The Treatment of Sedative-Hypnotic Dependence: Evaluating Clinical Predictors of Outcome

Dara A. Charney, M.D., F.R.C.P.C.;
Antonios M. Paraherakis, M.Sc.; and Kathryn J. Gill, Ph.D.

Background: The objectives of this 6-month prospective study were to evaluate the efficacy of detoxification treatment for sedative-hypnotic dependence, examine the demographic and clinical predictors of outcome, and determine whether anxiety or other psychiatric comorbidity has a negative impact on outcome.

Method: Eighty-two patients with alcohol or benzodiazepine dependence (DSM-IV diagnostic criteria) were consecutively recruited upon entering treatment and were assessed by clinical and semistructured interviews, the Global Assessment Scale, the Hamilton Rating Scale for Depression, the Beck Depression Inventory, the revised 90-item Symptom Checklist, and urine drug screening.

Results: Both alcohol- and benzodiazepine-dependent patients succeeded in reducing their reported use of sedative-hypnotic substances during the follow-up period. However, at 3 months, benzodiazepine-dependent patients fared less well than alcohol-dependent patients in terms of several outcome measures: they reported a lower rate of achieving abstinence, shorter periods of continuous abstinence, and more frequent drug use. At 6 months, the differences in outcome among the drug groups were not maintained. Variables such as sex, drug group, and indicators of psychiatric status had little impact on outcome measures. Benzodiazepine-dependent patients reported significant decreases in their level of anxiety over the follow-up period despite substantial reductions in benzodiazepine use.

Conclusion: Clinicians may be encouraged regarding the detoxification of patients who have used benzodiazepines at high doses or for long periods of time, or who have comorbid anxiety or other psychiatric disorders.

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Received March 9, 1999; accepted Oct. 14, 1999. From the Addictions Unit, Montreal General Hospital and the Department of Psychiatry, McGill University, Montreal, Canada.

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Reprint requests to: Dara A. Charney, M.D., F.R.C.P.C., Addictions Unit, Montreal General Hospital, 1604 Pine Ave. W., Montreal, QC H3G 1B4, Canada.

Benzodiazepines are prescribed for a number of acute psychiatric and medical illnesses; there are fewer indications for long-term use of benzodiazepines, as their benefits are offset by the risks of dependence and adverse events.[1–3] Benzodiazepine dependence is a common complication of high-dose or long-term benzodiazepine use[4–6] and is characterized by a well-described withdrawal syndrome.[4,7,8] Adverse effects of benzodiazepines include central nervous system depression with drowsiness, lightheadedness, increased reaction time, ataxia, dysarthria, anterograde amnesia, and impaired cognitive and motor function.[6,9–11] Among the elderly, benzodiazepine use is a major independent risk factor for cognitive decline,[12,13] accidental falls and hip fractures,[14–16] and injurious motor vehicle crashes.[17,18] Furthermore, benzodiazepine use is associated with a heavy burden on the health care system. Among 76 benzodiazepine-dependent patients, detoxification decreased the use of outpatient medical and mental health services from an average of 25.4 visits per year to 4.4 per year, and presumably diminished the costs of care.[19]

Acute detoxification is largely successful,[20] but longer-term outcomes are more variable—rates of abstinence from benzodiazepines, 6 months to 5 years after treatment, range from 38% to 92% in different studies.[21–24] A significant number of patients may experience intolerable anxiety or other withdrawal symptoms or may be unable to remain drug-free and consequently relapse after detoxification. Several drug variables are associated with a more severe withdrawal and a worse treatment outcome, including a higher dose, more rapid taper, longer duration of use, and shorter drug half-life.[25–27] However, the success of benzodiazepine detoxification is only partly related to drug variables; patient factors, such as Axis I and II psychopathology, may have important effects on outcome. Schweizer et al.[28] demonstrated that residual levels of anxiety and depression, at the beginning of detoxification, predict both increased withdrawal severity and decreased rates of achieving abstinence. Joughin et al.[24] showed that benzodiazepine-dependent patients with depressive disorders have worse outcomes after inpatient detoxification, whereas patients with anxiety disorders have better outcomes. Several authors found that patients with passive or dependent personalities experience more marked with-

drawal symptoms during benzodiazepine tapers[28–31] and are less likely to complete treatment.[28] In contrast, other authors reported that psychopathology has no impact on treatment outcome.[21,22]

The objectives of this 6-month prospective study were to evaluate the efficacy of detoxification treatment for the more prevalent forms of sedative-hypnotic dependence (i.e., alcohol versus benzodiazepine dependence), examine the demographic and clinical predictors of outcome, and determine whether anxiety or other psychiatric comorbidity has a negative impact on outcome.

METHOD

Subjects

The sample included male and female patients who sought treatment at the Montreal General Hospital (MGH) Addictions Unit. The Addictions Unit provides comprehensive ambulatory care to adults with all forms of psychoactive substance use disorders; it pursues a treatment philosophy of total abstinence and provides integrated care for comorbid psychiatric disorders. Subjects were consecutively recruited upon entering treatment. All patients were eligible for the study, since there were no exclusion criteria. Patients were explained the study's procedure as well as the risks and benefits of standard treatment; 120 provided signed informed consent, and 2 declined to participate. For the purposes of this analysis, only patients with alcohol or benzodiazepine dependence (DSM-IV diagnostic criteria) were included (N = 82).

Procedure

Initial interviews were conducted to collect information on demographics, education, employment, and alcohol and drug consumption. Subjects completed the Beck Depression Inventory (BDI)[32] and the revised 90-item Symptom Checklist (SCL-90)[33] and provided a urine sample for drug screening (cloned enzyme donor immunoassay). They also had a psychiatric assessment, consisting of a clinical interview, the Structured Clinical Interview for DSM-IV (SCID-IV),[34] the Global Assessment Scale (GAS),[35] and the 21-item Hamilton Rating Scale for Depression (HAM-D).[36] Psychiatric diagnoses were based on the SCID-IV and clinical interviews.

During the 6-month follow-up study, subjects were offered standard treatment: outpatient detoxification, one or two 90-minute psychoeducational group therapy sessions per week, 4 or more 50-minute supportive individual therapy sessions, and urine drug screens throughout treatment. The detoxification regimen for alcohol dependence included a 1- to 2-week tapering prescription of diazepam (starting doses ranging from 20 to 80 mg/day); the regimen for benzodiazepine dependence involved a 2- to 10-week tapering prescription of diazepam or clonazepam (starting doses ranging from 10 to 80 mg/day of diazepam or 1 to 8 mg/day of clonazepam). If subjects were unable to tolerate or adhere to outpatient protocols, they were offered inpatient detoxification. Additional psychiatric treatment was provided if indicated. Subjects were encouraged, but not required, to attend mutual help groups, such as Alcoholics Anonymous.

At 3 and 6 months, all subjects, including those who had dropped out of treatment, were recontacted and invited to attend follow-up interviews. During the follow-up interviews, subjects were questioned regarding the outcome of treatment (retention in treatment, abstinence, and substance consumption), psychiatric symptoms (HAM-D, BDI, and SCL-90), and psychosocial functioning (GAS). They were again asked to provide a urine sample for drug screening. Individuals who were unable or reluctant to return for follow-up visits were interviewed over the telephone.

Statistical Analyses

Data collected at the initial and follow-up visits were coded and entered into a database using the scientific software program RS/1 (version 4.3.1; BBN Software Products Corporation, Cambridge, Mass.). Statistical analyses were conducted using the microcomputer version of SPSS (version 7; SPSS Inc., Chicago, Ill.). Associations were examined using the chi-square test for categorical data, and comparisons between groups or time points were assessed using analysis of variance (ANOVA) techniques, including those for multiple variables and repeated measures (MANOVA). Post hoc tests were conducted using t tests with Bonferroni correction. Relationships between demographic variables, alcohol and drug use, and psychiatric status and outcome measures were assessed using multiple and hierarchical regression techniques. Data on retention in treatment was analyzed using the SPSS Survival program. Outcome variables were examined for outliers using the SPSS Explore program, leading to the removal of data for 3 subjects for the variables of substance consumption (percentage change at 3 and 6 months) and 3 subjects for the variable of benzodiazepine consumption (percentage change at 6 months).

RESULTS

Sample Description

Among the 82 patients with sedative-hypnotic use disorders, 41 patients were pure alcoholics (Alcohol-only group), 16 patients were alcoholics who used at least 1 other drug (Alcohol+ group), and 25 patients suffered from benzodiazepine dependence (Benzo group). The mean ± SD duration of their substance use disorders was 9.55 ± 8.91 years. The Benzo group had a briefer history of dependence than the Alcohol groups, i.e., older age at onset ($F = 66.93$, $df = 2,78$; $p < .001$) and shorter duration of problem use ($F = 5.17$, $df = 2,73$; $p = .008$).

The demographic characteristics of the sample at intake are presented in Table 1. The Alcohol+ group differed from the other groups with regard to most demographic variables; they were younger ($F = 8.42$, $df = 2,79$; $p < .001$) and more often single ($\chi^2 = 16.09$, $df = 6$, $p = .013$), unemployed ($\chi^2 = 30.66$, $df = 12$, $p = .002$), or receiving welfare ($\chi^2 = 23.32$, $df = 10$, $p = .010$). The Benzo group differed from the Alcohol groups only in terms of sex, as the Benzo group was predominantly female ($\chi^2 = 7.31$, $df = 2$, $p = .026$).

Psychiatric assessments revealed that 68.3% (N = 56) of the sample met DSM-IV criteria for a lifetime diagnosis of a mood disorder, 62.2% (N = 51) for a lifetime diagnosis of an anxiety disorder, and 32.9% (N = 27) for personality disorders. A total of 58.5% (N = 48) of subjects reported prior suicide attempts, whereas 39.5% (N = 32) reported a history of violent behavior. Both the Benzo and Alcohol+ groups had more psychopathology than the Alcohol-only group at intake, but differed in the nature of their psychiatric difficulties. The Benzo group was more anxious than the Alcohol-only group at intake, i.e., a greater lifetime prevalence of anxiety disorders ($\chi^2 = 16.61$, $df = 2$, $p < .001$), higher HAM-D anxiety subscale score ($F = 3.40$, $df = 2,79$; $p = .038$), higher SCL-90 anxiety subscale score ($F = 3.12$, $df = 2,78$; $p = .050$), and higher SCL-90 somatization subscale score ($F = 4.41$, $df = 2,78$; $p = .015$), whereas the Alcohol+ group was more impulsive than the other groups at intake, i.e., a greater lifetime prevalence of suicide attempts ($\chi^2 = 6.88$, $df = 2$, $p = .032$), violent behavior ($\chi^2 = 8.31$, $df = 2$, $p = .016$), personality disorders ($\chi^2 = 8.58$, $df = 2$, $p = .014$), and legal difficulties ($F = 10.21$, $df = 2,78$; $p < .001$).

Review of treatment files revealed that during the 6-month follow-up period, subjects attended a mean ± SD of 14.4 ± 13.0 group therapy sessions, 6.6 ± 5.4 individual therapy sessions, and 3.2 ± 2.6 psychiatric appointments. A total of 13.4% (N = 11) of subjects required inpatient detoxification, and 36.7% (N = 30) were prescribed antidepressant medications. The Benzo group received more treatment than the Alcohol groups; specifically, they had more individual therapy sessions ($F = 6.42$, $df = 2,78$; $p = .003$), and more psychiatric appointments ($F = 7.31$, $df = 2,78$; $p = .001$).

Table 1. Demographic Characteristics of the Sample at Intake[a]

Demographic Characteristic	Alcohol-Only (N = 41)	Alcohol+ (N = 16)	Benzo (N = 25)	Total (N = 82)	p Value
Age, y, mean ± SD	46.3 ± 11.9	33.8 ± 7.4	44.0 ± 9.5	43.2 ± 11.4	< .001
Sex					.026
Male	26 (63.4)	12 (75.0)	9 (36.0)	47 (57.3)	
Female	15 (36.6)	4 (25.0)	16 (64.0)	35 (42.7)	
Race					NS
White	36 (87.8)	16 (100)	24 (96.0)	76 (92.7)	
Visible minority	5 (12.2)	0 (0)	1 (4.0)	6 (7.3)	
Marital status[b]					.013
Single	13 (31.7)	13 (81.3)	7 (28.0)	33 (40.2)	
Married	18 (43.9)	1 (6.3)	14 (56.0)	33 (40.2)	
Divorced	8 (19.5)	2 (12.5)	3 (12.0)	13 (15.9)	
Education					NS
High school graduate	35 (85.0)	9 (56.3)	18 (72.0)	62 (76.2)	
University graduate	11 (27.5)	2 (12.5)	4 (16.0)	17 (20.9)	
Employment[c]					.002
Employed	23 (56.1)	3 (18.8)	7 (28.0)	33 (40.3)	
Unemployed	7 (17.1)	12 (75.0)	10 (40.0)	29 (35.4)	
Main income[b]					.010
Employment	18 (43.9)	3 (18.8)	5 (20.0)	26 (31.7)	
Family	10 (24.4)	1 (6.3)	7 (28.0)	18 (22.0)	
Welfare	6 (14.6)	10 (62.5)	9 (36.0)	25 (30.5)	

[a]All values shown as N (%) unless otherwise specified. Abbreviations: Benzo = patients with benzodiazepine dependence, Alcohol-Only = pure alcoholics, Alcohol+ = alcoholics who used at least 1 other drug.
[b]Values shown for only the 3 most frequently identified demographic categories.
[c]Values shown for only the 2 most frequently identified demographic categories.

Table 2. Outcome of Addiction Treatment at 3 Months

Outcome Measure	Alcohol-Only (N = 39)	Alcohol+ (N = 15)	Benzo (N = 23)	Total (N = 77)	p Value
Achievement of abstinence, N (%)	36 (92.3)	13 (86.7)	6/12[a] (50.0)	55/66 (83.3)	.003
Duration of abstinence, d, mean ± SD	51.6 ± 32.2	46.5 ± 34.8	23.7 ± 28.2	45.7 ± 33.3	.046
Frequency of daily use, N (%)	2 (5.1)	0 (0)	9 (39.1)	11 (14.3)	.004
Change in use, amount × frequency	–26.2	–48.6	–48.3	–36.5	NS
Retention in treatment, d, mean ± SD	71 ± 30	73 ± 32	78 ± 26	74 ± 29	NS

[a]Data missing for some patients.

Outcome of Addiction Treatment at 3 and 6 Months

Seventy-seven (93.9%) of the 82 patients with alcohol or benzodiazepine use disorders participated in the 3-month follow-up interviews (56 face-to-face and 21 telephone interviews), and 78 (95.1%) participated in the 6-month follow-up interviews (48 face-to-face and 30 telephone interviews).

The outcome of treatment at 3 months is summarized in Table 2. The Benzo group fared less well than the 2 Alcohol groups in terms of several addiction outcome measures at 3 months. They reported a lower rate of achieving abstinence ($\chi^2 = 11.98$, $df = 2$; $p = .003$), shorter periods of continuous abstinence ($F = 3.23$, $df = 2,62$; $p = .046$), and more frequent drug use ($\chi^2 = 29.15$, $df = 12$; $p = .004$).

The outcome of treatment at 6 months is summarized in Table 3. The differences in outcome among the Benzo and Alcohol groups were not maintained at 6 months. The Benzo group fared as well as the Alcohol groups in terms

Table 3. Outcome of Addiction Treatment at 6 Months

Outcome Measures	Alcohol-Only (N = 39)	Alcohol+ (N = 15)	Benzo (N = 24)	Total (N = 78)	p Value
Achievement of abstinence, N (%)	32 (82.1)	12 (80.0)	7/12[a] (58.3)	51/66 (77.3)	NS
Duration of abstinence, d, mean ± SD	55.4 ± 38.6	55.7 ± 41.0	41.9 ± 41.6	53.1 ± 39.4	NS
Frequency of daily use, N (%)	3 (7.7)	1 (6.7)	7 (29.2)	11 (14.1)	NS
Change in use, amount × frequency	–27.7	–42.1	–55.4	–38.7	NS
Retention in treatment, d, mean ± SD	128 ± 67	119 ± 67	129 ± 66	127 ± 67	NS
Positive urine toxicology screens, %	10.9	6.0	49.2	16.4	< .001

[a]Data missing for some patients.

of all addiction outcome measures, with the exception of a higher rate of positive urine drug screens ($F = 11.27$, $df = 2,66$; $p < .001$). (N.B.: the rate of positive urine screens at 3 months was not calculated, as lengthy benzodiazepine tapers resulted in positive screens during most of the first 3 months, which did not discriminate between prescribed use and possible abuse.)

Multiple and hierarchical regression analyses were conducted to determine independent predictors of outcome. Relevant demographic and clinical variables were factored into the analyses, including sex, drug group (Benzo, Alcohol-only, Alcohol+), frequency of drug use at intake, anxiety diagnosis, depression diagnosis, total and subscale scores on psychometric measures (HAM-D, BDI, SCL-90, and GAS), and use of antidepressant medication. Stepwise regression revealed that frequency of drug use at intake was the best predictor of many outcome measures at 3 and 6 months, including duration of continuous abstinence at 3 months ($R^2 = 0.236$, $p < .001$), duration of continuous abstinence at 6 months ($R^2 = 0.145$, $p = .002$), frequency of use at 6 months ($R^2 = 0.114$, $p = .006$), and rate of positive urine drug screens at 6 months ($R^2 = 0.310$, $p < .001$). Drug group did not generally emerge as an independent predictor of outcome. However, drug group was the second variable entered in the stepwise regression of positive urine drug screens at 6 months, where, together with the frequency of drug use at intake, it accounted for 35% of the variance in positive urine screens ($p < .001$). None of the psychiatric variables were independent predictors of outcome.

Anxiety Symptoms at 3 and 6 Months

At 3 months, the Benzo group remained more anxious than the Alcohol groups on all 4 measures of anxiety, i.e., HAM-D anxiety/agitation subscale ($F = 4.29$, $df = 2,53$; $p = .019$), HAM-D vegetative symptoms subscale ($F = 4.46$, $df = 2,53$; $p = .016$), SCL-90 anxiety subscale ($F = 5.44$, $df = 2,53$; $p = .007$), and SCL-90 somatization subscale ($F = 5.79$, $df = 2,53$; $p = .005$). At 6 months, the Benzo group was more anxious than the Alcohol groups on only 2 of the 4 anxiety measures, i.e., HAM-D anxiety/agitation subscale ($F = 4.64$, $df = 2,45$; $p = .015$), and SCL-90 somatization subscale ($F = 4.99$, $df = 2,45$; $p = .011$). Although differences in anxiety measures among the drug groups persisted throughout the follow-up period, the Benzo group did report significant decreases in their level of anxiety during the 6 months. The Benzo group became less anxious despite substantial reductions in benzodiazepine use ($t = 3.49$, $df = 20$, $p = .002$). Figure 1 depicts the changes in the Benzo group's anxiety symptoms during the follow-up period.

DISCUSSION

Both alcohol- and benzodiazepine-dependent patients succeeded in reducing their reported use of sedative-hypnotic substances during the course of treatment, as shown in Tables 2 and 3. However, at 3 months, benzodiazepine-dependent patients fared less well than alcohol-dependent patients in terms of several addiction outcome measures. They reported a lower rate of achieving abstinence, shorter periods of continuous abstinence, and more frequent drug use. Benzodiazepine withdrawal often requires more time than alcohol withdrawal; the literature on the treatment of benzodiazepine dependence suggests a careful, slow, and flexible taper of benzodiazepines lasting as long as 3 months in some instances.[26] Benzodiazepine-dependent patients are more likely to have had a worse outcome at 3 months due to protracted detoxification regimens (2 to 10 weeks) rather than to a lack of compliance with treatment recommendations.

By 6 months, the differences in treatment outcome among drug groups were not maintained. The only difference in outcome that persisted over the follow-up period was a higher rate of positive urine drug screens among benzodiazepine-dependent patients. Given that all other outcome measures were equivalent at 6 months, this may be best explained by the longer half-lives of many benzodiazepine compounds, in comparison to alcohol, which result in a greater likelihood of a positive drug screen several days after substance use.

In terms of demographic and clinical predictors of outcome, variables such as sex, drug group, and indicators of psychiatric status had little impact on outcome measures. Neither anxiety nor general psychiatric comorbidity impeded the successful treatment of sedative-hypnotic dependence. The lack of impact of psychopathology is consistent with the results of some outcome studies,[21,22] and with earlier findings,[37] but differs from the results of Schweizer et al.[28] This discrepancy may be partly explained by the comprehensive nature of the treatment of-

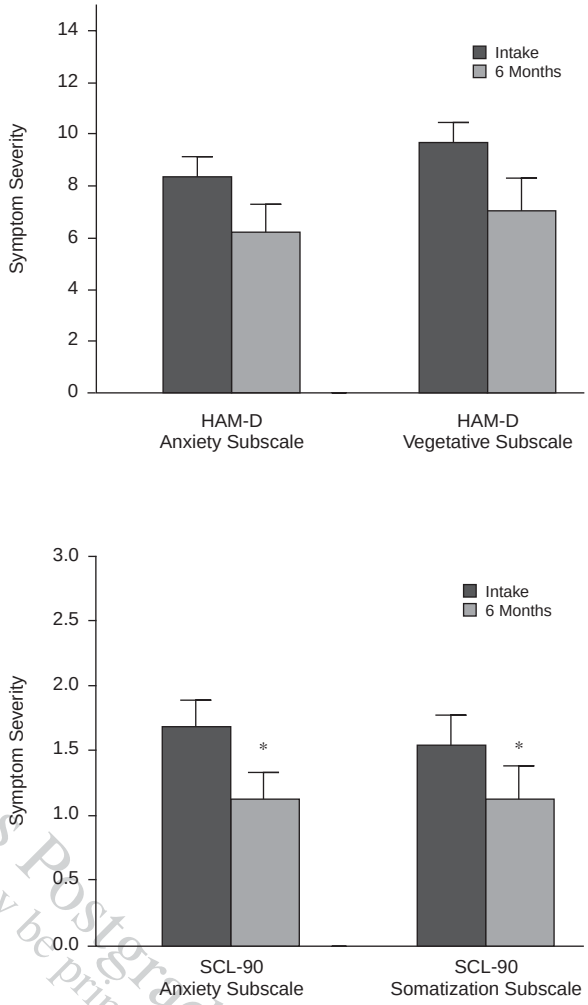
fered at the MGH Addictions Unit (i.e., psychiatric care was provided if indicated). Specific pharmacologic or psychological interventions may have mitigated the impact of psychopathology on outcome.

Benzodiazepine-dependent patients were more anxious than alcohol-dependent patients at intake and remained more symptomatic at both 3 and 6 months. However, despite substantial reductions in benzodiazepine use, benzodiazepine-dependent patients reported significant decreases in their level of anxiety over the follow-up period, as shown in Figure 1. Their diminished anxiety during detoxification suggests that these patients may not have been receiving much symptom relief from their drug use at intake. In this sample, most patients were initially prescribed benzodiazepines for anxiety symptoms and presumably benefited from these drugs at one time, i.e., 68% were prescribed benzodiazepines for anxiety, 16% used benzodiazepines for other indications, and 16% obtained benzodiazepines without a prescription. However, after chronic use and eventual dependence, it seems that they no longer obtained any clear anxiolytic effect and that subjective relief resulted from the attenuation of rebound or withdrawal anxiety.

There is still considerable debate regarding the long-term use of benzodiazepines for benzodiazepine-dependent patients with chronic anxiety disorders. Given the potential adverse effects of long-term use, and the fact that benzodiazepine-dependent patients may no longer experience much symptom relief from their drug use, an attempt to detoxify most of these patients is warranted. The finding of diminished psychiatric severity following benzodiazepine taper may encourage clinicians regarding the detoxification of addiction patients who have comorbid anxiety or other psychiatric disorders. Further research is needed to assess the relevance of this finding in a general psychiatric treatment population, to ascertain outcome over a longer follow-up period, and to evaluate whether the addition of specific anxiety management strategies results in a greater reduction in symptom severity either during or following benzodiazepine detoxification.

Drug names: clonazepam (Klonopin and others), diazepam (Valium and others).

Figure 1. Benzodiazepine-Dependent Patients: Anxiety Symptoms at Intake and at 6 Months[a]



[a]Benzodiazepine-dependent patients reported decreases in their level of anxiety on all 4 Hamilton Rating Scale for Depression (HAM-D) and Symptom Checklist-90 (SCL-90) anxiety subscales ($p < .05$) over the follow-up period. However, the differences in the HAM-D subscale scores were not significant when corrected for multiple comparisons; the differences in the SCL-90 subscale scores remained significant.
*$p < .0125$.

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