AGE-RELATED DIFFERENCES IN ACUTE CANNABINOID TOXICITY: A STUDY OF CASES MANAGED AT THE ALEXANDRIA POISON CENTER

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Submit Date: 22-04-2025
Revise Date: 26-8-2025
Accept Date: 01-09-2025

ABSTRACT:

Background: Cannabinoid abuse is increasing in Egypt, raising the risk of acute cannabinoid toxicity (ACT). Few studies have examined how ACT patterns differ across age groups. **Objectives:** This study aimed to compare the clinical patterns of ACT among young children, adolescents, and adults. At the same time, it sheds light on natural versus synthetic cannabinoid (SC) toxicity. **Methods:** A retrospective observational study was conducted at the Alexandria Poison Center, Egypt. All cases of acute lone natural/synthetic cannabinoid toxicity admitted over one year (January-December 2022) were recorded. **Results:** The total number of cases was 173 patients. Ages ranged from 6 months to 52 years, with a mean of 7.87 ± 12.79 years. They were divided into two groups according to age: Group I (≤ 12 years old) and Group II (> 12 years old) for comparison of results. Among group I, 55.88% presented with moderate PSS, and 48.52% had moderate Glasgow Coma Scale (GCS). For group II, 45.9% had mild PSS, and 75.64% had mild GCS, with significant differences between the two groups ($p \leq 0.001$). Death occurred in two adults who consumed synthetic cannabinoids (SCs). **Conclusion:** ACT in children was predominantly caused by the ingestion of natural cannabinoids, resulting in a moderately altered level of consciousness. SC toxicity was higher among adults who displayed significant symptoms like agitation, arrhythmia, and hypertension. Future research should conduct in-depth investigations into long-term outcomes and assess the effectiveness of targeted age-specific and product-specific strategies for prevention and treatment.

Keywords: Cannabis; Strox; Acute intoxication; Substance Abuse; Egypt.

INTRODUCTION

Cannabis (marijuana), a plant with a rich history dating back thousands of years, is known scientifically as Cannabis sativa **(Crocq, 2020)**. It is widely abused in Egypt for its psychoactive properties and is known informally as Bango or Hashish. There is also a surge in synthetic cannabinoid (SC) consumption worldwide, along with a rise in the number of cases of acute cannabinoid toxicity (ACT), which may lead to health complications and even death **(Hamdi et al., 2016, Grant et al., 2024)**. Spice, often known as synthetic marijuana, is the most widely used designer drug in Egypt and is being marketed under many names, including Voodoo and Strox. It is becoming more and more popular among all social groups **(Darke et al., 2020)**. Unfortunately, no official statistics are available

to determine the extent of the problem. Still, many indicators show that Strox is the most popular designer drug currently in use as the modern Egyptian equivalent of Spice **(Hashem et al., 2021)**.In Egypt, cannabinoid preparations are illegal to use, yet their use remains prevalent in many communities due to the inherited beliefs among Egyptians that cannabinoids are natural plants with recreational properties and do not cause addiction **(Kaka, 2017)**. Penalties in Egyptian laws are severe, even for small amounts of consumption or possession. This situation highlights the conflict between traditional practices and rigid drug laws. This conflict explains the almost always delayed seeking medical advice and denial of its consumption in patients admitted to poison centers with ACT, so as not to be exposed to legal penalties **(Abdel Kareem RH and Ali, 2018)**.

Cannabis products, including edibles and concentrates, pose a variety of exposure scenarios, especially for children, due to their curiosity and lack of awareness about potential dangers **(Kaka et al., 2022)**. The age of the patient, the potency of the cannabis product, how it is used, and whether or not other psychoactive substances are also consumed can all affect the symptoms of acute cannabis intoxication **(Takakuwa and Schears, 2021)**. The cytochrome P450 system metabolizes cannabis in the liver. The main psychoactive component, tetrahydrocannabinol (THC), is metabolized to 11-hydroxy-THC, which is then further metabolized to several other metabolites **(Maldonado et al., 2024)**. The plant produces over 100 compounds known as cannabinoids, with delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most well-known ones **(Spiller et al., 2019)**. Cannabinoids interact with the endocannabinoid system, which regulates energy balance, pain, mood, and memory. Activating cannabinoid receptors can lead to effects ranging from mild euphoria to severe toxicity and psychotic symptoms, along with potential cardiovascular, respiratory, and gastrointestinal issues **(Mastinu et al., 2018, Monte et al., 2019)**.

Synthetic cannabinoids (Spice), unlike natural cannabinoids, are artificially created compounds designed to mimic the effects of THC, the psychoactive component of cannabis **(Mouraouakkil et al., 2024)**. One of the key aspects of synthetic cannabinoids is their creation in laboratories, allowing for a wide range of chemical variations. These compounds are often sprayed onto plant material and marketed as herbal smoking blends or as a liquid to be vaporized in e-cigarettes. Those new psychoactive substances (NPs) are rapidly invading the market in Egypt. "Voodoo-Spice-Marijuana" NPs were placed on Schedule No.1 of the Egyptian Drugs Act in 2014 **(Hamdi et al., 2016)**. The Ministry of Social Solidarity's (MOSS) addiction treatment hotline stated that there is a significant rise in Strox addicts **(Hashim et al., 2020)**.

Despite regulatory efforts to limit their availability, SCs continue to pose significant risks to public health, precipitating a surge in emergency department visits, acute intoxications, and fatalities **(Geweda et al., 2024)**. One of the major concerns surrounding synthetic cannabinoids is their unpredictable and potentially dangerous effects. Users may experience heightened anxiety, hallucinations, seizures, and other adverse reactions not typically associated with natural cannabis **(Mastinu et al., 2018)**. WHO always stresses the need for data gathering and surveillance to fully comprehend the epidemiology of cannabis toxicity in different countries and communities. More cooperation amongst health organizations and standardized reporting procedures can help provide a clearer picture of trends **(Tweet MS et al., 2023)**. Although cannabis and synthetic cannabinoids are widely consumed in Egypt, few studies have examined clinical patterns of their toxicity and how these patterns vary across age groups. This study addresses this gap by providing a comparative overview of the clinical presentation, complications, and prognosis among cases of acute cannabinoid toxicity based on their ages (under or over 12 years). It also sheds light on natural versus synthetic cannabinoid (SC) toxicity by examining related cases admitted to the Alexandria Poison Center, which serves as a representative sample of the Egyptian population.

SUBJECTS AND METHODS

Study Design: A retrospective survey adopted an observational approach, including all cases admitted to the Alexandria Poison Center (APC), Egypt. The center is a part of the Alexandria Main University Hospital. According to the most recent census conducted in 2017, Alexandria is Egypt's second-largest city **(CAPMAS, 2017)**. As a tertiary hospital that directly serves most of the Northern and Western Egyptian governorates and the primary referral hospital for numerous remote governments (for elective and emergency cases) due to its reputation and proficiency in clinical toxicology, the study sample was well-representative of Egyptian patients.

Subjects and grouping: The current study recorded all cases of lone acute cannabis (marijuana) and lone acute synthetic cannabinoid toxicity admitted over one year from January 1, 2022, to December 31, 2022. Subjects were categorized by age into Group I (subjects aged 12 or younger) and Group II (those older than 12) for comparison of results. According to UNICEF (2022), Children include individuals below the age of 18 years. Within this broad category, further distinctions can be made: Early childhood (0–5 years), Middle childhood (6–12 years), Adolescence (13–19 years) **(UNICEF, 2022)**.

Eligibility criteria: The current study included acutely intoxicated patients who were exclusively exposed to cannabinoids; hence, the following cases were excluded: Cases with co-exposure to toxic agents other than cannabinoids.

- Cases with an unconfirmed diagnosis of ACT.
- Cases with missing data or incomplete files.
- Patients with chronic cardiovascular, neurological, or hepatic diseases.
- Drug abusers with no current history of acute overdose symptoms (as the study was not intended to study the chronic effects of cannabinoids among abusers).

Data collection and analysis: All data of patients who were admitted to the APC with acute cannabinoid toxicity during the study period were collected from records and were involved in the present study. Confirmation of diagnosis was done by history, congruent clinical presentation, and the toxicological screening of urine samples of suspected patients (urine samples were collected without a water flush toilet, detergents, or other potential adulterants). Urine specimens were screened using a multi-drug one-step test (An immunoassay test used to qualitatively identify drugs and/or their metabolites) for cocaine, THC, opium, tramadol, amphetamine, barbiturates, and benzodiazepines **(Hadland and Levy, 2016 Jul)**. Study variables included: demographic data (age, sex, residence), route of administration (inhalational or oral), and co-administration of other agents, as well as data regarding circumstances of exposure, and medical and drug history. Vital signs (pulse, blood pressure, respiratory rate, and temperature), level of consciousness using the Glasgow Coma Score (GCS), and pupil size were also reported. Data regarding substance abuse (onset and duration of abuse) were neither relevant to the scope of the study nor available in the records. Using the European Association of Poisons Centers and Clinical Toxicologists' PSS (EAPCCT), the severity of the poisoning was evaluated at the time of admission.

There are five grades on the score: None (0): no indications or symptoms of poisoning; minor (1): mild, temporary, and spontaneously resolving; moderate (2): pronounced or persistent; severe (3): severe or life-threatening; and fatal (4): death **(Junk et al., 2005)**. Data related to the clinical assessment and management of acute cannabinoid exposures were collected from registries and files of the APC. Standard treatment protocols for acute cannabis intoxication were applied; treatment was mainly supportive, with a focus on airway, breathing, circulation, and decontamination (ABCD protocol), followed by treatment of cannabis-related symptoms **(Boadu O et al., 2018)**. Patients with apnea or at risk for aspiration had undergone rapid sequence intubation and mechanical ventilation. In lethargic patients, measuring electrolytes, conducting blood gas analysis, and assessing rapid blood glucose were considered. Seizures were treated with benzodiazepines. Additionally, intravenous fluid administration was considered to correct hypovolemia **(Blohm E et al., 2019)**. Finally, the duration of hospital stay and outcome were

recorded. All collected data were arranged in a specially designed sheet.

Statistical analysis: The collected data were subjected to statistical analysis and tabulation using the SPSS program, version 20. The chi-square test was used to evaluate the association between categorical variables. Continuous variables (e.g., heart rate, respiratory rate) were compared using a t-test. The study considered $P \leq 0.05$ statistically significant (IBM SPSS Statistics for Windows 2012) **(Kirkpatrick and Feeney, 2013)**.

Ethical considerations: Approval of the study protocol was obtained from the Ethics Committee of the Faculty of Medicine, Alexandria University (IRB NO: 00012098, FWA NO: 00018699, approval number: 0305858) before starting the study. This study has respected patients' confidentiality and didn't include any identifying personal data by any means. This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

RESULTS

The study was conducted on all cases of acute cannabinoid intoxication admitted to the Alexandria Poison Center (APC) over one year. A total of 726 cases were recorded, representing 10.55% of all admissions (n=6882) during this time. Cases involving polysubstance intoxications (n=553, 76.17%) or co-ingestions, such as cannabis combined with ethanol or other psychoactive drugs (n=534 and 19, respectively), were excluded. Only cases of lone acute natural cannabinoid (n=142) and lone synthetic cannabinoid toxicity (n=31) were included in the study, resulting in a total of 173 studied cases, or 2.5% of all cases admitted to the APC. The age of the studied cases ranged from 6 months to 52 years, with a mean of 7.87 ± 12.79 years. The highest percentage (n=136, 78.6%) was among infants and children. **Table 1** shows the age group distribution. Cases were divided into two groups according to age: group I (≤12 years) and group II (>12 years) for comparison of results according to age. Group I constituted 136 cases (78.61%), and Group II constituted 37 cases (21.39%). Regarding sex, males accounted for nearly two-thirds of the cases (62.4%, n = 108), while females represented 37.6% (n = 65). In terms of residence, 95.5% of all cases of acute cannabinoid overdose were from urban areas, with only 4.5% from rural regions.

Table (1): Frequency Distribution of Total Studied Cases of Acute Cannabis Poisoning According to the Age Groups (n=173):

Age	Frequency (n)	Percentage (%)
Infant (1month: ≤1year)	44	25.4%
Child (>1: ≤12 years)	92	53.17%
Adolescent (>12: ≤17 years)	22	12.71%
Adults (> 17 years: ≤ 65)	15	8.67%
Elderly (> 65 years)	0	0%
Total	**173**	**100%**

Table 2 shows that 83.8% (n=145) of all acute cannabinoid poisoning cases were unintentional, primarily among individuals who were not regular cannabis users. In contrast, 16.18% (n=28) of the cases were due to acute overdoses among regular users, resulting from consuming an amount of cannabis or cannabinoid-containing products larger than they could tolerate. These cases reflect acute toxicity rather than chronic toxicity. Notably, there were no reports of homicidal or suicidal cases. Results indicated that ingestion was the primary route of exposure (n = 139, 80.3%), while inhalation occurred in 19.7% of cases (n = 34), with a significant difference between the two groups ($p < 0.001$). The study found that 71.67% of cases (n = 124) involved poisoning at home (either at family or relatives' homes), while 28.32% (n = 49) occurred at parties. A significant difference was observed between the two groups regarding the place of exposure (p=0.01), as 84.55% of Group 1 were poisoned at home compared to 74.6% of Group 2 exposed at parties. The time from poisoning to admission ranged from half an hour to 24 hours, with a mean of 5.68±4.62 hours. Synthetic cannabinoid poisoning occurred in 78.34% of Group II, while 98.53% of Group I were intoxicated by natural cannabinoids (Marijuana). There was a statistically significant difference in the type of cannabinoid consumed by both groups ($p < 0.001$).

Figure 1 shows that the highest number of acute cannabis poisoning cases occurred in June, followed by May.

Table (2): Distribution of the Studied Groups According to the Sex, Circumstances, Route, Type, and Place of Exposures (n=173):

		Group I		**Group II**		***Total***	***P***
		n= 136		**n= 37**		***(n=173)***	
		n	%	n	%		
Sex	Male	76	55.88%	32	86.49%	108	0.03
	Female	60	44.1%	5	13.5%	65	
Route of Poisoning:	Oral	135	99.26%	4	10.81%	139	<0.001*
	Inhalation	1	0.73%	33	89.19%	34	
Type of Cannabinoids	Natural Cannabis	134	98.53%	8	21.6%	142	<0.001*
	Synthetic cannabinoids (SCs)	2	1.47%	29	78.34%	31	
Circumstances of poisoning:	Unintentional	134	98.52%	11	29.73%	145	<0.001*
	Excessive use (unintended overdose)	2	1.47%	26	70.27%	28	
Place of Exposure:	Home	115	84.55%	9	24.32%	124	<0.001*
	Parties	21	15.44%	28	75.67%	49	

Chi-square test was used, P<0.05: statistically significant

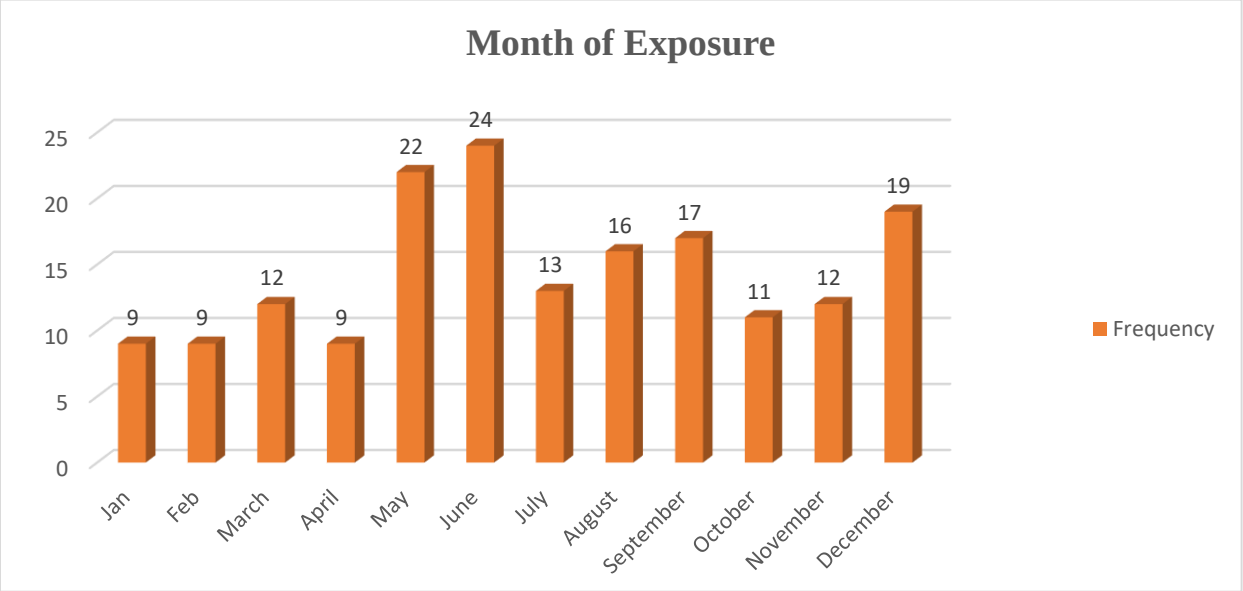

Figure (1): Distribution of Studied Cases according to Months of Exposure (n=173).

Figure 2 and Table 2 demonstrate a significant increase in the percentage of adolescents and adults presenting with a severe Poisoning Severity Score (PSS) compared to children under 12 years ($p < 0.001$). Meanwhile, more than half of Group I presented with a moderate PSS (55.88%).

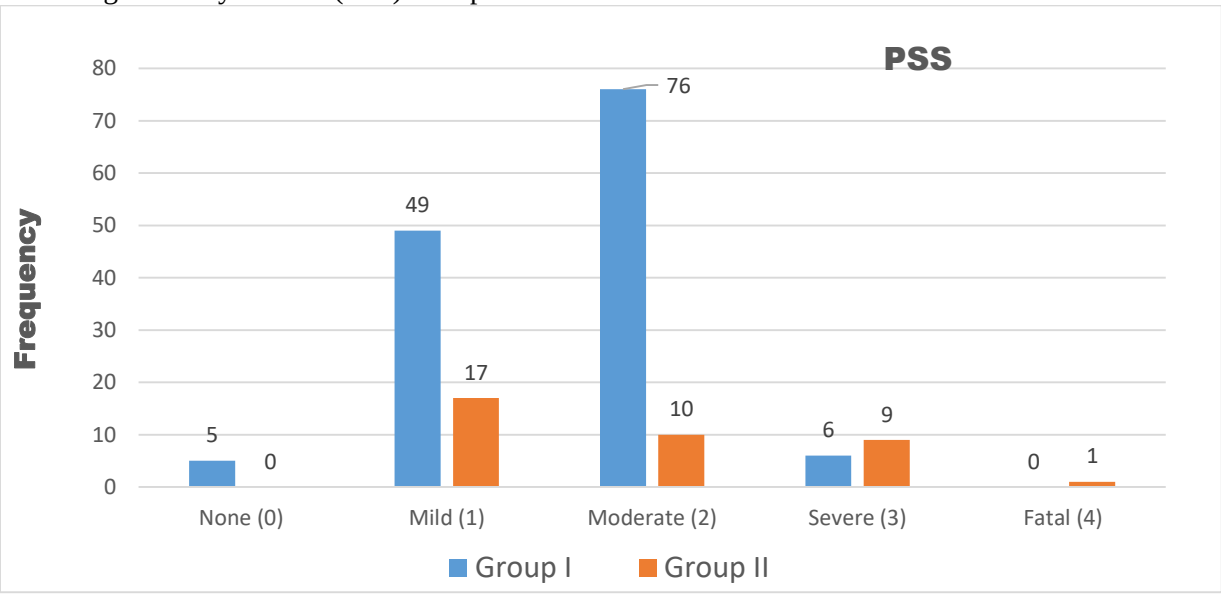

Figure (2): Distribution of studied patients according to poisoning severity score (PSS) among both groups at the time of admission (n=173).

Table 3 shows the distribution of the studied groups according to their clinical presentations**.** Upon admission, the level of consciousness was evaluated using the Glasgow Coma Scale (GCS). It was observed that a majority of cases in Group II (n=28, 75.6%) exhibited a mild alteration in their level of consciousness, with a GCS score between 13 and 15. In contrast, 48.5% (n=66) of individuals in Group I displayed a moderate level of impaired consciousness, with GCS scores ranging from 9 to 12. Additionally, 12.5% of Group I participants were classified as having a severe level of disturbed consciousness, with scores between 3 and 8. This distribution indicated a statistically significant difference between the two groups studied ($p < 0.001$*). Other neurological symptoms were observed in the studied sample. Muscle rigidity was present in 19.1% of patients (n=33), while seizures characterized by myoclonus occurred in 16.7% (n=29). A statistically significant difference was noted in the distribution of these neurological manifestations between both groups (p=0.001). Agitation was reported in only 9.25% of patients, with a notably higher incidence among Group II. Regarding pupil size, contracted pupils were observed in 19.1% of patients (n=33), and dilated pupils were noted in 25.4% (n=44). Eye congestion was present in 21 patients (12.3%). Additionally, a significant statistical difference in pupil size between the groups was found (p=0.003). The systolic blood pressure of the patients studied ranged from unrecorded to 170 mmHg, with a mean of 85 ± 20 mmHg. Hypotension was observed in 14 cases (8.1%), including one patient who was in shock. Additionally, 15.02% of the cases were classified as hypertensive. Tachycardia was recorded in 35 patients (20.23%), while bradycardia was observed in 5 cases (2.9%). There was a significant difference in the heart rate and blood pressure between the two groups studied ($p = 0.01$ and $p = 0.03$, respectively). Hyperthermia was present in 27.16% of the patients, primarily among Group I. Tachypnea was noted in 36 patients (20.8%). The data presented in Table 3 shows that some patients exhibited respiratory symptoms, with dyspnea occurring in 25 individuals (14.45%). In comparison, respiratory failure was noted in 4 cases (2.3%). When it comes to gastrointestinal symptoms, vomiting and/or abdominal pain affected 49.7% of the patients involved in the study, with no notable differences between the different groups. Skin flushing was observed in just 10.4% of the patients. Significant differences were found between the two groups concerning respiratory (p=0.001), gastrointestinal (p=0.03), and skin symptoms (p=0.02).

Table (3): Distribution of the Studied Groups According to Clinical Presentations of Acute Cannabinoid Toxicity (N=173):

		Group I (n=136)		**Group II (n=37)**		**Total (n=173)**	***P***
		n	%	n	%		
PSS	None (0)	5	3.67%	0	0	5	<0.001*
	Mild (1)	49	36.02%	17	45.9%	66	
	Moderate (2)	76	55.88%	10	27.02%	86	
	Severe (3)	6	4.41%	9	24.32%	15	
	Fatal (4)	0	0	1	2.7%	1	
GCS	Mild (13-15)	53	38.97%	28	75.64%	81	<0.001*
	Moderate (9-12)	66	48.52%	7	18.91%	73	
	Severe (3-8)	17	12.5%	2	5.4%	19	
Vital Signs	Hypotension	11	8.08%	3	8.3%	14	0.1
	Hypertension	16	11.76%	10	27%	26	
	Tachycardia	26	19.11%	9	24.32%	35	
	Bradycardia	1	0.73%	4	10.8%	5	0.01*
	Hyperthermia	36	26.4%	11	29.7%	47	0.1
	Tachypnea	23	16.9%	13	35.13%	36	0.03*
Eye manifestations	Mydriasis	39	28.67%	5	13.88%	44	0.01*
	Miosis	27	19.85%	6	16.21%	33	0.03*
	Eye congestion	18	13.23%	3	8.1%	21	0.03*
Gastro-intestinal manifestations	Abdominal pain and/or vomiting	70	51.4%	16	43.2%	86	0.3
Neurological manifestations	Disturbed level of consciousness	130	95.58%	16	44.44%	146	<0.001*
	Myoclonus	27	19.85%	5	13.5%	32	0.01*
	hallucinations	5	3.67%	6	16.2%	11	<0.001*
	Seizures	4	2.94%	2	5.4%	6	0.03*
	Agitation	1	0.73%	3	8.1%	4	<0.001*

PSS: Poisoning severity score, GCS: Glasgow coma scale
The chi-square test was used to compare qualitative variables

An independent samples t-test was used to compare quantitative variables
P<0.05: statistically significant

Table 4 compares the patterns of toxicity associated with natural cannabinoids (NC) and synthetic cannabinoids (SCs). It demonstrates that most of the cases with SC toxicity were among group II (>12 years old), and 100% of their intoxication was caused by smoking SC preparations. PSS significantly differed between the studied groups, while GCS showed no significant differences. Clinical presentations also significantly varied between NC and SC.

Table (4): Distribution of the Studied Groups according to the Type of the Consumed Cannabinoids (n=173):

		Natural cannabis ***(*Marijuana*)*** ***(n=142)***		***Synthetic Cannabinoids*** ***(Strox, Vodoo)*** ***(n=31)***		**Total (n=173)**	***P***
		n	**%**	**n**	**%**		
Age	Group I (≤12 years)	*134*	*94.3*	*2*	6.45	136	<0.001*
	Group II (>12 years)	*8*	*5.6*	*29*	93.55	*37*	
Sex	*Male*	*78*	*54.92*	*30*	96.77	*108*	*0.04**
	Female	*64*	*45.07*	*1*	3.23	*65*	
Route of administration	*Oral*	*139*	*97.89*	*0.00*	0	139	<0.001*
	inhalational	*3*	*2.11*	*31*	100	*34*	
Circumstances of toxicity	*Accidental*	*142*	*100*	*3*	9.68	145	<0.001*
	Overdose	*0*	*0.00*	*28*	90.32	*28*	
PSS	None (0)	*5*	*3.52*	*0*	*0.00*	5	
	Mild (1)	*60*	*42.25*	*6*	19.35	66	
	Moderate (2)	*70*	*49.30*	*16*	51.61	86	<0.001*
	Severe (3)	*7*	*4.93*	*8*	25.81	15	
	Fatal (4)	*0*	*0.00*	*1*	3.23	1	
GCS	Mild (13-15)	*66*	*46.48*	*15*	*48.39*	81	0.3
	Moderate (9-12)	*61*	*42.96*	*12*	*38.71*	73	

	Severe (3-8)	*15*	*10.56*	*4*	*12.90*	19	
Vital signs	Hypotension	*8*	*5.63*	*6*	*19.35*	14	<0.001*
	Hypertension	*1*	*0.70*	*25*	*80.65*	*26*	
	Tachycardia	*23*	*16.20*	*12*	*38.71*	*35*	*0.003**
	Bradycardia	*2*	*1.41*	*3*	*9.68*	*5*	
	Hyperthermia	*36*	*25.35*	*11*	*35.48*	*47*	*0.1*
	Tachypnea	*23*	*16.20*	*13*	*41.94*	*36*	*0.05**
Eye manifestations	Mydriasis	*39*	*27.46*	*5*	*16.13*	*44*	*0.03**
	Miosis	*22*	*15.49*	*11*	*35.48*	*33*	*0.01**
Neurological signs	Disturbed level of consciousness	*126*	*88.73*	*20*	*64.52*	*146*	*0.01**
	seizures	*0*	*0*	*6*	*19.35*	6	<0.001*
	hallucinations	*2*	*1.41*	*9*	*29.03*	11	<0.001*

PSS: Poisoning severity score, GCS: Glasgow coma scale
The chi-square test was used to compare qualitative variables
An independent samples t-test was used to compare quantitative variables
P<0.05: statistically significant

Table 5 shows that the majority of cases, 87.28% (n=151), achieved complete recovery. Additionally, 20 cases were discharged against medical advice without receiving complete management or recovery. Only 1.2% of cases (n=2) resulted in death; they occurred in Group II, and the cause of death was acute heart failure. There was a significant difference in outcomes between the two groups (p=0.01). The analysis of arterial blood gases (ABG) showed that respiratory acidosis was present in 35.26% (n=61) of the cases examined. In comparison, metabolic acidosis was found in 19% (n=33) of patients. None of the cases had significant abnormalities in blood electrolyte levels. Every patient underwent gastrointestinal decontamination and received supportive treatment, including intravenous fluids, oxygen therapy, antiemetics, and purgatives. Only nine patients in Group I required endotracheal intubation, mechanical ventilation, vasopressors, and sodium bicarbonate. The duration of hospital stays ranged from one hour to 5 days, with a mean stay duration of 48.8 ± 3.4 hours. Admission to the intensive care unit (ICU) was necessary for 14 cases (8.1%), while 159 patients (91.9%) were treated in the ward. A significant difference was observed in the need for ICU admission and the duration of hospital stay between the two groups, with a notably higher percentage of ICU admissions among children.

Table (5): Distribution of the Studied Groups according to the Outcomes and the Period of Hospital Stays (n=173):

Studied Variables		Group I (n=136)		Group II (n=37)		Total (n=173)	*p*
		n	%	n	%		
Place of management	Ward	127	93.38	32	86.48	159	0.01*
	ICU	9	6.62	5	13.51	14	
Outcome	Complete recovery	127	93.38	24	64.86	151	0.01*
	DAMA	9	6.62	11	29.72	20	
	Death	0	0	2	5.4	2	
Duration of hospital stays	< one day	125	91.91	32	86.48	157	0.001*
	1-5 days	11	8.09	5	13.5	16	

DAMA: Discharge Against Medical Advice

The chi-square test was used to compare qualitative variables

P<0.05: statistically significant

DISCUSSION

The global prevalence of cannabinoid use is on a steady upward trajectory, with an estimated 200 million individuals classified as regular users around the world. This growing trend solidifies cannabinoids' position as the most commonly abused illicit substance globally. **(Matheson and Le Foll, 2023)**. In Egypt, the situation is particularly concerning, as cannabinoids have been identified as the leading substance of abuse, according to reports from the Fund for Drug Control and Treatment of Addiction. Consequently, this widespread use heightens the risk of acute toxicity associated with cannabinoid consumption, posing significant public health challenges **(Abdelmoneim et al., 2022, Hashem et al., 2021)**. This study reported cases of acute toxicity resulting from natural and synthetic cannabinoids managed at the Alexandria Poison Center (APC) between January 1 and December 31, 2022. As the primary treatment facility for poisoning incidents in the Alexandria Governorate and surrounding rural areas, APC plays a vital role in managing these situations. Between 2017 and 2021, the center managed a total of 36,853 poisoning cases, underscoring its vital role in addressing poisoning emergencies in the region **(Said NM et al., 2023)**. In the current study, the total number of acute cannabinoid poisoning cases represented 10.55% of all cases admitted to APC during the period of the study. This was consistent with the findings of an earlier research at APC **(Kaka et al., 2022)**. A total of 173 cases of lone cannabinoid toxicity were reported, which constitutes 2.5% of all admitted cases. This percentage aligns with previous epidemiological studies conducted in Egypt that examined acute toxicity cases in various poison centers across the country **(Elhelaly and Salah Eldin, 2022, Kaka, 2017, Hamdi et al., 2016,**

Abdelmoneim et al., 2022, Kaka et al., 2022, Said NM et al., 2023). Therefore, the findings of this study can be generalized further. The study established a toxicity ratio of 4.5:1 between natural cannabinoids and synthetic cannabinoids, which aligns with a recent study conducted in Egypt by Elhelaly et al. **(Elhelaly and Salah Eldin, 2022)**. Over five years, researchers examined the acute toxicity of natural cannabis compared to synthetic cannabinoids. They found that 721 patients experienced toxicity from natural cannabis, while only 113 patients reported toxicity from synthetic cannabinoids, resulting in a 6:1 ratio. This data underscores the contrast in consumption patterns between natural and synthetic cannabinoids in Egypt, where the use of natural cannabinoids continues to surpass that of synthetic options. In this study, the ages of patients experiencing cannabinoid intoxication ranged from 6 months to 52 years, with the highest percentage occurring among children aged 12 and under. This observation aligns with findings from Robert G. Hendrickson et al. (2020), who reported no cases of acute cannabis exposure in older adults during their 17-month study **(Hendrickson et al., 2020)**. Other former studies have proved an increased incidence of acute cannabinoid toxicity among children, whether in developing or developed countries **(Le Garrec et al., 2014, Boadu et al., 2020, Campbell and Brown, 2020)**. At the same time, in a previous six-month-duration Egyptian study in Ain Shams University Hospital, preschool children constituted 24% of the total cannabis-intoxicated patients **(Mohammed et al., 2021)**. Similar findings were reported in another toxicological study that was carried out in the United States **(Noble MJ and S, 2019)**. Children have an underdeveloped cytochrome system, which makes them less efficient at metabolizing Tetrahydrocannabinol (THC) compared to adults. This increased inefficiency raises their risk of experiencing toxic effects from exposure. Furthermore, since THC is stored in fat tissue and children have a higher body fat percentage, they may retain higher levels of THC in their bloodstream for a longer duration **(Eike et al., 2019)**. These findings raise a critical concern for public health worldwide. Pediatric overdose cases often result from marijuana ingestion, which can be potent and long-lasting. Children may mistake marijuana for regular food or ingest it out of curiosity. Accidental ingestion can also occur if a family member (substance abuser) improperly stores cannabis products at home **(Matheson and Le Foll, 2023)**. Exposure and acute toxicity may also occur from secondhand smoking in cases of children who are close to adults abusing cannabis at home or at social parties **(Wilson KM et al., 2018)**. The present findings consolidated this concept, as 84.5% of intoxicated cases were exposed to toxicity at home. In terms of sex prevalence, the current study found that males outnumbered females, which is consistent with findings by Mohamed et al. **(Mohammed et al., 2021)**, who reported a male predominance of 54.3%. A similar result was noted in another Egyptian study on synthetic cannabinoids **(Abdelmoneim et al., 2022)**. This pattern was also observed in another study that involved drivers admitted to the APC **(Kaka, 2017)**. In contrast, Pélissier et al. reported a predominance of females among patients in their French study **(Pélissier F et al., 2014)**. This discrepancy may be attributed to differences in epidemiological structures and characteristics across various countries. The present study found that nearly all cases (95.5%) of acute cannabinoid poisoning (APC) occurred in urban areas, which was explained by the fact that APC serves mainly urban areas. This aligns with Mohamed et al.'s study in Cairo, the capital of Egypt **(Mohammed et al., 2021)**. These results highlight the need to report demographic patterns of acute cannabinoid toxicity, especially the higher rates among children under 12. Understanding these trends is crucial for developing effective public health interventions that target vulnerable populations. The current study revealed that the highest frequency of cases was in June and May; this could be explained by the Egyptian tradition of increased parties and picnics in summer, with a favorable use of psychoactive or recreational substances in such parties, thus increasing the risks of toxicities **(Hamdi et al., 2016)**. In this study, ingestion was identified as the most common exposure route for children under 12, consistent with previous research **(Boadu et al., 2020, Campbell and Brown, 2020, Le Garrec et al., 2014)**. This may be due to the

predominance of children in the study, who tend to discover substances by tasting or ingesting them **(Kaka et al., 2022)**. Moreover, intoxication was mainly accidental among group II (98.5%), who were intoxicated by cannabinoids, whereas it was primarily due to unintentional overdose among group II (70.27%). Similar results were obtained in Elhelaly and Salah Eldin's study **(Elhelaly and Salah Eldin, 2022)**. Accidental exposure occurred in 100% of cases in the Mohammed et al. study **(Mohammed et al., 2021)**, as their study population was only preschool children. The finding of increased accidental exposures was explained in another study to be related to the increased accessibility of marijuana/cannabis in certain communities **(Boadu et al., 2020)**. A significant difference was found between the current groups regarding cannabis exposure. Young Children (Group I) were mostly exposed at home (84.55%), while adolescents and adults (Group II) encountered it more often at parties (75.67%). Similarly, Mohamed et al. **(Mohammed et al., 2021)** reported that 95.5% of preschool children in their study had been intoxicated at home, either at their residence or a relative's. The current study found that 19.1% of Group I experienced tachycardia, while bradycardia was more common in Group II. Tachycardia has also been reported in previous studies on acute cannabis toxicity in children **(Richards et al., 2020, Mohammed et al., 2021, Tweet MS et al., 2023)**. Bradycardia was more common among adults in other studies **(Hendrickson et al., 2020, Franz and Frishman, 2016)**. These studies explained that tachycardia can occur in cases of acute cannabis toxicity due to the anticholinergic activity of cannabis. This activity leads to a blockage of the parasympathetic system by binding to cannabinoid receptors in the heart; however, it is not typically life-threatening. Additionally, the anticholinergic effect may explain the hyperthermia found in 27.16% of cases, which aligns with the findings of Mohammed et al. in their study **(Mohammed et al., 2021)**. Hypotension was observed in both groups at nearly equal percentages (8%), consistent with Richards et al. **(Richards et al., 2017b)** and Dowd **(Dowd, 2018a)**. Hypertension was present in adolescents and adults (27%) more than in young children (11.7%), aligning with Hendrickson et al. **(Hendrickson et al., 2020)**. This study found that sinus tachycardia, hypertension, and tachypnea were more common in adolescents and adults (Group II) than in young children (Group I). These significant discrepancies highlight distinct respiratory and cardiovascular responses potentially related to different toxicokinetic or exposure profiles among both groups, where 78.34% of Group II used synthetic cannabinoids (SCs). Forrester **(Forrester, 2012)** and Castaneto et al. **(Castaneto et al., 2014)** reported that hypertension and tachycardia are the most prominent clinical findings in SC toxicity. Nelson **(AM, 2021)** explains that synthetic cannabinoids (SCs) have a central sympathetic-stimulating effect involving the paraventricular nucleus of the hypothalamus and the amygdala. These effects are opposite to those seen with cannabis, highlighting that SCs produce different responses when interacting with the same systems **(López Dyck et al., 2017, Spiller et al., 2019)**. In the present study, gastrointestinal manifestations were present in the form of vomiting and/or abdominal pain in 51.4% of group I (young children), and this was consistent with other studies about acute cannabis poisoning in children. **(Eike et al., 2019, Dowd, 2018b)** Similar gastrointestinal complaints were noted among group II, comprising adolescents and adults, which aligns with the findings of Hesham et al. **(Hashem et al., 2021)** and Keung et al **(Keung et al., 2022)** in their studies on adults. Robinson et al **(Robinson et al., 2013)** explained that repetitive vomiting and abdominal pain are caused by cannabinoid toxicity due to their anticholinergic effect, thus, delayed stomach emptying and splanchnic vasodilatation. Studies on cannabis-induced hyperemesis in younger age groups after unintentional ingestion have likewise been published by Thomas and Mazor **(Thomas and Mazor, 2017)**.

There was a statistically significant difference in PSS between the two groups ($p < 0.001$). Group I had a higher proportion of patients with moderate (55.88%) and severe (4.41%) toxicity, while Group II showed a greater frequency of severe (24.32%) and fatal (2.7%) cases. This suggests that Group II may represent

a more critically affected cohort, potentially due to factors such as higher THC concentration or synthetic cannabinoid use. In the current study on neurological presentations, the most common symptom observed was a disturbed level of consciousness, affecting 84.39% of the participants. This symptom was particularly prevalent among children, with an incidence of 95.58%, indicating more pronounced CNS effects in this group. These findings were consistent with previous studies **(Tweet MS et al., 2023, Mohammed et al., 2021)**. Whereas only 44.44% of Group II had an altered level of consciousness, which agreed with Keung, M.Y. **(Keung et al., 2022)**. Immature metabolic systems and smaller body size of young children increase the severity of toxicity symptoms, leading to a higher risk of hospitalization or ICU admission **(Fong et al., 2021)**. On the other hand, the excitatory neurological manifestations in this study were significantly higher in adolescents and adults, which was in agreement with what was proven by Abdelmoneim et al **(Abdelmoneim et al., 2022)**. They stated that neuro-psychiatric side effects were the most experienced by cannabinoid intoxicated adults. Most toxicities from synthetic cannabinoids in this study were found in Group II, showing significant excitatory neuropsychiatric effects. Severe neurological symptoms, such as extreme agitation or convulsions, occurred in only 5.7% of cases, mainly among adults and adolescents, aligning with the findings of Hashem et al. **(Hashem et al., 2021)**, in which 5.81% of patients expressed severe neurological manifestations. Predominance of these manifestations among adults who abused SCs was also reported by Riederer et al. **(Riederer et al., 2016)** in their study. Harris and Brown described how synthetic cannabinoid (SC) toxicity affects the brain by inhibiting gamma-aminobutyric acid (GABA) neurotransmission and lacking phyto-cannabinoids such as cannabinol and cannabidiol, resulting in a loss of anticonvulsant properties **(Harris and Brown, 2013)**.

Ocular signs such as mydriasis (28.67% in Group I vs. 13.88% in Group II; $p = 0.01$) and miosis (19.85% vs. 16.21%; $p = 0.03$) were significantly more frequent in Group I, suggesting differing autonomic responses in different ages. These findings may reflect variations in cannabinoid type (natural vs. synthetic) or receptor affinity. Previous studies proved that miosis was of high incidence among preschool children intoxicated with cannabis **(Richards et al., 2017a, Mohammed et al., 2021)**. Red eyes were observed in 12.13% of cases in the current study, with a significant difference in incidence between the groups. Pélissier et al. **(Pélissier F et al., 2014)** recorded a higher incidence of red eye (16.7%) in their studied group in France. This sign is caused by vasodilation of conjunctival blood vessels. In this study, respiratory distress was observed among the cases examined, with a notable increase in group II, where the consumption of SC was higher. This finding aligns with several previous studies that studied the acute toxicity of SCs **(Elhelaly and Salah Eldin, 2022, Alon and Saint Fleur, 2017, Abdelmoneim et al., 2022)**. Multiple modes of action are involved in the effect of SCs on respiration. Three hypotheses have been put forth: the first is that chemoreceptor and baroreceptor stimulation causes an increase in bronchial airway resistance; the second is that bronchiolar epithelial damage and disruption of the alveolar surfactant layer result from the release of chemical gases following SC inhalation; and the third is that ineffective gas exchange leads to hypoxia, hypercapnia, and acidosis **(Alon and Saint Fleur, 2017, Keung et al., 2022)**.

Regarding morbidity and mortality following acute cannabinoid toxicity, in the present study, the majority of patients recovered without any complications during the hospital stay, and there were no recorded deaths among young children. These results were similar to what was reported by Eike et al. **(Eike et al., 2019)**, who concluded that all young children admitted to the hospital after being intoxicated by cannabis ingestion had fully recovered. Death occurred in only two cases (1.15%) in the present study, who consumed SCs, and the cause of death was cardiotoxicity. Both cases developed cardiac arrest and were mechanically ventilated, which was very similar to what was reported by Hashem et al. in their study **(Hashem et al., 2021)**. A mortality rate of 1.2% was also recorded in another study **(Riederer et al., 2016)**. In the

current study, ICU admission was done in 19.6% of cases, compared to 68.7% of patients in the Mohammed et al study **(Mohammed et al., 2021)**. This difference may be attributed to the varying sampling methods in the two studies. In both studies, the most common reason for ICU admission among children was coma, either alone or in combination with other complications. For the adult group that consumed SCs more frequently, the primary cause of ICU admission was arrhythmia. This was in line with the results obtained in a previous Egyptian study **(Elhelaly and Salah Eldin, 2022)**. There have been other studies that have connected the increased risk of death in SCs exposure to direct toxicity, pre-existing cardiac disease, behavioral toxicity resulting in excited delirium, trauma, accidents, or overconsumption of other medications **(Shanks and Behonick, 2016, Darke et al., 2020, Abdelmoneim et al., 2022)**.

CONCLUSIONS

This study highlighted the increased incidence of unintentional acute cannabis toxicity among young children, especially in urban societies. There was a clear seasonal pattern in exposure events, with significantly higher frequencies occurring during the summer months (May and June) and lower frequencies in the winter months. Acute cannabinoid toxicity presents with variable clinical patterns, influenced by age, dose, route of exposure, and type of cannabinoid (natural vs. synthetic). The statistically significant differences in PSS, GCS, vital, and neurological signs reflect different mechanisms of toxicity and substance profiles. Synthetic cannabinoids were associated with more severe outcomes, including seizures, hallucinations, and fatalities. These findings have critical implications for clinical management, forensic toxicology, and public health policy. Regarding acute toxicity associated with natural cannabis, young children exhibit more pronounced clinical effects since they metabolize it differently and are more sensitive to lower doses. These findings highlight the necessity for age-specific and product-specific strategies for prevention and treatment.

RECOMMENDATIONS

These findings underscore the importance of differentiating between natural and synthetic cannabinoid toxicity in clinical settings, as well as the need for tailored diagnostic and therapeutic approaches depending on symptom severity and presentation. Future research could build on these findings by examining a larger population sample, long-term outcomes, exploring risk factors for severe toxicity, and evaluating the effectiveness of targeted interventions for different age groups.

STRENGTHS OF THE STUDY

The fact that the current study is the first in Egypt to analyze such a pattern of natural and synthetic cannabinoids in children versus adults is a key strength. The retrospective cohort design is appropriate for examining trends and patterns in cases of acute toxicities. Focusing on lone cannabis and synthetic cannabinoid toxicity cases helps isolate the effects of these substances.

The one-year study period (January-December 2022) provides a recent snapshot of ACT patterns. Dividing cases into two age groups (≤12 years and >12 years) allows for meaningful comparisons between children and adults

The study provides a comprehensive overview of this health concern, aiding in the development of better managerial policies and programs. A significant strength is that it was conducted at the Alexandria Poison Center, the main center on Egypt's northeastern coast, which handles acute poisoning cases from the north coast and the Nile Delta.

LIMITATIONS OF THE STUDY

It was anticipated that a significant number of missed cases were treated at other hospitals or healthcare centers, or were not admitted to hospitals at all, due to concerns about legal liability. As this was a retrospective study, the author encountered challenges related to incomplete case recordings in registries, which led to the exclusion of some cases due to insufficient data. Additionally, there were difficulties in accurately estimating the doses received by the cases.

Further large-scale studies collecting data from various toxicological centers are needed to

assess the epidemiological pattern of ACT and estimate the magnitude of the problem in Egypt.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

FUNDING

This research did not receive specific funding from public, commercial, or nonprofit agencies.

ACKNOWLEDGMENT

The author is extremely grateful to colleagues at the Alexandria Poison Center for their help in data collection, without which this research would not be possible. The author also expresses special thanks to the statistician for the statistical analysis of the collected data.

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الملخص العربي

الاختلافات المرتبطة بالعمر في التسمم الحاد بالقنب:

دراسة الحالات التي تم علاجها في مركز السموم بالإسكندرية

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الخلفية: يتعاظم تعاطي القنّب في مصر، مما يزيد من خطر التسمم الحاد به. وقد تناولت دراسات قليلة كيف تختلف أنماط التسمم الحاد بالقنّب بين الفئات العمرية. **الأهداف:** هدفت هذه الدراسة إلى تقديم نظرة عامة مقارنة للنمط السريري للتسمم الحاد بالقنّب بين الأطفال والبالغين، وفي الوقت نفسه، إلقاء الضوء على سمية القنّب الطبيعي مقابل القنّب الاصطناعي .**المنهجية:** أُجريت دراسة وصفية بأثر رجعي في مركز الإسكندرية للسموم، مصر. وسُجلت في الدراسة الحالية جميع حالات التسمم الحاد الوحيد بالقنّب الطبيعي/الاصطناعي التي استُقبلت على مدار عام واحد (يناير - ديسمبر 2022). **النتائج:** بلغ العدد الإجمالي للحالات 173 مريضًا. تراوحت الأعمار من 6 أشهر إلى 52 عامًا، بمتوسط 7.87 ± 12.79 عامًا. وقُسموا إلى مجموعتين حسب العمر: المجموعة الأولى (≥ 12 عامًا) والمجموعة الثانية (< 12 عامًا) لمقارنة النتائج بشكل علمى منهجى. في المجموعة الأولى، أظهر 55.88% درجة خطورة التسمم (PSS) متوسطة و 48.52% درجة غلاسكو للغيبوبة (GCS) متوسطة. أما بالنسبة للمجموعة الثانية، فقد أظهر 45.9% درجة خطورة التسمم خفيفة و 75.64% درجة غلاسكو للغيبوبة خفيفة، مع وجود فروق ذات دلالة إحصائية بين المجموعتين (قيمة الاحتمالية ≥ 0.001). حدثت وفاة في بالغين اثنين تعاطيا القنّب الاصطناعي (SCs). **الخلاصة:** كان التسمم الحاد بالقنّب لدى الأطفال ناتجًا بشكل أساسي عن ابتلاع القنّب الطبيعي، مما أدى إلى تغير متوسط في مستوى الوعي. وكانت سمية القنّب الاصطناعي أعلى بين البالغين الذين أظهروا أعراضًا جسيمة مثل الهياج وارتفاع ضغط الدم. يجب أن تجري البحوث المستقبلية تحقيقات متعمقة في النتائج طويلة الأجل وتقييم فعالية التدخلات المستهدفة المصممة خصيصًا للفئات العمرية المختلفة و طبيعة مادة القنب.

الكلمات المفتاحية: القنب - الاستروكس - التسمم الحاد - ادمان المواد - مصر