

Original Article

Street Drug Use among Emergency Patients in a Public Hospital in Turkey

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ABSTRACT

Background: Country-specific numbers of street drug (SD) users are well documented. However, little data exists regarding these patients' clinical presentations and outcomes in the emergency department (ED). Therefore, management of these patients in the emergency setting is still a subject of debate.

Objectives: The aim of this study is to determine the symptoms and signs of SD users presenting to the ED, and to report the substances, treatments, and outcomes.

Materials and Methods: In this single-center study, symptoms, clinical findings, diagnoses, and outcomes of patients who reported to have used SDs or were diagnosed as SD users were investigated within a 1-year study period. Chi-square and Mann-Whitney U tests were performed to compare independent variables.

Results: Mean age of the 425 study patients was 25 ± 9 years (range: 12-64 years), and 6.1% ($n = 26$) of the patients were females. SDs used before presentation to the ED were mostly synthetic cannabinoids and "ecstasy." Overall prevalence of SD user admissions in ED was 0.24%. The most common presenting complaint was weakness/faintness in 21.1% ($n = 90$). Depressed level of consciousness was the most common physical sign (33.3%, $n = 142$). Incidences of altered mental status were significantly higher among ecstasy and/or bonsai users ($n = 14$, 27.5%; $P = 0.027$ and $n = 46$, 64.8%; $P < 0.001$, respectively), compared to other SD users. While 23.1% ($n = 98$) of the SD users did not warrant any medical intervention, 6.6% of the users ($n = 28$) underwent advanced life support. **Conclusions:** Self-reported SD users were mostly young males who were treated symptomatically and discharged. Almost one-third-mostly ecstasy and bonsai users-had depressed level of consciousness and required resuscitation.

KEYWORDS: Adverse drug effect, cannabis, ecstasy, emergency medicine, street drug user

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INTRODUCTION

Commonly consumed illicit drugs worldwide include cannabis, synthetic cannabinoids, amphetamines, cocaine, heroin, and hypnotic drugs.^[1,2] Using easily obtained chemicals, these drugs can be modified to slightly different molecules, which may not be registered as "illegal". This is why these drugs are referred as "street drugs" (SD) and can easily be available. The number of synthetic drugs has soared in recent years.^[1-4]

Increased use and an increase in the variety of SDs have created legal and public health problems because of their related morbidity and mortality. As a result, in

2014, a total of 497 illicit drug-induced deaths were reported twice as many as in 2013.^[3]


SD use is a global threat for the youth and remains a challenge in which almost all countries are involved. These chemicals may cause addiction at an early age and during the first use.^[1] Although the problems associated with repeated use of SD are well-defined,

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the specific incidences and clinical characteristics need clarification. The different effects of SD such as intoxication, withdrawal, dependence, and substance-induced psychosis could lead to the patients' emergency department (ED) presentation.

These patients are commonly admitted to EDs due to problems related to the first use or repeated use of SD associated with a wide variety of symptoms. Another important issue of debate is that this specific group of patients tend to hide illegal use of SD for the fear of being involved in a crime. Therefore, in many cases, emergency physician (EP) may not be aware of SD use. Remaining abreast of emerging drugs of abuse continues to challenge EPs. Sources of information and surveillance should be available so that EPs remain knowledgeable of current trends. The prevalence of SD users and their complaints, clinical findings, and outcomes of the SD users presenting to an ED in the country and in different regions/cities is a mystery. The objective of this study is to determine the symptoms and signs of SD users presenting to the ED, as well as to document reported substances, treatments, and outcomes.

MATERIAL AND METHODS

Study design and setting

The study protocol for this cross-sectional, prospective, observational survey was approved by the institutional review board. The study centre is a tertiary care training and research hospital, which comprises 30% of the ED admissions, with the ED handling an annual patient volume of 160,000–200,000.^[6,7] The neighborhood surrounding the hospital is a low-income area known for illicit drug distribution in the city of four-million people in the west of the country.

Selection of participants

Patients over 14 years of age presenting to the ED between January 1st and December 31st, in 2014, who were admitted with self-reported SD use by the patient or after questioning by the physician regarding any toxic drug intake, because of patient's abnormal agitated or depressed mental state and/or behavior, and, who had a history of SD intake reported by eyewitnesses or ambulance personnel were included in the study. Participants were asked to sign the informed consent form. Patients with altered mental status and/or under 18 years of age were included in the study after receiving consent from their parents and relatives. Excluded from analysis were patients who declined to sign informed consent, denied recent SD use, reported use or addiction only to alcohol, cigarettes, or inhaled hydrocarbons (sniffers/buffers of gasoline, paint thinner, glue, etc.), were addicted to prescription drugs, and who were initially unconscious and found to have an alternate

diagnosis explaining the depressed mental status. The study was reviewed and approved by the local ethics committee.

Survey content and administration

Patients are routinely cared for by emergency medicine residents, with 24/7 on-site supervision by the EP. Once the physician became aware of SD use, data regarding age, mode of transport (walk-in, ambulance, or via police), previous SD use, chief complaint, physical findings, diagnoses (in relation to International Statistical Classification of Diseases and Related Health Problems/ICD-10 code), and outcomes (endurance, leave against medical advice, discharge, admission, death) were recorded prospectively. All patients' records were searched by the investigators in the next morning including police reports and ICD10 diagnoses for SD users. ICD10 codes (Z72, Z72.2, and Y14 particularly, T96, X64, X85, Y14, Y57.8, Y57.9). Blood or urine work-up was not performed to verify and characterize SD use, because of resources were not available for urine or blood testing in the present hospital. These patients were searched for admission to drug abuse and treatment centres until the end of the study.

Data analysis

Statistical analyses were carried out using Microsoft Office Excel program. Demographic properties and qualitative data were presented as numbers of observations and percentages (%), whereas quantitative data were presented as median \pm standard deviation and range. The relationship between dependent and independent variables were analyzed with chi-square and Mann–Whitney U tests (free software program at <http://graphpad.com/quickcalcs/contingency1.cfm>). Total number of annual cases of SD users within the total volume of ED admissions was calculated as SD user prevalence.

RESULTS

During the study period, 177,035 patients presented to the ED. Data was collected for 471 patients, and 46 patients were excluded from analysis (denial of SD use in 24, only ethanol intake in 10, inhalant use in 8, substances other than SD use in 2, and prescription drug addiction in 2 patients). Data from the remaining 425 study patients, (0.24% of all ED patients during the study period) revealed a median age of 23 ± 8.6 years (range: 12–63 years), male predominance (93.9%, $n = 399$), and one (0.2%) pregnant patient. Regarding age distribution, 17.6% ($n = 75$) were under 18 years of age, and 67.8% ($n = 288$) were between 18 and 34 years old. Arrival was by ambulance in 48.7% ($n = 207$), by foot in 46.6% ($n = 198$), and under police supervision in 4.7% ($n = 20$). Most commonly reported SDs used before presentation to

the ED were “Jamaica” [known JWH-018: 1-pentyl-3-(1-naphthoyl) indole, a synthetic THC analogue] in 46.1% ($n = 196$), marijuana in 43.8% ($n = 186$, also called as “cigarette,” “weed,” and “Holland”), “Bonsai” in 43.5% ($n = 185$, same as Jamaica, a synthetic THC analogue), “Ecstasy” in 40.9% ($n=174$, 3,4-methylenedioxy-methamphetamine; MDMA: also called yellow star, Bugatti, or Superman), clonazepam or diazepam in 19.5% ($n = 83$), cocaine in 1.6% ($n = 7$, called “crack”), and khat in 2.1% ($n = 9$, a plant: *Catha edulis*) [Table 1]. In Table 1, the presented data is compared with national and worlds annual reports.^[1-5]

No patient reported any recent use of heroin or other opioids. Multiple substances were used by 7.0% ($n = 30$); of these, 93% ($n = 28$) were co-ingestions with cannabis and 23% ($n = 7$) were co-ingestions with alcohol. During the study period, 13.9% ($n = 59$) had repeat visits involving SDs.

Primary complaints on presentation to the ED were weakness/faintness in 21.1% ($n = 90$), agitation in 11.5% ($n = 49$), deteriorated general status in 11.2% ($n = 48$), nausea and vomiting in 9.5% ($n = 40$), feeling guilty from substance abuse in 9% ($n = 38$), and being assaulted in 5% ($n = 22$) [Figure 1].

Physical signs among all SD users were defined as follows: 33.3% ($n = 142$) depressed level of consciousness (Glasgow Coma Scale score; GCS < 15), 30.5% ($n = 130$) anxiety, 14.2% ($n = 60$) asymptomatic (patient brought into the ED by parents), traumatic extremity injury (10.2%, $n = 43$), verbal or visual hallucination (2.6%, $n = 11$), muscular rigidity (1.4%), dehydration

(1.4%), tachycardia (0.7%, $n = 3$), pregnancy (0.2%, $n = 1$), gunshot wound (0.2%, $n = 1$), and cardiopulmonary arrest (0.2%, $n = 1$). The mean GCS on presentation was 13 ± 2 . Altered mental status (GCS score <15) were significantly higher in users of ecstasy and/or bonsai ($n = 14$, 27.5%; $P = 0.027$ and $n = 46$, 64.8%; $P < 0.001$, respectively) compared to other groups of SD users. Median systolic blood pressure (BP) was 121 ± 19 mmHg (range: 53-211 mmHg), median diastolic BP was 71 ± 15.6 mmHg (range: 28-131 mmHg), median oxygen saturation (Sat O₂) in room air was $98 \pm 10\%$ (range: 33-110 by pulse oximeter), and median respiratory rate was 18 ± 21 (range: 6-30) breaths/min. Body temperature was elevated in 2.8% ($n = 12$) and all of these were found to have a simple infectious etiology. Blood biochemical parameters and complete blood count tests were performed in 69.4% ($n = 295$) of the SD users, whereas abnormal values were leucocytosis in 7.5% ($n = 22$), elevated creatine kinase in 5.4% ($n = 16$; normal range 0–145 U/L), hypernatremia in 4.1% ($n = 12$; normal range 136–146 mmol/L), elevated blood urea nitrogen (BUN) level/creatinine (Cr) in 1.3% ($n = 4$, BUN > 22 mg/dL or Cr > 1.1 mg/dL), elevated liver enzymes in 0.3% ($n = 1$), hyperglycemia in 0.3% ($n = 1$; normal range 74–106 mg/dl), hypoglycemia in 0.3% ($n = 1$), hypokalemia in 0.3% ($n = 1$; normal range 3.5–5.1 mmol/L), anemia in 0.3% ($n = 1$). Median value of finger stick glucose was 108 ± 46 mg/dL (range: 20–386 mg/dL, $n = 174$, 40.9%). Analyses of venous blood gases (VBG) were performed in 73.6% ($n = 313$) of the patients, and the mean values were as follows: blood pH 7.36 (range: 7.02–7.45), pCO₂ 43.0 ± 11.8 mmHg

Table 1: Estimates of Street drug use in the study compared with 2014 annual reports from Turkish National Drug (TUBİM) Centre, European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), and World Drug Report Centre (UNODC).

Patients admitted due to street drug abuse (15 to 64 years of age)	Study prevalence		Turkey Prevalence (%)	EMCDDA (European) Prevalence (%)	UNODC (global world) Prevalence (%)
	Percentage of study population by SD users (%), $n = 425$	SD user Prevalence among total ED population in the study hospital (%), $n = 177, 035$			
Total drug abuse	100	0.24	2.7	21.7	5.2 (3.5-7.0)
Cannabis	43.8	0.5	0.7	5.3	3.8
Synthetic cannabinoids	89.7	0.9	4-5.8		
Opioid/opiates	-	-	0.2-0.5	4.0	0.7-0.35
Cocaine	1.6	0.04	-	0.9	0.37
Sedatives/ hypnotics	19.6	0.2	-	-	-
Ecstasy (MDMA)	40.9	0.4	3.1	0.5	0.4
Amphetamines	-	-	3.4	0.4	0.7
Katinons	2.1	0.02			
Death (drug related)	0	0.2*	6.4	17.1	40.0 (20-49.3)

(range: 17–118), and lactate 1.7 ± 2.6 mmol/L (range: 0–29). The differences of mean VBG values (any change of Sat O₂, pH, PCO₂, PO₂, COHb, HCO₃, and lactate level) with respect to groups of each substance (taken or not: cannabis, ecstasy, and synthetic cannabis derivatives) were calculated. Statistically significant relationships were detected by ecstasy taken and SatO₂ ($P = 0.015$), pH changes ($P = 0.02$), PCO₂ changes ($P < 0.001$) and/or COHb ($P = 0.034$). Statistical differences were found between consumption of synthetic cannabis derivatives and SatO₂ in room air ($P = 0.02$), PCO₂ changes ($P = 0.031$), and PO₂ changes ($P = 0.034$).

Electrocardiography was performed in 40.2% of SD users ($n = 171$), and revealed normal sinus rhythm in 60.2% ($n = 103$). The abnormal cardiac findings were reported in another article. Diagnoses were categorized as SD intoxication in 80.2% ($n = 341$), metabolic or other nontraumatic problem in 27.2% ($n = 116$), nonpenetrating injury in 5.0% ($n = 21$), penetrating injury (including assaults) in 4.2% ($n = 13$), orthopedic trauma in 4.2% ($n = 18$), drug withdrawal in 2.4% ($n = 10$), victim of a motor vehicle accident in 1.6% ($n = 7$), and suicide attempt in 0.2% ($n = 1$), respectively [Table 2].

One hundred and fifty-nine patients (37.4%) of total SD users required no treatment in the ED, whereas 29.8% ($n = 126$) received medications, 19.3% ($n = 82$) were given IV fluids, 2.8% ($n = 12$) underwent endotracheal intubation, 1.2% ($n = 5$) received noninvasive ventilation, 0.7% ($n = 3$) had coronary percutaneous angioplasty or electrical cardioversion, and cardiopulmonary

resuscitation in 0.2% ($n = 1$). Medication administration included benzodiazepines (mostly midazolam) in 13.6%, antiemetic in 6.6%, haloperidol or biperiden in 6.1%, nonsteroidal analgesics in 3.5%, flumazenil in 1.2%, and antiepileptic in 0.4%. Trauma-related treatments ($n = 64$, 14.9% of all SD users) were administered as wound dressing ($n = 2$), laceration closure ($n = 2$), emergent surgery ($n = 1$), and splinting in one case. Distribution of final diagnoses of SD users is presented in Table 2.

Consultations (16%, $n = 68$ of the cases) were obtained from anesthesiology (46%, $n = 31$), internal medicine/cardiology (28%, $n = 19$) pediatrics (19%, $n = 13$), psychiatry (18%, $n = 12$), and orthopedics (10%, $n = 7$). Hospitalization occurred in 11.3% ($n = 48$) of SD cases to intensive care ($n = 33$), pediatric ward ($n = 7$), coronary intensive care ($n = 4$), and internal medicine ward ($n = 4$). Likewise, 6.6% of the patients ($n = 28$) had life-threatening SD abuse and/or use, which was characterized by at least one of the following findings: presented with a depressed level of consciousness (GCS < 10), progression of depressed GCS, pCO₂ >40 mmHg on VBG analysis, cerebral, pulmonary-cardiac-renal or vascular complications, and cardiopulmonary arrest. One patient (0.2% of all cases) died in the hospital after synthetic THC analogue ingestion. Seventy-five patients (17.6%) left the ED without notifying the staff or against medical advice.

Median length of stay in the ED was 180 ± 220 minutes (range: 2 minutes to 21 hours). During the

Table 2: Diagnoses recorded in SD users[&]

N = 425	Frequency	%
Acute SD intoxication*	341	80.2
Drug withdrawal	10	2.4
Metabolic or other non-traumatic problem; 27.2% of total		
Cardiovascular/pulmonary event	50	11.8
Neurologic event	2	0.5
Internal problem ⁺	64	15.0
Traumatic events: 14.9% of total		
Orthopedic trauma	18	4.2
Non-Penetrating injury	21	5.0
Penetrating injury and/or victim of assault [°]	13	3.5
Motor vehicle accident	7	1.6
Head trauma	5	1.2
Suicide attempt	1	0.2

[&]Multiple features can be present

*Only diagnosed with consumption of SD, no intervention

⁺ Internal problem: BUN-Creatinine increase, blood urea increase, hyponatremia, hypoglycemia, hypothermia

[°] Including blunt and/or penetrating injuries and self-inflicting injuries. Among them, one SD user died secondary to head trauma after being assaulted

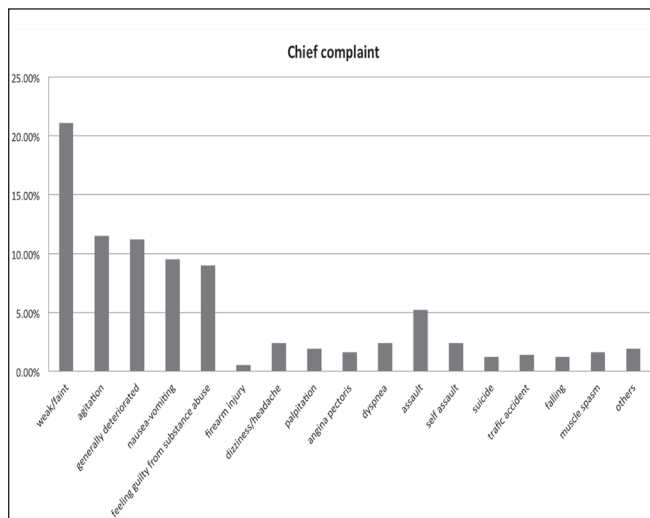


Figure 1: Chief complaints of SD users

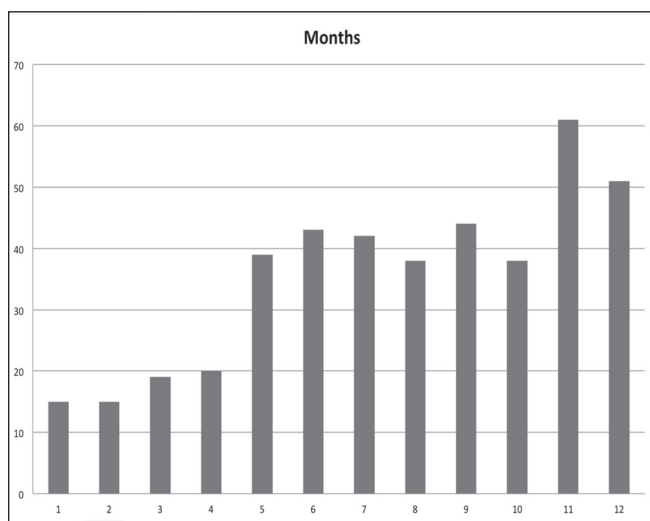


Figure 2: Admission numbers of street drug users by months during the study period

study period, the numbers of SD users identified by the EPs increased every month [Figure 2]. Fifty-nine (13.9%) patients were being followed-up at our provincial drug abuse treatment centre within 1 month of discharge. Table 1: Estimates of Street drug use in the study compared with 2014 Turkish National drug report, 2014 European Monitoring Centre for Drugs and Drug Addiction report, and 2014 World Drug Report. of SD users, 0.4% was opioid user (1.3 million persons), while 3.1% (10.6 million) of adults (age 15 to 64) had used ecstasy, and 3.4% amphetamines in their lifetime

SD, Street drug; ED, Emergency department; TÜBİM, Turkish Drug Report; EMCDDA, European monitoring Center for Drugs and Drug Addiction; UNODC, United Nations Office on Drug and Crime

* Annual report from TÜBİM in 2014; drug-related fatality was 5.6%. Table 2: Diagnoses recorded in SD users &

*Only diagnosed with consumption of SD, no intervention

+ Internal problem: BUN-Creatinine increase, blood urea increase, hyponatremia, hypoglycemia, hypothermia

% Including blunt and/or penetrating injuries and self-inflicting injuries. Among them, one SD user died secondary to head trauma after being assaulted

DISCUSSION

Illicit drug intoxication is an increasing public health problem because of its increased use by adulteration, substitution, and recreational trend.^[1-4,8-10] Interventions to reduce complications and recidivism in these patients have not been effective in improving substance use outcomes.^[11] Newly emerged drugs of abuse are changing constantly and involve manipulation of basic chemical structures to avoid legal issues. Emergency physicians may not be aware of this patient group in their practise, frequently due to deceived medical history. Intoxicated SD users often seek emergency medical treatment, however, relevant data is scarce regarding detection and care of SD users in ED. To date, ED use by SD users is mentioned in only a few reviews.^[2,8,11] This research provides data regarding SD user admissions in ED in a big city, and demonstrates that nearly one-fourth of SD users did not warrant any medical intervention in ED. However, a small part of the sample underwent advanced life support. In addition, use of ecstasy and/or synthetic cannabinoids was found to be significantly related with altered mental status.

Diagnosing and treating SD intoxications in ED requires a clinician trained to recognize specific signs and symptoms of these drugs.^[12-15] SD may have affected a majority of the patients' consciousness at presentation and render them unable to give a real history of the ingestion. The time, route, and intent of use of illicit drugs help the caregivers regarding the scheme of treatment best matching the victim. Similarly, the patients' perceived cause of consumption of SD (recreational vs. suicidal) is of utmost importance to order psychiatric consultation and/or admission or transfer for mental health care.^[8] Diagnosis is based on the clinical history and examination findings along with a urine toxicology test.^[12] Management generally involves symptomatic goal-directed supportive care, with benzodiazepines being used for those with sympathomimetic findings.^[8,12-15] However, more work is needed to determine how drug use disorders may be addressed effectively in

the ED.^[1,10,15,16] The findings of the present study demonstrated the management of SD users in the ED from the beginning to the end. While a minority of the patients warranted advanced life support, some others left the ED against medical advice before receiving any treatment. Of note, these patients could not receive necessary care with psychiatric consultations and possible transfer to a drug addiction centre. SD abusers who had presented to the ED with secondary trauma and/or suicidal pattern were followed up. It can also be postulated that the EPs' capability of detecting these patients increased throughout the study. For example, some patients presented with nausea, vomiting, and chest pain and were diagnosed with abuse of SD after insistent inquiry of the physician.

Cannabis, in one form of cigarette with JWH-18 powder or another, is used by approximately 4% of the world's population, and by 4-6% in our country.^[17] of the world's population, and by 4-6% in our country. Synthetic cannabis derivatives have a high affinity for cannabinoid receptors and are clinically 30–800 times more potent than THC.^[13,15,18] SDs typically stimulate the reward system through the dopaminergic pathway in the brain.^[19] Mortality related to these substances is usually due to adverse cardiovascular (e.g., myocardial infarction, sudden death, cardiomyopathy), cerebrovascular, and peripheral vascular effects, or due to accidents while under the influence.^[13,17-20] During the study period, cardiac complications after SD use were observed, which have not been reported in the literature.^[22,23] This is reported in another article.^[21] Subarachnoid hemorrhage was identified in one "Bonsai" user patient who had also been subjected to physical assault. He left the ED in the first admission against medical advice, and was readmitted into the ED with deterioration and cardiopulmonary arrest.

Amphetamines, the next most commonly used SD, result in increased attention and performance.^[24-26] However, amphetamine abuse may lead to lethal cerebrovascular, cardiac, and/or gastrointestinal problems.^[25,26] Use of synthetic amphetamines such as MDMA may result in stereotypical movements, as well as visual, auditory, and tactile hallucinations. "Bad trips" may also be experienced; users believe that they will die, are afraid of instant blackouts, or feel paralyzed.^[26] Ecstasy was the most popular synthetic amphetamine reported by our patients. Several of the MDMA users had increase in their blood creatine kinase (CK), CK-MB, and lactate level, which may have resulted in the agitated mood or muscular discomfort. In addition, this research revealed that ecstasy users comprise a special high-risk population, which is detectable by the changes in the blood gases.

Previous trends of SD use toxicity in ED from England (UK) (documented an increase in the use of cocaine, while use of ketamine, MDMA, and cannabis declined)^[10] and National Survey from the USA (high among with heroin and inhalant dependence; while lower in marijuana)^[27] are changed currently. The results of the presented study suggest that SD users in ED are higher with cannabis and their synthetic forms, as well as synthetic amphetamines. However, the admission rates in the research suggest that the prevalence is significantly lower. This may be linked to SD users' avoidance to be admitted to the ED unless they are seriously ill or there is no other solution. Most SD users in ED were healthy young men. Males have nearly double the rates and are 1.3 times more likely to have a substance use disorder than females.^[28] Similarly, in the present study, vast majority of SD users were males. This may have reflected a cross-cultural difference on this kind of addiction. SD use is less among females for a variety of reasons.^[29] Studies have found a complex interplay between genetic and environmental factors in the etiology of drug abuse.^[30]

In the present study, the most common reason for presenting to the ED was a mental status change, which may have resulted from diffuse cerebral vasculopathy likely from vasospasm, in accordance with the literature.^[8,31] Previous reports demonstrate that VBG test can provide information regarding carboxyhemoglobin, lactate, and electrolytes, which is mentioned by detecting fatal drug exposure.^[32] Although beyond the scope of this article, the present findings showed a significant relationship between the use of synthetic cannabinoids and/or ecstasy and the alterations of oxygen and CO₂ partial pressures on VBG. The value of obtaining a VBG in SD users can be researched in a controlled prospective study. Till date, clinical findings, laboratory data, and outcomes in SD users in the ED have not been reported. These study findings contain a compact strategy of management of SD users in ED.

Referral to treatment centres may result in lower recidivism rates and decreased morbidity and mortality among SD users.^[33] During the study period, there was no regular program of screening, brief intervention, or referral to treatment.^[33] Such activities may be appropriate for use in the ED setting, providing opportunities for early intervention with at-risk substance abuse, before more severe consequences occur.

Limitations

This a single-center study conducted in the hospital, which has the biggest annual volume in the city. The results may not be extrapolated easily to the population. Even so, findings regarding all types of SDs are ED-based, and the users were observed at the discretion of

the physician's routine management in this survey study. Qualitative testing for particular substances were not available in the hospital laboratory; hence, self-report by the patients were relied on for inclusion in the study.^[16] The detection of the drug or substance used by the patient was not included in the objectives of the study. Instead, self-reports were relied upon. Routine drug screening is expensive and time-consuming, and offers help for management in only a small percentage of poisoned patients.^[8,16] Results of confirmatory tests such as those of gas chromatography-mass spectrophotometer are often delayed.^[8,16-18] Nonetheless, assessment of individuals using self-reports is more cost-effective and is fairly accurate.^[16]

CONCLUSION

SD use is on the rise worldwide, however, the rate of admission of these patients to a single ED seems to be lower than expected. Self-reported SD users presenting to the ED were mostly young males, who were treated symptomatically and discharged. Nearly one-third of the SD users were noted to have depressed level of consciousness and some of them required advanced life support (mostly ecstasy or bonsai users). Physicians staffed in ED must be well trained on SDs. Sources of current information are needed to recognize this patient group in ED as well as to increase referral rate to a high level support facility.

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Conflicting Interest

There are no conflicts of interest.

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