics of the log-rank test were $\chi 2(1)=44.42$, $p<0.001$. The Cox-regression revealed a significant impact of SCs-consumption on opioid withdrawal and craving. For the ending withdrawal symptoms within 14 days HR was 0.17 (95% CI: 0.098; 0.31), $p<0.001$. For craving ending within 20 days the HR was 0.34 (95% CI: 0.23; 0.5), $p<0.001$.

After the confirmation of the SCs impact on the course of withdrawal symptoms, we explanatorily analyzed characteristics of SCs intake: the dosage of SCs, duration of SCs consumption, the number of SCs intakes in the last 30 days, the time of the last SCs intake and the routes of SCs administration.

The duration of SCs use was positively significantly correlated with the dosage of SCs ($r=0.3$, $p=0.04$) and with the number of SCs intakes in the last 30 days ($r=0.47$, $p=0.001$). The impact of demographic and clinical variables on the ending of the opioid withdrawal and craving were assessed in Cox regression. Firstly, in the univariate analysis the factors that had prognostic significance were detected. For withdrawal syndrome there were following: (i) combination of duration of SCs and number of SCs intakes in the last 30 days ($p=0.004$), (ii) time of the last SCs intake ($p=0.001$). For craving we detected following: (i) combination of duration of SCs use and dosage of SCs ($p<0.001$), (ii) the duration of SC use and number of SCs intakes in the last 30 days ($p=0.005$). Secondly, the multivariate analysis was applied to estimate the most important influencing factors. Regarding craving, that was duration of SCs use in combination with dosage of SCs ($p<0.001$). For opioid withdrawal symptoms we detected duration of SC use combined with number of SCs intakes in the last 30 days ($p=0.045$) and time of the last SCs intake ($p=0.033$) as significant factors. The results of the two Cox analyses are shown in Table 2.

4. DISCUSSION

To the best of our knowledge this is the first study assessing the impact of SCs on the course of opioid withdrawal syndrome while additionally detecting novel patterns of use of SCs. Our results showed that patients with opioid addiction in combination with regular use of SCs show a significantly longer duration of withdrawal and craving symptoms in comparison to patients with opioid addiction without SCs use. Further, within-group analyses showed that the duration of SCs use, the dosage of SCs, the number of SCs intakes in the last 30 days were associated with prolongation of opioid craving and withdrawal symptoms. On the contrary, the risk of opioid withdrawal and craving decreased with the increase of time since the last use of SCs. Taken together, these results are consistent with the study hypothesis that SCs use can worsen clinical course of primary opioid addiction including through the prolongation of withdrawal and craving symptoms.

Several previous studies have observed the positive life-prevalence of SCs consumption among subjects with opioid addiction (Bonar et al., 2014; Nurmedov et al, 2015;) and the effect of naltrexone on SCs-related withdrawal symptoms (Rodgman et al, 2014). Our study confirms the findings of previous reports showing an association between SCs and opioids in clinical practice and more severe drug dependence in case of polydrug use (Wagner et al, 2014). Additionally, our findings indicate that certain characteristics of SCs use can increase risks of prolonged opioid-related withdrawal and craving symptoms.

Bi-directional interactions between cannabinoids and opioids have been reported in a wide number of studies. These links have been detected on biochemical, physiological, anatomic and clinical levels. The key point of this interconnection is the modulating activity of both cannabinoids and opioids on the reward, antinociception and motor systems. Both antagonistic and agonistic interactions between opioids and cannabinoids have been reported in animal (Maguire and France, 2016; Wakley *et al*, 2011) as well as in human studies (Haney *et al*, 2007). The acute concomitant use of opioids and cannabinoids can lead to increase extracellular levels of endogenous opioids, facilitation of their signaling, and modulation of mu-opioid receptors; the chronic concomitant use of opioids and cannabinoids can increase the amount of endogenous opioids and can activate the noradrenergic pathways of locus coeruleus (Scavone *et al*, 2010). According to animal studies, the agonistic influence of cannabinoids supports the growth of antinociceptive tolerance as well as it attenuates and modulates morphine withdrawal syndrome (Gerak *et al*, 2015). However, contrasting findings exist: for example, Nava et al. did not detect significant correlations between chronic cannabis use and heroin withdrawal/ craving in patients receiving methadone maintenance therapy (Nava *et a*l, 2007), while Wasserman et al. revealed the acceleration of heroin relapses during cannabinoid consumption in a similar group of methadone-treated patients (Wasserman *et al*, 1998).

The available evidence on opioids-cannabinoids interaction is mostly focused on natural cannabis, while data on SCs is fragmental and very limited. Taking into account the similarity between natural cannabinoids and SCs as well as some resemblance in biochemical mechanisms, some authors empirically observed similar dependence and withdrawal patterns related to the two types of substances (Gunderson *et al*, 2012). However, the stronger affinity of SCs to cannabinoid receptor types 1 and 2 (CB1 and CB2) in comparison with natural cannabis explains the earlier emergence of addiction and the more severe dependence and withdrawal symptoms related to SCs (Fantegrossi *et al*, 2014). The available literature data on positive lifetime-prevalence of SCs use among subjects with opioid addiction empirically support the idea of potential interactions between this class of NPSs and opioids. One of the few publications regarding the interaction between SCs and opioids was the case report of Rodgman et al. in which the effects of naltrexone on SCs-related withdrawal were described.

The authors reported that naltrexone had controlling potential against SCs-related craving (Rodgman *et al,* 2014).

To the best of our knowledge, there are no studies investigating the biological nature of SCs-opioids interaction in withdrawal period. Prolonged SCs intake results in inhibition of GABA and glutamate neurotransmission as well as in desensitization and internalization of CB1 receptors (Atwood *et al*, 2010), thus providing a growth of tolerance and addictive effects the substances. Mu-opioids pathways, including mu-receptors modulation and dopamine mediation are also involved in acute and chronic SCs-effects. Specifically, SCs can increase mu-opioids signaling and potentiate opioid antinociceptive effects (Gerak and France, 2016), which can contribute to explain our study finding of individuals using SCs as an alternative to opioids. The cross-tolerance of SCs and opioids can lead to co-addictive effects for both classes of substances (Gerak et al, 2015). Further, the empirical clinical data of Rodgman et al on control of SCs-related craving treated with naltrexone indirectly confirms a certain degree of homogeneity between SCs and opioids withdrawal and craving mechanisms (Rodgman *et al*, 2014). The correlation of longer duration of withdrawal symptoms with clinical characteristics of SCs such as the duration of SCs consumption, the dosage of SCs and the number of SCs intakes in our study can be speculatively explained assuming the existence of a SCs-addiction (Spaderna *et al*, 2013) complicating the primary opioid use disorder and potentiating the severity of its psychopathological symptoms (EMCDDA. 2009).

A number of limitations of this study relate to its case-control design. Among these, (i) the study had a limited sample size due to the strict inclusion/exclusion criteria; (ii) the main anamnestic information was received through retrospective analyses from medical documentation of two hospitals, thus the inter-observer variability cannot be excluded; (iii) reliable information on the type of SCs was limited to those assessed in express-urine tests which are available in routine use in Kazakhstan hospitals (i.e. JWH-18 and JWH-73); (iv) the retrospective analyses of SCs consumption did not allow to carefully explore the patterns of SCs and opioid co-use; (v) the recruitment of the participants to the study did not follow a randomization procedure and was made only in two Kazakhstan areas (Pavlodar and Almaty), therefore the generalization of our findings should be made cautiously; (vi) the impact of episodic use of SCs was not investigated. All the mentioned limitations mainly derive from the naturalistic design of the study, which on the one hand can increase certain methodological limitations and on the other hand provide information more closely resembling the "real" (i.e. non experimental) world, thus being more clinically reliable. The major strength of our study was the prospective design, which allowed the assessment of the association between regular SCs use and changes in opioid withdrawal symptoms over time. Further, (i) patients with opioid addiction with and without SCs consumption did not differ in withdrawal and craving severity at baseline, thus increasing the reliability of the longitudinal findings; (ii) the case and control groups

were matched in key clinical characteristics; (iii) the prospective design was combined with retrospective observations; and (iv) the SCs consumption was confirmed (or excluded) with series of urine tests for 6 months

Taken together, the results of the present study suggest that the regular use of SCs influences the recovery from opioid addiction and prolongs the duration of withdrawal and craving symptoms. Further studies are needed (i) to gain more accurate knowledge of opioid addiction complicated by SCs use, (ii) to more accurately understand the clinical and molecular cross-talks between these groups of substances, and (iii) to develop more specific guidelines for detoxification therapies.

CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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