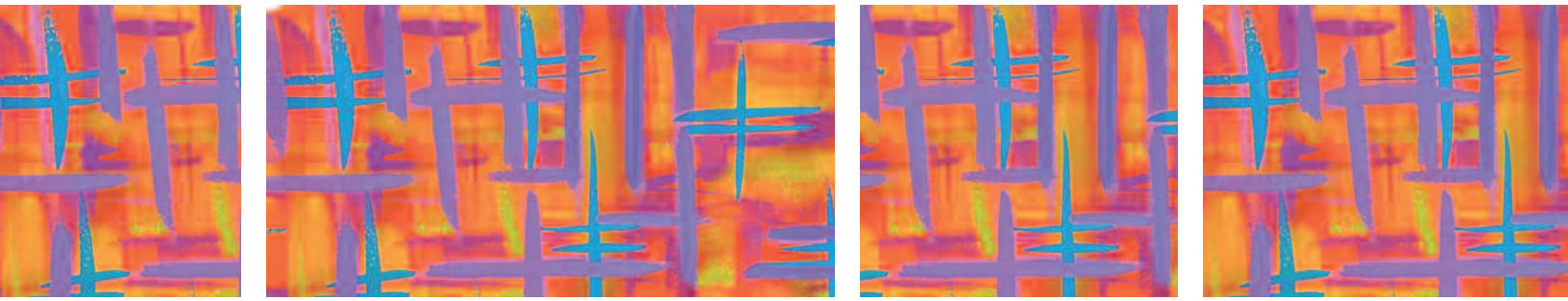
Adult ADHD: Issues and Answers

CME Newsletter of the Adult ADHD Program, Department of Psychiatry, NYU School of Medicine



Study Shows 5% to 35% of College Students May Use Nonprescribed Stimulants

A recent meta-analysis of the literature identifying 21 studies and representing 113,104 subjects showed that between 5% and 35% of college-age individuals used nonprescribed stimulants in the past year.[1] In addition, 16% to 29% of students with stimulant prescriptions were asked to give, sell, or trade their medications in the last 12 months. This presents 2 problems. First, medications are being diverted away from legitimate patients to individuals seeking the stimulant or euphoric effects of immediate-release stimulants. Second, patients who need the medications to control attention-deficit/hyperactivity disorder (ADHD) are going without their prescriptions and may be experiencing ADHD symptoms, undermining their quality of life.

Research suggests that whites, members of fraternities and sororities, individuals with lower grade point averages, individuals who use immediate-release vs extended-release preparations, and individuals who report persistent ADHD symptoms are at greatest risk for misusing and diverting stimulants.[1] Reported reasons for use, misuse, and diversion of stimulants include:

1. To improve concentration
2. To improve alertness
3. To get high
4. To experiment

Plenty of work remains to be done to curb the misuse and diversion of stimulant medications. Clinicians should advise patients of the potential for serious adverse outcomes, such as cardiovascular risks,

Table 1.
Supporting Studies in Which Adults Were Asked if They Misused Stimulants

Study	Patient Population	Type of Study	Age Group	Results	Comments
Teter et al[2]	4580 full-time undergraduates at large Midwestern US university	Web-based survey	Mean 20 years	8.3% lifetime stimulant misuse; 5.9% past-year misuse (76% Adderall, 25% Ritalin, 96% oral, 38% intranasal)	Whites and Hispanics report 3x more misuse than blacks and 2x more than Asians; Motive: study (60%), alertness (48%), get high (31%), experimentation (30%)
Upadhyaya et al[3]	Convenience sample of 334 students from a 4-year state college	Self-reported survey conducted in class	Mean 20.6 years	23% of sample was ever prescribed ADHD medications; of those, 25% used medications to get high, 29% gave/sold medications in their lifetime	High percentage of subjects had ADHD symptoms; results relate to substance use, not dependence/ abuse; 60% female
Hall et al[4]	381 undergraduate students	Student self-reported written survey via mail and in person	Mean 19.4 years	17% men and 11% women reported stimulant misuse for recreation and academics	Men's misuse predicted by knowing where to get stimulants, while women's misuse predicted by being offered stimulants

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Statement of Need
Research into attention-deficit/hyperactivity disorder (ADHD) has continued to expand our understanding of this chronic psychological disorder. Recent studies have explored differences between the sexes with regard to the manner in which ADHD manifests, its severity, and the complexity of its presentation, especially among female adults.[1] Additionally, with improvements in medical therapies for ADHD have come increasing concerns about misuse and diversion of ADHD-related therapeutics to individuals other than those for whom they were prescribed.[2] As our knowledge has expanded, early data from several small studies have implicated new potentially comorbid conditions and related underlying metabolic processes. Among these have been the newly described Internet addiction, restless legs syndrome, and iron deficiency as a possible contributing factor in several related disease states.[3,4] This newsletter will address the latest research in these areas and provide physicians with an improved understanding of ADHD, its comorbid conditions and manifestations, and a newly identified, potentially related metabolic process.

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Learning Objectives
After completing this activity, you should be able to:

- Discuss how ADHD presents in women and its contrasting manifestations, severity, and associated comorbidities
- Identify the potential for diversion and misuse of stimulant medications, the groups most at risk for such behavior, and strategies for prevention
- Recognize Internet addiction, discuss its definition and its possible link to ADHD
- Discuss recent research into the iron hypothesis as it relates to ADHD, restless legs syndrome, and Tourette syndrome

Method of Participation
Read this newsletter, complete the CME Posttest Answer Form and Activity Evaluation Form, and fax or mail the forms to Medical Education Resources, Inc. at the address listed. You will receive a certificate by fax or mail. There is no certificate processing fee.

Intended Audience
This activity was developed for psychiatrists, primary care physicians/internists, neurologists, and psychologists.

Effective Dates
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Use of Brand and Generic Names
Brand names of products for treating attention-deficit/hyperactivity disorder (ADHD) are used throughout this continuing medical education (CME) activity so that participants can distinguish among the many different formulations (duration of action, delivery system) of products with the same generic name.

Unlabeled Use Disclosure Statement
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Please consult the appropriate package insert for full prescribing information on all drug therapies discussed.

when misusing these drugs recreationally or through various routes of administration, such as snorting. Indeed, the FDA has asked manufacturers of amphetamines to include the following statement within the black box warning in the package inserts: "Misuse of amphetamines may cause sudden death and serious cardiovascular adverse risks." In addition, there are potential legal consequences of misuse or diversion of these Schedule II controlled substances to which the patient should be alerted. Also, individuals with ADHD for whom stimulants have been prescribed should be educated about secure storage of the medication. Instead of immediate-release stimulants, the use of nonstimulants or extended-release or prodrug stimulants is preferred in older high school and college students, particularly for individuals with known conduct disorder or substance abuse (SA) issues who are at the greatest risk for diverting or misusing their medication. Individuals identified for stimulant misuse should be evaluated for SA and other potential problems and they should be educated about the pitfalls of misuse and diversion of stimulants. Individuals suspected of misusing stimulants for cognitive improvement who also manifest symptoms of ADHD or learning disabilities may benefit from further evaluation. Although it remains to be shown, the identification and optimal treatment of high school and college students with ADHD may result in lower rates of misuse and diversion of stimulants.

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Evaluate Internet Addicts for ADHD, Depression

One of the newest addictions, to the Internet, is being linked to ADHD in a number of new Asian-based studies.[1-3] Internet addiction disorder (IAD) refers to the problematic use of the Internet, including the various aspects of its technology, such as e-mail and the Web. It has been defined as "an individual's inability to control his or her use of the Internet, which eventually causes psychological, social, school, and/or work difficulties in a person's life."[4] Although IAD has been formally recognized as a disorder by the American Psychological Association, it is not listed in the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, Fourth edition, text revision (2000). In June 2007, the American Medical Association declined to recommend to the American Psychiatric Association that they include IAD as a formal diagnosis in the 2012 edition of the *DSM*.

IAD research continues

One study of Chinese adolescents assessed whether IAD is related to impulsivity.[1] Researchers used the Diagnostic Questionnaire for Internet Addiction (YDQ) to identify 50 students who were diagnosed with IAD (mean age, 15 years) and 50 students with normal Internet usage (mean age, 15 years). The 2 groups were assessed using Barratt Impulsiveness Scale 11 (BIS-11) and behavioral measure of impulsivity (GoStop Impulsivity Paradigm). The IAD group had significantly higher scores on the BIS-11 subscales of attentional key, motor key, and total scores than the control group ($P<0.05$). The IAD group scored higher than the control group on the failure to inhibit responses of GoStop Impulsivity Paradigm ($P<0.05$). A significant positive correlation was observed between YDQ scores and BIS-11 subscales and the number of failure-to-inhibit responses of GoStop Impulsivity Paradigm.

Another study sought to determine the association between IAD and depression, self-reported symptoms of ADHD, social phobia, and hostility in adolescents and to evaluate the gender differences of association between IAD and the aforementioned psychiatric symptoms among adolescents.[2] The study found that adolescents with IAD are more likely to be male, have higher academic grades, and use the Internet more than 20 hours/week. Playing online games (42%) is the most frequent Internet activity of Internet addicts, followed by online chatting (30%), downloading (5%), e-mail (2%), and adult sex Web sites (0.9%). Adolescents with IAD had higher scores on The Center for Epidemiological Studies' Depression Scale (CES-D), Social Phobia Inventory (SPIN), Attention-Deficit/Hyperactivity Disorder Self-Rated Scale (ADHDS), and The Chinese Hostility Inventory-Short Form (CHI-SF) for males, females, and all students ($P<0.001$ for all comparisons). Thus, the results demonstrated that adolescents with IAD had higher ADHD symptoms, depression, social phobia, and hostility. Yet another study revealed that adult ADHD and depressive disorders were associated with IAD among college students.[3] However, depressive disorders were associated with IAD in males but not in females.

Theories have been proposed to explain the relationship between adult ADHD and IAD. First, a shortened reward-delay gradient is reportedly one of the 4 endophenotypes of ADHD.[5] It is demonstrated in delay aversion, which is the preference for immediate small reward rather than delayed large reward.[5] The feeling of control, synchronous reward of chatting, and immediate reward provided by online gaming may satisfy students with this endophenotype more than other activities.[3] Also, the abnormal brain activity associated with the impaired inhibitory performance seen in ADHD may hinder an individual's ability to control or stop Internet use after engaging in these activities.[6] Regardless of which hypothesis is the more valid, persons with IAD should be evaluated and treated for ADHD and depressive disorders.

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Patient Improves With Longer-Lasting Formulation and CBT

Joe, 33, is a computer technician who is out on the road every day performing various jobs as part of his routine. He presents to his psychiatrist for an evaluation of his ADHD treatment. He was initially diagnosed with ADHD 10 years ago after he presented to his physician for treatment of chronic depression. His doctor determined that the depression was secondary to ADHD. Since then, Joe has been taking immediate-release methylphenidate (MPH) 10 mg, 3 times daily. However, he has actually been taking his medication only twice daily because he frequently forgets his midday dose while out on the job. Hence, he still has significant problems with procrastination, inattention, planning, paying bills on time, initiating tasks, and remembering what is said or read. These symptoms affect his work performance and his situation at home: he rarely pays his bills on time and his wife complains frequently that he does not listen to her. His father, recently diagnosed with ADHD himself, corroborates Joe's onset of procrastination and difficulty paying attention in early childhood, which consistently hampered his academic performance. Joe feels that ADHD partly contributed to his inability to finish college, even after changing schools 3 times. There is no current evidence of depression and no history of substance use disorders or mania. He presents with full affect and a euthymic mood. His psychiatrist switched his MPH to the longer-acting dexmethylphenidate hydrochloride extended-release (*d*-MPH XR; Focalin XR), which would allow for better medication adherence and treatment of symptoms throughout the day. This formulation would also boost treatment at the end of the day when the patient is impaired at home. The *d*-MPH XR was started at 10 mg each morning and titrated to 15 mg each morning with good response. Cognitive behavioral therapy was added and was successful in treating residual issues with planning and organization.

Key points of this case:

1. Extended-release MPH formulation can address issues of nonadherence and symptom reemergence
2. Medication can be coupled with cognitive behavioral therapy for a more complete response to quality-of-life issues

The Iron Hypothesis

Early but increasing evidence implies that ADHD, Tourette syndrome (TS), and restless legs syndrome (RLS) may be comorbid. Comorbid ADHD has been observed in up to 70% of patients with TS.[1] As many as 44% of ADHD patients have been found to have RLS or its symptoms, and up to 26% of RLS patients have been found to have ADHD.[2] In addition, the 3 conditions may be part of a spectrum in which iron deficiency contributes to the underlying pathophysiology. Iron deficiency might lead to ADHD, RLS, and TS symptoms via its effect on the metabolism of dopamine and other catecholamines, which have been involved in the pathophysiology of ADHD, TS, and RLS. This is called the iron hypothesis and it may affect the ways in which these 3 abnormalities are treated.[3]

The common thread among all these conditions, although still inconclusive, is lower levels of serum ferritin, the most widely used marker of total body iron stores. Iron deficiency causes abnormal dopaminergic neurotransmission and may contribute to the pathophysiology of these diseases, albeit in different and not fully understood ways.[4] For example, research has shown that iron deficiency leads to increased dopamine production and an elevation of extracellular dopamine.[4] Regardless of its cause, various studies show lower ferritin levels in patients with these conditions:

- ADHD—In a study of 53 children and 27 matched controls, serum ferritin levels were abnormal (<30 ng/mL) in 84% of children with ADHD and 18% of controls ($P<0.001$).[5] Also, low serum ferritin levels were correlated with more severe general ADHD symptoms measured with Conners' Parent Rating Scale ($P<0.02$), suggesting that iron deficiency might contribute to ADHD.
- RLS—Cerebrospinal fluid (CSF) and serum were obtained from 16 patients with idiopathic RLS and 8 age-matched healthy control subjects.[6] Patients with RLS had lower CSF ferritin levels (1.11 ng/mL vs 3.50 ng/mL; $P<0.001$) compared with control subjects. Decreased iron and ferritin have been reported in stained sections of substantia nigra of patients with RLS.[7]
- TS—In a study of children and adults with TS (63 TS, 44 controls), researchers showed significantly lower ferritin and serum iron levels (although still within the normal range) in TS patients.[8] Moreover, the caudate and putamen, which have been involved in the pathophysiology of TS, were smaller in the TS subjects who had lower ferritin levels than in the comparison subjects who had lower ferritin levels.

Although the research has been scanty, treatment with iron supplementation has shown some promise in this spectrum of diseases:

- ADHD—In a study of 23 nonanemic children (ages 4 to 8 years) with lower serum ferritin levels, the mean Clinical Global Impression-Severity score significantly decreased at 12 weeks with ferrous sulfate 80 mg/day, without change in the placebo group ($P<0.01$)[9]
- RLS—Earley and colleagues showed the effectiveness of 1000 mg of intravenous iron dextran in adult patients with RLS.[10] They reported that 6 of 10 patients with RLS had almost complete or complete relief from all RLS symptoms for at least 2 weeks, and for most patients the relief lasted longer than 2 months
- TS—No formal studies on TS and iron supplementation appear to have been published

If the iron hypothesis is to be accepted by the medical community, additional, more robust clinical studies must be performed to see if these conditions are truly related and, if so, to assess whether the same treatment could control this triad, simplifying the management of these disorders when they are comorbid.

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Journal reviews

Women with borderline personality disorder have high rates of ADHD

A recent German study suggests that childhood ADHD is associated with greater emotional abuse in childhood as well as more severe borderline psychopathology in adult women with borderline personality disorder (BPD).[1] Thus, ADHD in childhood may be considered a risk factor that predisposes to BPD in adulthood in a subgroup of patients. According to this study, clinicians should be aware of childhood ADHD and co-occurring

adult ADHD among patients with BPD so they can be treated for persistent ADHD symptoms. Future treatment development might focus on whether different interventions are needed for subgroups of patients with BPD who either have current ADHD or reported childhood ADHD. In addition, the effect of methylphenidate and noradrenergic psychopharmacological agents, such as amphetamines, should be systematically investigated in patients with BPD and co-occurring ADHD.

Trauma may be a predictor of ADHD

A study has suggested that adults with ADHD are more prone to high-energy traumas such as motor vehicle accidents.[2] Here, 58 adults who were admitted to the hospital with musculoskeletal trauma were evaluated to determine the presence of ADHD in childhood and adulthood and were matched to 30 controls. There were 36 (62%) cases of ADHD in the patient group compared with 4 (13%) in the control group. When the level of trauma was evaluated, ADHD was identified in 23 of the 26 (89%) patients with high-energy traumas compared with 14 of the 32 (44%) patients with low-energy traumas (such as falls from a sitting or standing position). This study demonstrates that adults with ADHD are more prone to injuries, particularly high-energy traumas, which may be the result of inattentiveness, a symptom of adult ADHD. Patients who have repeated high-energy traumas should be evaluated by a psychiatrist for ADHD.

Women may have more severe ADHD than men, study shows

A new study explored gender differences in adults with ADHD in 2 large, placebo-controlled, multicenter studies that were conducted several years ago.[3] In those studies 34% of patients were women. Women were rated as more impaired on every measure of ADHD symptoms including total Conners' Adult ADHD Rating Scale-Investigator Format (CAARS-INV), total Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), and most subscales of both measures. More women (75%) had combined type compared with men (62%). Women showed a more complex presentation, with higher scores on the Hamilton Rating Scale for Anxiety (HAM-A) and the Hamilton Rating Scale for Depression, 17-item version (HAM-D[17]), more sleep problems, and more past *DSM-IV* Axis I diagnoses. Women experienced significantly (P=0.003) greater rates of emotional dysregulation (37%) compared with men (29%) as defined by a cluster of symptoms on the WRAADDS. The emotional dysregulation factor is derived by combining 3 symptoms, temper control, mood lability, and emotional overreactivity, from the Utah Criteria for ADHD in adults. These symptoms are considered associated symptoms in the *DSM-IV* description of ADHD. Women also experienced greater improvement (P=0.011) on this symptom factor. In clinical practice, the higher level of emotional symptoms and more complicated presentation in women may obscure the diagnosis of ADHD. Thus, the assessments of adults with ADHD should include an exploration of the emotional dimensions of the condition.

ADHD medication use is on the rise

Improved identification of ADHD in adult and female patients has contributed to rapid growth in ADHD medication use, a recent study concluded.[4] Using pharmacy claims data for a large population of commercially insured Americans, the study measured ADHD treatment prevalence and drug use from 2000 to 2005. The results showed that in 2005, 4.4% of children (ages 0 to 19 years) and 0.8% of adults (ages 20 years and older) used ADHD medications. Treatment rates were higher in boys (6.1%) than in girls (2.6%), but the rates for men and women were approximately equal (0.8%). During the study period, treatment prevalence increased rapidly (12% per year) for the population as a whole. Treatment rates grew more rapidly for adults than for children, more rapidly for women than for men, and more rapidly for girls than for boys. Although treatment rates in adults have increased rapidly, the rates remain relatively low. In this study population, only 1.2% of young adults (ages 20 to 44 years) received treatment for ADHD; this is well below the 4.4% estimated prevalence of the condition in a national sample of adults (ages 18 to 44 years) conducted by Kessler et al in 2006. The expansion of ADHD treatment in adults has been most prominent among women; treatment prevalence has increased by 18% per year for women compared to 13% per year for men. The average use of ADHD medications is high, approximately 200 therapy days per year, suggesting that ADHD is generally being treated as a chronic health condition.

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Posttest

Please select only one answer for each question. Circle the letter corresponding to the correct answer on the answer form on the next page.

1. All but which of the following groups are at highest risk for misusing and diverting stimulants?
   A. Whites
   B. Members of fraternities and sororities
   C. Individuals with higher grade point averages
   D. Individuals who use immediate-release preparations
2. What class of adverse events did the FDA recommend manufacturers of amphetamines include in their black box warning?
   A. Cardiovascular
   B. Neurological
   C. Hepatic
   D. Gastrointestinal
3. All but which of the following steps would be valuable in reducing the misuse and diversion of stimulants?
   A. Advising patients as to the safe storage of the medication
   B. Prescribing more immediate-release formulations
   C. Identifying ADHD patients who also have substance abuse issues
   D. Educating patients about potential side effects of the drugs
4. In a study of 4580 full-time undergraduates at large Midwestern US university, what ethnic group tended to misuse stimulants the least?
   A. Whites
   B. Hispanics
   C. Blacks
   D. Asians
5. What is the most frequent activity of Internet addicts?
   A. Chatting
   B. Downloading
   C. e-mailing
   D. Gaming
6. One study found that adolescents with Internet addiction are more likely to have which of the following characteristics?
   A. Female gender
   B. Lower academic grades
   C. Higher economic status
   D. Use of the Internet more than 20 hours/week
7. The iron hypothesis suggests that all but one of the following conditions may be comorbid:
   A. Conduct disorder
   B. ADHD
   C. Tourette syndrome
   D. Restless legs syndrome
8. Which structure of the basal ganglia tends to be smaller in patients with Tourette syndrome?
   A. Amygdala
   B. Caudate
   C. Nucleus accumbens
   D. Substantia nigra
9. The emotional dysregulation factor derived from the Utah Criteria for ADHD in adults combines all but which of the following symptoms?
   A. Temper control
   B. Mood lability
   C. Loss of sleep
   D. Emotional overreactivity
10. The expansion of ADHD treatment in adults has been most prominent among which group?
    A. Women
    B. Men
    C. Blacks
    D. Whites

Adult ADHD: Issues and Answers

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2. How relevant was the content of this activity to your practice?
   Not relevant at all 1 2 3 4 5 Very relevant
3. To what degree were you able to meet each of the learning objectives of the activity? Please respond to each learning objective listed below:
   a) Discuss how ADHD presents in women and its contrasting manifestations, severity, and associated comorbidities
   Poor 1 2 3 4 5 Outstanding
   b) Identify the potential for diversion and misuse of stimulant medications, the groups most at risk for such behavior, and strategies for prevention
   Poor 1 2 3 4 5 Outstanding
   c) Recognize Internet addiction, discuss its definition and its possible link to ADHD
   Poor 1 2 3 4 5 Outstanding
   d) Discuss recent research into the iron hypothesis as it relates to ADHD, restless legs syndrome, and Tourette syndrome
   Poor 1 2 3 4 5 Outstanding
4. Based on your knowledge and experiences, the level of the activity was:
   Basic Appropriate Complex
5. How would you rate the activity overall?
   Poor 1 2 3 4 5 Outstanding
6. Do you believe this activity was fair, balanced, and free of commercial bias?
   a) Yes No
   b) If No, please state the reason:
   _____
   _____
   c) How much did this activity enforce your current clinical opinions?
   Not at all 1 2 3 4 5 A lot
   d) How much new information did you find in this activity?
   None 1 2 3 4 5 A lot
   e) As a result of this activity, will you alter your practice?
   Yes No
   f) If Yes, please describe any change(s) you plan to make:
   _____
   _____
   g) How committed are you to making these changes?
   Not at all committed 1 2 3 4 5 Very committed
   h) If No, why not? _____
7. Additional comments about this activity?
   _____
   _____
8. Do you feel future activities on this subject matter are necessary and/or important to your practice?
   Yes No
9. Please list any other topics that would be of interest to you for future educational activities.
   _____
   _____

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We are pleased to also offer this issue of **Adult ADHD: Issues and Answers** online through the Adult ADHD Program at NYU School of Medicine Department of Psychiatry Web site at:

http://www.med.nyu.edu/psych/psychiatrist/adultadhdnewsletter.html

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