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ORIGINAL PAPER

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Comorbid substance abuse and neurocognitive function in recent-onset schizophrenia

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Abstract Despite the high prevalence of comorbid substance use disorder (SUD) up to 65% in schizophrenia there is still few knowledge about the influence of substance abuse on neurocognitive function. In a prospective design we recruited 68 patients (aged 18–40 years) diagnosed as recent-onset schizophrenia or schizoaffective disorder consecutively admitted to hospital. The patients received standardized psychopathological evaluation of schizophrenic symptoms [Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS)], depressive symptoms [Montgomery Asberg Depression Rating Scale, (MADRS)] and global ratings [Clinical Global Impressions Scale (CGI), Global Assessment of Functioning Scale (GAF)]. Out of this sample 44 subjects underwent after stabilization (4–6 weeks after admission) neuropsychological investigation focusing on early information processing (Trail-Making-Test A, Digit Span), visuo-spatial ability (Corsi Block Tapping), verbal fluency (Verbal Fluency Test, semantic and letter category), and executive functioning and cognitive flexibility [Trail-Making-Test B, Wisconsin Card Sorting Test (WCST)]. About 36% of patients reported drug abuse [European Addiction Severity Index (EuropASI)] with a high prevalence for cannabis. Compared with nonabusers the sample of substance abusers was younger, predominantly male and had lower socioeconomic status. Attentional impairment according to the SANS subscale was less in abusers than in nonabusers on admission, no other psychopathological differences could be detected. Schizophrenic patients without substance abuse demonstrated significantly better performance only in a few neurocognitive tasks (Verbal Fluency, letter category and at trend level Digit Span, backwards), while there tended to be an advantage for substance abusers in executive functioning (WCST, not significant). These results are consistent with other studies of first-episode patients. The lack of higher cognitive disturbance in young schizophrenic patients with comorbid substance abuse may encourage clinicians to develop integrated treatment programmes using cognitive strategies of drug therapy.

Key words substance abuse · recent-onset schizophrenia · first-episode psychosis · neurocognition · dual diagnosis

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Introduction

Substance abuse in individuals with schizophrenia is very common and has risen to the most prevalent comorbid psychiatric condition associated with schizophrenia [1]. Estimated life-time prevalence rates for substance abuse in schizophrenia range from approximately 10–65% [2–4]. Prevalence rates vary with different screening instruments, evaluation settings (inpatient or outpatient) and depend on different social and cultural factors. In a more recent epidemiological study of an urban population in UK comorbid non-alcohol lifetime substance misuse was reported in 16% of the overall population and can-

nabis abuse in male schizophrenics under the age of 36 years in 60% [5]. Persisting comorbid substance use disorder (SUD) has been associated with a negative outcome, including more frequent and longer periods of hospitalization, higher relapse rate even in first-episode patients, higher non-compliance, elevated EPS-rate in general and during antipsychotic treatment, unemployment, homelessness, violence, incarceration, suicide, and HIV infection [2, 6–15]. Besides the legal substances tobacco and alcohol, cannabis seems to be the most illicit drug abused in schizophrenics and has been discussed as an important risk factor for developing schizophrenia [16–18].

Neurocognitive deficits have been recognized as an important feature, or even a core deficit, of schizophrenia [19, 20]. A meta-analysis reviewing 204 studies looking at performance of patients with schizophrenia relative to healthy controls reported broad-based cognitive impairment with varying degrees in several cognitive domains, e.g. general intellectual function, global and selective verbal memory, nonverbal memory, visual and auditory attention, executive function, language, spatial ability, motor performance, and interhemispheric tactile transfer test performance [21]. Some of these deficits including reduced function in verbal memory and learning, visual memory, abstraction, cognitive flexibility, language abilities and attention have been found even in untreated, first-episode patients [22]. Cognitive functioning is a correlate of global and specific functional outcome in schizophrenia and contributes to poor judgement and lack of insight [23]. Cognitive impairments account for significant variance in measures of functional status [24]. Substance abuse and dependence has been associated with deleterious consequences on cognitive function, mostly reported in patients consuming alcohol and cocaine [25, 26], but also found in patients with long-term cannabis abuse [27].

Despite the high prevalence of comorbid SUD in schizophrenia there is still few knowledge about the influence of substance abuse on neurocognitive function in schizophrenic patients. Studies to date revealed inconclusive results [28]. Patients with comorbid SUD (cocaine and alcohol consumers) presented greater cognitive deficits than patients without substance abuse [29–32], whereas other studies demonstrated no differences between users and nonusers or even better performance of patients with concomitant SUD [28, 33–40]. Most studies involved patients with chronic schizophrenia and longer duration of illness. Only limited research has been conducted in assessing the effect of comorbid substance abuse in recent-onset schizophrenia or first-episode patients [28]. The aim of this prospective study was to examine the association between substance abuse and cognitive functioning in patients with recent-onset schizophrenia and to compare patients with and without comorbid SUD in regard to cognitive dysfunction. Additionally the effect of substance abuse on positive, negative and depressive psychopathology was examined and correlated with neuropsychological performance. To evaluate the stability or variability of cognitive and clinical patterns over time we decided to repeat the psychopathological rating and the neuropsychological assessment after stabilization (4–6 weeks after admission).

Materials and methods

In a prospective design we studied 68 inpatients in the age between 18–40 years with recent-onset psychosis consecutively admitted to hospital. On admission, all patients experienced their first hospitalization due to schizophrenic symptoms, and illness duration since the onset of first psychotic symptoms did not precede more than 3 years. Patients had not received antipsychotic medication longer than 6 weeks prior to admission. All patients were able to give informed consent to enter the study and did not present a diagnosis of mental retardation. Diagnoses were based on clinical interview according to ICD-10 criteria, and were consented within all members of the study group and the treating clinical psychiatrist, who was blind to the aims of the study. Patients were excluded from the study if they met any of the following criteria: organic central nervous system disorder (e.g., epilepsy, traumatic brain injury, infectious or toxic or cerebrovascular disease), mental retardation, age less than 18 years or greater than 40 years, or inadequate knowledge of the German language. The final study sample comprised of 44 patients diagnosed as schizophrenia or schizoaffective disorder, who received the psychopathological rating, and completed the initial and follow-up neuropsychological assessment. Drug screens (urine) were performed on admission and in the course of the study, but not systematically on the day of the follow-up neurocognitive testing.

Recorded were socioepidemiological (age at recruitment, years of education, status of employment, family status, family history of psychiatric diseases) and clinical data. All patients received standardized psychopathological evaluation. For the assessment of positive, negative and general psychopathology the 18-item version of the Brief Psychiatric Rating Scale (BPRS, [41]), and the Scale for the Assessment of Negative Symptoms (SANS, [42]) was used. For further analyses and statistical comparisons the five subscales anxiety/depression, anergia, thought disturbance, activation, and hostility/suspiciousness of the BPRS and the subscales of the SANS, affective flattening, alogia, avolition/apathy, anhedonia and attentional impairment were used. Additionally, depressive symptoms were assessed by the Montgomery Asberg Depression Rating Scale (MADRS, [43]). More global clinical evaluation was performed using the Clinical Global Impressions Scale (CGI, [44]) for disease severity and the Global Assessment of Functioning Scale (GAF), used in DSM-IV (Axis V), measuring an individual's functional capacity [45]. Substance use patterns and severity of substance use was assessed by the German version of the European Addiction Severity Index (EuropASI), a standardized clinical interview demonstrating high reliability and validity in patients with alcohol and drug dependence [46].

Patients underwent as soon as possible after admission and after further stabilization (4–6 weeks later) detailed neuropsychological investigation. Cognitive functioning was assessed by a comprehensive battery of cognitive measures often used in studies with schizophrenic patients. Visual spatial ability, motor speed and attention was examined by the Trail-Making-Test (TMT, Trails A, completion time in seconds, [47]), executive functioning and cognitive flexibility by the Wisconsin Card Sorting Test (WCST, number of correct trials, total errors, and perseverative errors, [48]) and the Trail-Making-Test (TMT, Trails B, completion time in seconds, [47]), verbal fluency by the Verbal Fluency Test [49]

Table 1 Comparison of sociodemographic characteristics

	Abusers	Nonabusers	*p*
No. of patients (% of all patients)	21 (48%)	23 (52%)	–
Age; in years (mean, SD)	22.1 ± 3.9	29.0 ± 6.4	***<0.001***
Male gender; No. (% of group)	18 (86%)	11 (48%)	***0.009***
Unmarried (% of group)	100%	65%	***0.003***
Education less than 10 years (% of group)	76%	48%	*0.056*
Unemployed (% of group)	62%	26%	***0.008***
Family history (in % of group)			
Severe Mental Illness (SMI)	4.8%	34.8%	***0.015***
Substance Use Disorder (SUD)	23.8%	4.3%	***0.030***
Others	4.8%	13.0%	0.345

p = probability, Mann–Whitney-*U*-Test; SD = standard deviation

(Version A, letter category: words beginning with the letter F; Version B, semantic category: names of cities), short-term memory by Digit Span Test (recognition of a sequence of 2–8 orally presented digits, forward and backward, subtests of the Wechsler Memory Scale Revised Form, WMS-R, total score, [50], adapted German version, [51], visual short-term memory and implicit visual-spatial learning by the Corsi Block Tapping Test, a subtest of the WMS-R [52]. Premorbid intelligence was estimated by perfoming a test of verbal knowledge and language (MWT-B, [53]).

Statistical analyses were carried out using the SPSS-PC package (Version 10.0) [54]. For the comparison of psychopathological items and neurocognitive test variables non-parametric procedures (e.g. Mann–Whitney-*U*-test) were used due to the finding, that not all variables showed normal distribution. The alpha level was set at 0.05. In addition, an analysis of covariance (ANCOVA) was performed to test the influence of age, gender and education on neurocognitive measures.

Results

According to structured clinical interview (Europ-ASI) lifetime drug abuse was reported by 32 of 68 patients with recent-onset schizophrenia or schizoaffective disorder. The abused drug (lifetime) was in 31 patients cannabis (THC), in 9 patients stimulants (amphetamines, ecstasy), in 6 patient cocaine, in 4 patients opiates, in 4 patients hallucinogens, and in 4 patients alcohol. In all cases the patients experienced their first hospitalization due to schizophrenic psychopathology. In 20 patients delta-9-tetrahydrocannabinol (THC) or metabolites, in 2 patients derivates of amphetamines, and in 2 patients both substances could be detected in urine at the time of admission.

Sociodemographic characteristics divided by the subgroups of schizophrenic patients with comorbid SUD and without substance abuse are presented in Table 1. Compared with nonabusers the sample of substance abusers was significantly younger, predominantly male, less married or living with a partner, had a lower level of education, had lower income and rate of employment, and revealed higher rates of first and second degree relatives with SUDs (mostly alcohol use disorder) and lower rates of family members with severe mental illness (SMI) (e.g. schizophrenic spectrum disorders, bipolar disorder and major depression).

Only slight differences in psychopathology concerning negative symptoms could be detected. Attentional impairment, expressed through the SANS subscore, was significantly less in abusers than in nonabusers on admission. There were no other significant differences in positive, negative and general psychopathology assessed by BPRS according to the subscales and SANS (composite score and remaining subscales). In addition, depressive symptoms (MADRS) in schizophrenic patients with SUD were similar to those of patients without substance abuse. Clinical ratings of disease severity (CGI) and global functioning showed similar results in both patients groups. Table 2 presents more detailed results.

Since it has been demonstrated that acute and chronic administration of antipsychotic medication, benzodiazepines and anticholinergic drugs impair performance on neurocognitive tasks requiring vigilance, attention, and especially motor speed in schizophrenic patients [55], and second-generation antipsychotics provide benefits in neurocognitive peformance [56], the pattern and dosage of administered psychotropic medication was compared between abusers (SUD) and nonabusers (NSUD) in our study sample. There was no significant differences between these subgroups in regard to this. Patients were treated mostly with first-generation antipsychotics (SUD vs. NSUD; near admission: 87% vs. 90%; 4 weeks later: 69% vs. 78%), due to increasing antipsychotic-induced parkinsonism with anticholinergic medication (biperiden) (near admission: 17% vs. 22%; 4 weeks later 39% vs. 42%) and with benzodiazepines (near admission: 87% vs. 89%; 4 weeks later 54% vs. 72%). Scoring for extrapyramidal symptoms (EPS) revealed no significant differences between schizophrenic patients with and without SUD (Mann–Whitney-*U*-test), additionally there was no significant difference in mean chlorpromazine equivalents (Mann–Whitney-*U*-test).

Because not all patients were willing to complete cognitive testing, a series of tests were conducted to examine whether sociodemographic variables and psychopathology differed between study participants for whom cognitive functioning data were available at

Table 2 Comparison of clinical characteristics on admission

	Abusers	Nonabusers	*p*
No. of patients (% of all patients)	21 (48%)	23 (52%)	–
CGI (mean, SD)	6.4 ± 0.8	6.4 ± 0.8	n.s.
GAF (mean, SD)	28.1 ± 8.3	29.2 ± 10.3	n.s.
BPRS total score	56.3 ± 10.8	51.3 ± 21.2	n.s.
BPRS-subscales (mean, SD)			
Anxiety/depression	12.9 ± 3.7	11.5 ± 5.2	n.s.
Anergia	9.4 ± 4.6	11.2 ± 4.7	n.s.
Thought disorder	13.9 ± 4.1	12.5 ± 5.9	n.s.
Activation	9.9 ± 4.5	8.8 ± 4.0	n.s.
Hostility/suspiciousness	10.3 ± 4.9	8.3 ± 3.2	n.s.
SANS-composite score, (mean, SD)	38.1 ± 26.6	42.5 ± 23.9	*0.063*
SANS-subscales (mean, SD)			
Affective flattening	7.2 ± 8.9	10.7 ± 8.3	n.s.
Alogia	5.0 ± 4.0	7.7 ± 5.1	*0.062*
Avolition/apathy	5.6 ± 3.6	5.4 ± 3.1	n.s
Anhedonia	8.3 ± 5.4	11.0 ± 5.1	n.s.
Attentional impairment	3.1 ± 2.4	4.8 ± 2.5	***0.024***
MADRS (mean, SD)	16.0 ± 8.5	19.6 ± 10.8	n.s.

p = probability, Mann–Whitney-*U*-Test; SD = standard deviation; n.s. = not significant; CGI = Clinical Global Impressions; GAF = Global Assessment of Functioning; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; MADRS = Montgomery Asberg Depression Rating Scale

initial assessment, at follow-up and for subjects who did not complete or participate in neurocognitive testing. There was no significant difference between these groups (68 patients vs. 44 patients) in sociodemographic or clinical data.

As shown in Table 3 schizophrenic patients with and without SUD showed similar performance in most cognitive domains, when acute schizophrenic episode was stabilized (4–6 weeks after admission). A significant advantage for patients without SUD could only be detected in terms of Verbal Fluency (only category letter; $p = 0.029$, Mann–Whitney-*U*-test) and at trend level in short-term memory (only Digit Span backwards; $p = 0.050$, Mann–Whitney-*U*-test). Subjects with comorbid SUD seemed to perform slightly better in executive function comparing the means of WCST, however the difference was not significant. If we corrected the results of Verbal Fluency and in a separate analysis the results of Digit Span backwards for age, gender and education as potential confounding factors (covariates), only Verbal Fluency remained different between groups. There was better performance in schizophrenic patients without SUD ($p = 0.030$, ANCOVA).

To detect an influence of psychopathology on neurocognition we performed correlations between BPRS total score, SANS composite score, the related subscales and the results of neurocognitive tests (Pearsons's product-moment correlations). No significant correlation between psychopathological items and neurocognitive domains could be found.

Discussion

One of the aims of the study presented here was to investigate if neuropsychological function differs in schizophrenic patients with and without comorbid substance abuse even in the early course of the disorder. It could be expected that schizophrenic

Table 3 Comparison of neurocognition after stabilization

	Abusers	Nonabusers	*p*
No. of patients (% of all patients)	21 (48%)	23 (52%)	–
Premorbid IQ (mean, SD)	106 ± 11.8	102 ± 9.6	n.s.
TMT-A (mean, SD), seconds	39.6 ± 15.6	39.5 ± 16.9	n.s.
TMT-B (mean, SD), seconds	101.9 ± 54.3	100.0 ± 55.8	n.s.
Digit-Span, forward (mean, SD), total score	6.7 ± 0.9	6.8 ± 0.9	n.s.
Digit-Span, backward (mean, SD), total score	3.9 ± 1.3	4.8 ± 1.4	***0.050***
Verbal fluency, letter (mean, SD), no. of words	9.6 ± 2.6	12.3 ± 4.2	***0.029***
Verbal fluency, semantic (mean, SD), no. of words	13.6 ± 4.8	13.8 ± 5.7	n.s.
Corsi (mean, SD), total score	5.6 ± 1.0	5.4 ± 1.2	n.s.
WCST (mean, SD), no. of correct trials	37.2 ± 2.9	34.9 ± 4.9	n.s.
WCST (mean, SD), no. of total errors	5.7 ± 3.6	8.6 ± 5.4	n.s.
WCST (mean, SD), no. of perseveration errors	1.1 ± 1.4	1.7 ± 1.8	n.s.

p = probability, Mann–Whitney-*U*-Test; SD = standard deviation; n.s. = not significant; TMT = Trail Making Test; Corsi = Corsi Block Tapping Test; WCST = Wisconsin Card Sorting Test

patients with substance abuse would perform worse on neurocognitive testing due to literature describing poor outcome of schizophrenic patients with comorbid SUD and with regard to the knowledge that the extended use of substances (e.g. alcohol, cannabis and cocaine) can lead to cognitive impairment.

The presented study could not confirm this suggestion. In our sample patients with recent-onset schizophrenia or schizoaffective disorder and comorbid substance abuse (SUD) showed no significant differences in a wide range of cognitive domains including verbal fluency, visual-spatial ability and motor speed, short-term memory and early information processing, attention, and executive functioning and cognitive flexibility. The significant better results of the nonabuser group in only one of two tests for short-term memory (Digit Span backwards) and Verbal Fluency (only category letter) could not sufficiently confirm superior performance in these cognitive domains. In this sample, in contrast to our expectations, younger age in the subgroups was not associated with better test performance. In consequence significant differences in age between the schizophrenic patients with and without SUD may not serve as a major confounding factor for cognitive function in this sample. The described sociodemographic characteristics in both patient subgroups are consistent with literature, revealing younger age, minor level of education, and higher rates of unemployment and marriage in the substance abuser group [1, 2, 10, 13, 57]. The prevalence of substance abuse in recent-onset schizophrenia observed in our study sample is also in line with the reported rates in first-episode schizophrenic spectrum disorder [10, 58–60]. The pattern of abused drugs is similar to that observed in European studies, presenting high prevalence of cannabis and low prevalence of other drugs in contrast to US surveys showing high rates of cocaine consumers [61, 62]. One large first-episode study demonstrated that drug abuse preceded the first schizophrenic symptom, emerged within the same time range or followed it, each pattern in nearly similar percentage [63]. Therefore a unidirectional causality between substance abuse and schizophrenia is not supported, and different etiological models have been developed. In another study a strong association between the use of cannabis and an earlier age at first psychotic episode in males (patients were about 7 years younger than nonabusers) was detected [64]. In contrast, gender but not cannabis use predicted an earlier age at first social dysfunction and negative symptoms. All together these findings point towards the hypothesis that substance abuse may influence the age of onset of positive symptoms in a subgroup of individuals, but other explanations for the mentioned study results cannot be ruled out. Differences in psychopathology between abusers and nonabusers were reported inconsistently in the recent literature. Comorbid substance abuse has been associated with higher positive symptomatology [65–67], lower negative symptoms [17, 66, 68], and fewer positive and negative symptoms [57]. Because the overall differences in psychopathology between substance using and nonusing schizophrenics were small [66], our results of similar scores in positive, negative and general symptoms except lower attentional impairment according to SANS subscale in comorbid SUD, are not surprising.

Most studies did not find an additional cognitive impairment in individuals with schizophrenia who use substances, especially focusing on alcohol and cannabis abuse [28, 33–35]. One study found even better neuropsychological performance of patients with lifetime history of cannabis abuse in verbal and spatial recognition or recall [37], but differences of memory function were no longer significant after adjustment on covariables (e.g. age, gender, education). In contrast to these cognitive domains subjects with comorbid cannabis use disorder performed poorly on an interference task (Stroop-Test). In another study including patients with bipolar disorder individuals with past or current substance abuse, mostly alcohol and cannabis, had better nonverbal functioning than those who never abused drugs or alcohol [69]. This result suggests premorbid advantage for the substance abuser group, taking into consideration the observed better instrumental role functioning compared to the nonabuser group in this study. Examining the relative effect of cognitive impairment and substance abuse on rehospitalization, a study found that substance abuse predicted prior hospitalizations (frequency), and cognitive impairment on the WCST was a significant predictor of the months hospitalized (duration) [70]. However, substance abuse was not significantly associated with cognitive measures. A recent study demonstrated more impaired memory function in older schizophrenic patients with comorbid alcohol abuse [31]. Some studies indicated that cognitive impairment in drug abusers occurs after prolonged and excessive use [71]. Considering the younger age, shorter illness duration and fewer amount of lifespan drug intake in our patients with recent-onset schizophrenia compared to subjects with chronic disease, it is possible that the effects of substance use on cognitive impairment are not yet evident. Additive effects on cognitive dysfunction may be seen only in patients with chronic use of certain (e.g. alcohol) or multiple substances [72]. Another study examining the impact of substance abuse, particular alcohol and cannabis, on neurocognitive function in a sample of first-episode patients revealed no significant associations, similar to our results [28]. There may be an alternative and more important explanation of our findings. Substance abuse may contribute to an earlier onset of schizophrenia and induce psychotic disorder before neurocognitive impairment becomes prominent assuming an interaction between neurodevelopmental

and neurodegenerative processes in the etiology of schizophrenia. This suggestion may be limited by the results of studies evaluating that only a subset of schizophrenic patients used drugs prior to the onset of schizophrenia [59, 67]. A recent study comparing schizophrenia, affective disorder and substance-induced psychotic disorder in young people with first-episode psychosis demonstrated that neurocognitive performance of the substance-induced psychosis group lay between the neuropsychological profile of schizophrenic and affective disease [73]. One interpretation of the authors was, that the similarity in performance of schizophrenia and substance-induced psychosis could reflect some degree of diagnostic overlap with a percentage of subjects in the induced-psychosis group progressing to schizophrenia as their illness evolves. In addition to the herein presented results of similar cognitive performance of schizophrenic patients with and without SUD, we found fewer subtle abnormalities of brain morphology in schizophrenic patients with comorbid substance abuse [74]. This may argue for substance abuse as a main risk factor progressing to schizophrenia in a subgroup of individuals.

There are several limitations of our study. The sample size may be too small to detect significant differences in neurocognitive measures, nevertheless it seems comparable to other studies (e.g. 73]. We did not match the group of abusers with nonabusers for age, gender or education and had no comparison with a healthy control group. The intention of the study was an analysis of neurocognitive function in a consecutive sample of patients with recent-onset schizophrenia eligible for inpatient treatment. Therefore our results should be interpreted as findings in a naturalistic and not experimental sample. Naturalistic designs may have more clinical implications than investigations of a strongly selected sample of patients, although studies showed that patients included in clinical trials were representative of the patient encountered in routine clinical practice [75]. The presented results should be interpreted with caution, have to be replicated and need further investigation on larger samples including neurobiological parameters (e.g. volumetric measurement of multiple brain regions by magnetic resonance imaging, genetics, functional MRI, event related potentials) and longer follow-up periods to correlate neurocognitive function with the course of schizophrenic disorder in the large subgroup of individuals with comorbid substance abuse.

Conclusions

In patients early in the course of schizophrenia substance abuse seems not to be related to cognitive functioning and patients with comorbid SUD do not reveal higher cognitive impairment compared to patients without substance abuse. The lack of higher cognitive disturbance in schizophrenic patients with comorbid substance abuse may encourage clinicians to design psychological approaches, for instance cognitive behavioural approaches of drug therapy, to prevent persisting substance abuse to reduce the high rates of acute exacerbations and hospitalizations, and to influence the unfavourable course in this subgroup of patients by integrated treatment programmes using cognitive strategies.

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