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Acute health problems due to recreational drug use in patients presenting to an urban emergency department in Switzerland

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Summary

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QUESTIONS UNDER STUDY: To describe acute toxicity of recreational drugs including novel psychoactive substances.

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METHODS: We included all cases presenting at the emergency department (ED) of the University Hospital of Basel, Switzerland, between October 2013 and September 2014 with acute toxicity due to self-reported recreational drug use or with symptoms/signs consistent with acute toxicity. Isolated ethanol intoxications were excluded. Intoxications were confirmed with immunoassays and liquid chromatography coupled with mass spectrometry (LC-MS/MS), which also detected novel psychoactive substances.

RESULTS: Among the 47,767 attendances at the ED, 216 were directly related to acute toxicity of recreational drugs. The mean patient age was 31 years and 69% were male. Analytical drug confirmation was available in 180 cases. Most presentations were related to cocaine (36%), cannabis (31%), opioids (13%), 3,4-methylenedioxy-methamphetamine (MDMA, 9%), other amphetamines (7%), benzodiazepines (7%), and lysergic acid diethylamide (LSD, 5%). The substances most commonly detected analytically were cannabis (37%), cocaine (33%), opioids (29%), benzodiazepines (21%), and amphetamines including MDMA (13%). Notably, there were only two cases of novel psychoactive substances (2,5-dimethoxy-4-bromophenethylamine [2C-B] and pentylone). The most frequent symptoms were tachycardia (31%), anxiety (27%), nausea or vomiting (23%), and agitation (22%). Severe complications included myocardial infarction (2), psychosis (10), seizures (10), and 1 fatality. Most patients were discharged home (68%), 8% were admitted to intensive care and 9% were referred to psychiatric care.

CONCLUSION: Medical problems related to illicit drugs mostly concerned cocaine and cannabis and mainly involved sympathomimetic toxicity and/or psychiatric disorders. ED presentations associated with novel psychoactive substances appeared to be relatively rare.

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Key words: recreational drugs; acute toxicity; psychoactive substances

Introduction

The misuse of illegal psychoactive substances for recreational purposes is common. It is estimated that nearly a quarter of the adult population in the European Union have used illicit substances at some point in their lives [1]. Novel psychoactive substances have emerged in recent years in response to market trends and legislative control [2].

Currently, approximately one novel psychoactive substance is identified in Europe per week [3]. Novel psychoactive substances are typically not detected with the immunoassays commonly used as screening tests. There are limited data on drug-related health emergencies, in particular regarding novel psychoactive substances [4, 5]. The study centre is part of the European Drug Emergencies Network (Euro-DEN), which collects data on acute recreational drug and novel psychoactive substance toxicity [4].

The present study aimed to describe demographics, clinical findings, substances used and short-term outcome of patients with acute medical problems due to recreational illicit substance use presenting to a large urban emergency department in Switzerland over a period of 1 year. Additionally, the study screened for novel psychoactive substances in serum using a liquid chromatography coupled with mass spectrometry (LC-MS/MS) screening method.

Material and methods

This study was approved by the ethics committee. We included all patients admitted to the Emergency Department (ED) of the University Hospital of Basel with acute recreational drug-related medical problems between 1 October 2013 and 30 September 2014. The ED is both a primary care facility (walk-in patients) and a tertiary referral centre for hospitals in the greater Basel area. Additionally, all patients brought by paramedics are first admitted to the ED.

All ED presentations are entered into the comprehensive electronic patient chart database from which cases were retrieved at monthly intervals using a comprehensive full-text search algorithm. In brief, the sensitive automatic search identified all cases with notions of abuse, intoxication or related terms and a large number of substance names including abbreviations and misspellings. The charts of all cases were reviewed, including notes by paramedics. Only patients with acute toxicity were included. A recreational drug was defined as “a psychoactive compound that was taken for the purpose of recreational activities rather than for medical or work purposes or for self-harm”. We identified the recreational drug(s) associated with the presentation based on one or a combination of the following: the patient’s self-reported use, information retrieved from witnesses, the opinion of the physician assessing the patient and/or the analytical confirmation. Cases in which no information was available from the patient (because of coma on presentation, unwillingness to cooperate, language problems, etc.) but the symptoms on presentation and the analytical test results – if available – were typical of acute recreational drug toxicity were also included. Data were abstracted in a standardised manner [4, 6] by one of the authors for the entire study. Data were collected within the Euro-DEN project [4]. Exclusion criteria were: isolated ethanol intoxication, drug withdrawal and secondary complications of chronic drug use (e.g. infected injection sites).

We recorded the patient demographics (age, sex, hour and week day of ED admission), the substances used as reported by the patient or witnesses, the clinical effects, and clinical outcome. Clinical variables included the Glasgow Coma Scale (GCS) score, heart rate, blood pressure, respiratory rate, body temperature, laboratory tests and

electrocardiography (ECG) findings. In cases where the Glasgow Coma Score was not recorded, either 'alert', 'drowsy' or 'coma' was used, based on the notes of the treating clinician. Hyperthermia was defined as a temperature ≥ 39 °C, hypertension as a systolic blood pressure ≥ 180 mm Hg, hypotension as a systolic blood pressure ≤ 90 mm Hg. Severity of poisoning was assessed using the Poison Severity Score for grading acute poisoning [7]. Mild toxicity refers to mild, transient and spontaneously resolving symptoms, moderate toxicity refers to pronounced or prolonged symptoms, and severe toxicity indicates severe or life-threatening symptoms.

The CEDIA immunoassay (Thermo Fisher Scientific, Passau, Germany) was used to screen for barbiturates, amphetamines (including 3,4-methylenedioxy-methamphetamine [MDMA]), benzodiazepines, cocaine, tetrahydrocannabinol (THC), methadone and 6-monoacetyl morphine (6-MAM). The DRI immunoassay (Thermo Fisher Scientific, Passau, Germany) was used to screen for tricyclic antidepressants and opiates. Ethanol blood levels were determined with an enzyme assay. Additionally, liquid chromatography coupled with mass spectrometry (LC-MS) analysis with a method covering over 700 substances was applied for confirmation and to detect additional substances in 100 of the cases (64%) [8]. Levels of γ -hydroxybutyrate (GHB) were determined with an enzymatic assay (Bühlmann, Allschwil, Switzerland).

| Table 1: Patient characteristics. | |
|------------------------------------------------------------------|------------------------------------|
| | Number of cases N = 216 (%) |
| Male | 148 (69) |
| Female | 68 (31) |
| Age, years | |
| 16–20 | 42 (19) |
| 21–30 | 79 (37) |
| 31–40 | 55 (25) |
| >40 | 40 (19) |
| Time of presentation | |
| Night arrival (20:00 – 8:00 h) | 118 (55) |
| Weekend arrival (Friday 17:00 h – Monday 8:00 h) | 125 (58) |
| Ethanol co-ingested (self-reported) | |
| Yes | 103 (48) |
| No | 8 (4) |
| Not known | 105 (49) |
| Self-reported drug use | |
| 1 substance | 129 (60) |
| >1 substances | 61 (28) |
| No drug use | 8 (4) |
| No information available from the patient (language, coma, etc.) | 18 (8) |
| Laboratory-confirmed drug use | |
| 1 substance | 63 (29) |
| >1 substances | 96 (44) |
| No drugs confirmed (absence or insufficient sensitivity of test) | 21 (10) |
| No drug test performed | 36 (17) |

Results

From a total of 47,767 patient admissions to the ED during the study period, 216 cases were related to acute drug toxicity and therefore included in the present study. During the same time period there were 476 admissions due to acute recreational ethanol use with or without co-use of other recreational drugs. Sixty percent of the patients reported use of only one substance. Concomitant use of alcohol was reported in 48% of the cases. In 18 cases (8%) there was no information available on the agents taken and 8 patients (4%) denied having used any drugs. These patients were included because they were judged by the assessing physician as being acutely intoxicated based on the symptoms and/or analytical confirmation. The demographic data are presented in table 1. The mean patient age was 31 years and most patients were male. Most patients were

admitted to the ED at night and/or on weekends, and half of them were brought to the ED by ambulance.

The most commonly self-reported recreational drugs were cocaine and cannabis (table 2). Sixteen patients (7%) reported that they had used a substance without knowing what it was. An analytical confirmation was available in 83% of the total cases (immunoassay in 180 cases, additional LC-MS/MS in 100 cases) (table 2).

| | Number of cases N = 216 (%) | |
|------------------------------------------|-----------------------------|----------------------------|
| | Self-reported (%) | Analytically confirmed (%) |
| Cocaine | 77 (36) | 72 (33) |
| Cannabis | 68 (31) | 79 (37) |
| Benzodiazepines | 16 (7) | 45 (21) |
| Barbiturates | | 1 (<0.5) |
| Opioids (excluding methadone and heroin) | 4 (2) | 33 (15) |
| Heroin | 15 (7) | 6 (3) |
| Methadone | 9 (4) | 23 (11) |
| MDMA/ecstasy | 19 (9) | 28 (13) |
| Amphetamine/methamphetamine | 15 (7) | |
| LSD | 11 (5) | 5 (2) |
| GHB | 2 (1) | 1 (<0.5) |
| Magic mushrooms/psilocybin | 1 (<0.5) | 1 (<0.5) |
| Pentylone | | 1 (<0.5) |
| Mescaline | | 4 (2) |
| Poppers (alkyl nitrites) | 2 (1) | |
| Methylphenidate | 4 (2) | |
| 2C-B | 1 (<0.5) | |
| Laughing gas (N2O) | 3 (1) | |
| Dextromethorphan | 1 (<0.5) | |
| Ketamine | 1 (<0.5) | |
| Testosterone | 1 (<0.5) | |
| Intoxicative inhalant | 1 (<0.5) | |
| Antidepressants | 1 (<0.5) | 12 (6) |
| Neuroleptic agents | | 5 (2) |
| Unknown agent | 16 (7) | |
| Ethanol | 103 (48) | 75 (35) |

2C-B = 2,5-dimethoxy-4-bromophenethylamine; GHB = γ -hydroxybutyrate; LSD = lysergic acid diethylamide; MDMA = 3,4-methylenedioxy-methamphetamine

Table 3 summarises the medical problems. The most commonly reported symptoms were tachycardia, anxiety, nausea or vomiting, and agitation. Most patients (68%) were medically discharged after spending less than 24 hours at the ED; in 21 cases (10%) the patients took their own discharge or left the ED before being seen by a doctor (table 4). Seventeen patients (8%) were admitted to the critical care unit, and in 11 cases (5%) the patients were hospitalised in other wards of the hospital. Twenty patients (9%) were admitted to a psychiatric institution and one patient was admitted to the gynaecology and to the forensic departments because of suspected rape.

In 174 cases (81%) medical treatment including oxygen and intravenous fluid administration was provided. Tracheal intubation was performed in 5 cases (2%). Sedating drugs were administered including benzodiazepines in 51 cases (24%), propofol in 3 cases (1%), and antipsychotics (chlorprothixene and haloperidol, each used in one case). Naloxone was administered in 17 cases (8%), flumazenil in 6 cases (3%), activated charcoal in one case, and biperiden for dystonia in one case.

| Table 3: Clinical characteristics of acute recreational drug intoxications. | |
|-----------------------------------------------------------------------------|-----------------------------|
| | Number of cases N = 216 (%) |
| Cardiovascular | |
| Chest pain | 22 (10) |

| | |
|---------------------------------------------------------------------------|----------|
| Palpitations | 25 (12) |
| Dyspnoea | 15 (7) |
| Hypertension (systolic blood pressure >180 mm Hg) | 3 (1) |
| Tachycardia (>100 beats per minute) | 68 (31) |
| Myocardial infarction | 2 (1) |
| Elevated troponin (without infarction) | 1 (<0.5) |
| Hyperthermia >39.0 °C | 1 (<0.5) |
| Hypotension (systolic blood pressure <90 mm Hg) | 4 (2) |
| Arrhythmias | 2 (1) |
| QRS >120 msec | 1 (<0.5) |
| QTc >450 msec | 54 (25) |
| Psychiatric | |
| Anxiety or nervousness | 58 (27) |
| Psychosis | 10 (5) |
| Hallucinations | 8 (4) |
| Agitation or aggression | 47 (22) |
| Panic attack | 12 (6) |
| Insomnia | 5 (2) |
| Suicidal ideation | 6 (3) |
| Fear | 2 (1) |
| Depersonalisation | 1 (<0.5) |
| Neurological | |
| Impaired consciousness, GCS <9 at presentation | 17 (8) |
| Impaired consciousness, GCS 9-13 at presentation | 19 (9) |
| Unconscious at presentation or pre-hospital | 37 (17) |
| Impaired consciousness, GCS <15 (but >3), at presentation or pre-hospital | 65 (30) |
| “Alert” at presentation | 79 (37) |
| “Drowsy” at presentation | 9 (4) |
| Vertigo | 25 (12) |
| Headache | 8 (4) |
| Paraesthesia | 5 (2) |
| Alterations in perception | 3 (1) |
| Seizure | 10 (5) |
| Tremor | 1 (<0.5) |
| Amnesia | 12 (6) |
| Cerebellar features (e.g. ataxia) | 5 (2) |
| Miosis | 12 (6) |
| Mydriasis | 15 (7) |
| Respiratory depression | 18 (8) |
| Miscellaneous | |
| Hyperventilation | 7 (3) |
| Nausea or vomiting | 49 (23) |
| Diarrhoea | 1 (<0.5) |
| Sweating | 8 (4) |
| Haemoptysis | 3 (1) |
| Abdominal pain | 9 (4) |
| Dry mouth | 2 (1) |
| Muscle cramps | 4 (2) |
| Priapism | 1 (<0.5) |
| Pneumothorax | 1 (<0.5) |
| Sepsis | 2 (1) |
| Injuries (fracture, wound etc) | 9 (4) |
| Epistaxis | 2 (1) |
| Elevated creatine kinase (>250 U/l) | 58 (27) |
| Weakness, walking impairment | 13 (6) |
| GCS = Glasgow coma scale | |

Among all 216 cases, 40 (19%) presented with severe intoxication and there was one fatality after intravenous drug use. In 28 of the 40 severe intoxication cases concomitant use of alcohol was reported and/or analytically confirmed.

Two cases of myocardial infarction (both without ST elevation) were observed, of these patients one reported use of amphetamine and LSD (amphetamine and THC use analytically confirmed) and the other was a regular drug user in a methadone substitution programme who reported having used cocaine (cocaine, cannabis, benzodiazepine and methadone use were analytically confirmed). Both patients were

hospitalised, the first was initially admitted to the critical care unit and underwent coronary angiography; stenting was not needed.

Ten cases (5%) of seizures occurred. From these patients, three had a medical history of epilepsy and five were regular drug users. Two of the patients were kept by the police at the moment of the seizure (one in jail and one in a sobering-up cell). Hyponatraemia (sodium 116 mmol/l on presentation, reference range 135–145 mmol/l), hyperventilation, insomnia, alcohol withdrawal, cannabis withdrawal, and i.v. use of contaminated heroin were considered as differential diagnoses regarding the cause of the seizure in four of the cases. In eight cases the seizure was observed by others (seven cases of generalised seizures and one case of extremities' spasms without loss of consciousness). In one case a seizure during the night was suspected because of enuresis and creatine kinase elevation, and in one case the diagnosis of a seizure was based on the patient's report only. Three of the patients with seizures reported use of cocaine, three of cannabis, one of heroin, one of MDMA, one of an unknown agent, and in one case there was no information available. Substances that were analytically confirmed among these cases were cocaine, cannabis, methadone, opioids, MDMA, and benzodiazepines (in one of the cases given by the paramedics). According to the self-reports, nine of the ten patients had used only one substance, in the toxicological analysis however, more than one substances were found in six of the ten cases.

Among the 10 cases with psychosis the substances that were self-reported were cocaine, cannabis, heroin, MDMA, ketamine, methadone, LSD and tramadol (use of only one substance in five cases (50%) according to self-report). The toxicological analysis of those cases revealed also the use of opioids (other than tramadol), mescaline (in two cases), amphetamine (other than MDMA), benzodiazepine, and pentylone (in the tramadol self-report case). According to the analytical confirmation one substance was used only in one of the ten cases (10%). In the case of LSD self-report (patient naked and very aggressive on presentation) a high LSD blood concentration was found. The symptoms that the patients experienced were paranoia and persecutory delusions of being followed, conspired against, harassed, and/or spied on, in one case in combination with auditory hallucinations (being followed by voices that were talking about death and murder in Italian, although the patient didn't speak Italian), change of character, depersonalisation, and delusional parasitosis (two cases). Four of the patients (40%) were admitted to a psychiatric clinic and three patients (30%) left the ED against medical advice.

Table 4: Severity of poisoning and outcome.

| | Number of cases N = 216 (%) |
|----------------------------------------------|-----------------------------|
| Severity of poisoning | |
| Minor | 81 (38) |
| Moderate | 94 (44) |
| Severe | 40 (19) |
| Fatal | 1 (<0.5) |
| Outcome | |
| Medically discharged home | 146 (68) |
| Self-discharged | 21 (10) |
| Admission to ward but not critical care unit | 12 (6) |
| Admission to critical care unit | 17 (8) |
| Admission to psychiatric clinic | 20 (9) |

Discussion

In this study we described acute medical problems due to recreational drug use. The number of presentations due to acute toxicity from recreational drugs was less than half that due to acute alcohol intoxication during the same period. Most patients reported use of only one recreational drug; however, more than one substance was analytically detected in almost half of the cases (44%). Possible reasons for this difference include

the detection of substances in blood that have been taken as co-medication and not for recreational purposes (e.g. benzodiazepines or opioids), substances that can be detected in blood after the acute intoxication (2–3 days in the case of THC) and are therefore not directly related with the acute medical problem at presentation, and/or substances that have been given as a treatment by the paramedics before presentation at the emergency department (e.g. benzodiazepines in the case of a seizure). However, it can be assumed that in many cases the patients did not report all the substances they had used. Ethanol co-use was reported in almost half of the cases. Severe toxicity was more frequent in combination with ethanol use, thus it is possible that the impaired consciousness that contributed to the characterisation of an intoxication as “severe” was in many cases due to alcohol use and not directly related to the recreational drugs. In accordance with the use in recreational setting, most visits occurred during night time and/or on weekends. In contrast to survey data showing that amphetamines are more prevalent than other stimulants in central Europe [1], amphetamines were not often reported and/or analytically detected in our study. The substances most commonly used were cocaine and cannabis, which is more in line with data from south and west Europe [1].

The most commonly used prescription drugs (except opioids) were benzodiazepines. Benzodiazepines were taken in combination with other substances (12 of the 16 self-reported cases), most commonly with opioids (7 cases) and/or cocaine (4 cases). There was one case of reported antidepressant misuse. However, in most of the cases, antidepressants or neuroleptics were not reported to be misused but analytically detected as part of the prescribed medication of the patients.

During the study period only two cases related to the use of novel psychoactive substances were found, one case of self-reported 2C-B use and one of analytically detected pentylone.

In the case of pentylone, a 53-year-old female patient was admitted because of delusional parasitosis for the last 2 days and was later admitted to the psychiatric clinic. Because of chronic back pain the patient regularly used tramadol. Tramadol and pentylone were identified with LC-MS. Pentylone is a β -keto-analogue of MDMA, similar to methylone and butylone, and has recently been identified as novel designer cathinone [9]. *In-vitro* studies show that pentylone inhibits all of the monoamine transporters with potency approximately equal to that of cocaine, but also releases serotonin similarly to MDMA [10]. In our case the delusional parasitosis was initially linked to tramadol as part of a serotonin syndrome; however, the detection of pentylone makes delusion and hallucinations caused by pentylone a possible diagnosis [11, 12].

In the 2C-B case, a 30-year-old male reported having consumed 2C-B 19 hours before presentation. The patient was not able to sleep because of fear that he would forget to breathe. The somatic clinical examination and the routine laboratory test were normal. 2C-B (or 2,5-dimethoxy-4-bromophenethylamine) is a synthetic drug with hallucinogenic activity similar to LSD [13] and has been reported to cause unpleasant hallucinations and sympathomimetic stimulation [13, 14].

A fatal intoxication occurred in a 46-year-old patient presenting with complaints of generalised pain, shivering, drowsiness and dyspnoea after intravenous injection of beer and cocaine. The medical history included intravenous drug use for 20 years, a tetralogy of Fallot with three surgical corrections, previous mitral valve endocarditis, hepatitis C, and an ischaemic stroke after injecting cocaine into a central venous catheter. Transoesophageal echocardiography showed severe mitral valve insufficiency with vegetations and four blood cultures were positive for *Staphylococcus aureus*, consistent with mitral valve endocarditis. Because of the complexity of the case and lack of compliance, a decision of conservative treatment was reached including adequate

antibiotic treatment. Within 3 weeks the patient's condition deteriorated and the patient died of sepsis and heart failure.

In two cases the patients suffered a myocardial infarction (both without ST elevation). One of the two patients was a 43-year-old male who reported use of cocaine. Cardiovascular problems including myocardial infarction are well-known medical complications of cocaine [15, 16]. Cocaine use has been observed in about 25% of 18–45-year-old patients with myocardial infarction [17]. Myocardial infarction may result from vasospasm [18] and excessive sympathetic activation. However, most cardiac deaths occur in patients with chronic cocaine use [19] and may involve structural cardiovascular disease including myocardial hypertrophy and microangiopathy [20, 21]. In line with these findings, the patient in the present study was a chronic cocaine user. The second patient with a myocardial infarction was a 31-year-old male who reported use of amphetamine and LSD. Except for tobacco smoking there was no other known cardiovascular risk factor. Coronary angiography was normal. Acute myocardial infarction related to amphetamine abuse is rare compared with cocaine. In most of the cases the coronary arteriography is normal [22]. A population-based epidemiological study of hospitalised young adults showed a modest, but significant, association between amphetamine abuse and acute myocardial infarction [23]. Mechanisms may include coronary artery vasospasm, catecholamine-induced platelet aggregation and atherosclerotic plaque rupture, as well as excessive catecholamine discharge resulting in ischaemic myocardial necrosis and increased myocardial oxygen demand [22, 23]. Cases have been reported after inhalation, intravenous, or oral administration [22].

In almost all of the cases with psychosis, use of psychoactive substances known to induce transient paranoia or psychosis [24] was self-reported or analytically detected.

In our study most of the patients who suffered a seizure had used agents known to have a potential to induce seizures. However, cannabis was self-reported in three cases (30%) and was analytically detected in six cases (60%). Cannabis is not associated with seizures and could actually have a medical use for the treatment of epilepsy [25], as it is thought to be protective for new-onset seizures [26]. On the other hand, withdrawal (particularly from alcohol and/or benzodiazepines) is associated with seizures [27]. In alcohol withdrawal seizures usually occur within 12 to 48 hours after the last drink, but may occur after only 2 hours of abstinence [28]. This could have played a role in the four cases with self-reported and/or analytically confirmed alcohol co-use in our study. Furthermore, in three cases the patients had a medical history of epilepsy. Another important element that was not always known in our cases is the presence of triggers such as loud music, flashing lights, lack of sleep, emotional stress (two of the patients were held by the police at the moment of the seizure).

This study has limitations. There were missing data and the initial patient histories and clinical data were not recorded in a standardised manner. In addition, it is possible that patients who used synthetic cannabinoids went undetected, because these cannot be detected with the LC-MS method used in the present study. Similarly, co-use of GHB may have gone undetected because of the small time period in which it can be detected in blood or urine samples. On the other hand, acute (co-) use of cannabis may have been slightly overestimated because it can be detected up to 2 days after the acute intoxication in the serum assay used. The data from only one large ED is not representative and may reflect local drug using trends. Additionally, severe toxicity may have been overrepresented because the ED acts as referral centre for the Basel area, including parts of France and Germany.

Our study has also several strengths. We had detailed patient and clinical data documentation, in contrast to studies based on coded diagnoses or analyses of poison centre data. Especially, the exposure was confirmed in blood for the majority of the

patients by use of immunoassays and LC-MS, which, in combination with the self-reports, provides a good picture of the actual recreational substances being used.

In conclusion, most acute medical problems related to recreational drug toxicity were due to cocaine and cannabis use, and mainly included sympathomimetic toxicity and/or psychiatric disorders. Cases with acute toxicity linked to novel psychoactive substances appear to be uncommon, with only two novel substances (pentylone and 2C-B) found. It could be that novel designer drugs are not frequently used or infrequently lead to ED attendance.

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