TOXICITY AND SUICIDAL TENDENCY LINKED TO THE ANTIEPILEPTIC MEDICATIONS

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ABSTRACT

Background: Antiepileptic drugs (AEDs) are increasingly used, usually as an unlicensed usage, in patients with psychiatric disorders who are at increased risk of self-harm. This is expected to raise the likelihood that these drugs are used as means of overdose. **Objectives:** The current study was conducted to assess the AEDs–acutely intoxicated cases and to assess the relation between the administration of antiepileptic drugs and committing suicide. **Methods:** The study included 127 cases who were intoxicated with antiepileptic drugs presented at the national environmental and clinical toxicology research center **(NECTR)** for six months period from May to October 2018. Data were analyzed with respect to socio-demographic data, primary data for patients' assessment, data concerning physical examination on admission, manner of overdose intake, the status of admission, period of hospitalization, and outcome. **Results:** The most common age group was those between 20-40 years with female dominance (75.6%). Carbamazepine was the most common ingested AED (73.2%). The most common manner of overdose intoxication was suicidal (73.2%), and most of the cases were cured. **Conclusion**: Suicidal mode of AEDs-intoxication comprised a significantly higher frequency among females & among the adult age group. So, psychiatric evaluation & monitoring of these vulnerable patients are recommended.

Keywords: Antiepileptic drugs, toxicity, suicidality, carbamazepine

INTRODUCTION

Antiepileptic drugs (anticonvulsants) are not only used in the treatment of epilepsy, but they are also used in the treatment of some neurological conditions such as trigeminal nerve pain, bipolar disorders, migraine headache, beside cardiac arrhythmia, and wound healing **(Sane and Goudarzi, 2013)**

Because antiepileptic drugs are used for many indications (most properly unlicensed indications), and because patients who suffer essentially from epilepsy always also suffer from other psychiatric illnesses such as depression, this kind of patient is liable for self-poisoning **(Nixon et al., 2008)**.

Being of narrow therapeutic windows, they are liable to cause intoxication even at the therapeutic doses. In addition, acute toxicity caused by antiepileptic drugs can result from suicidal intake **(Gök, 2006)**. According to the annual report of the National Poison Data System (NPDS) of the American Association of Poison Control Centers (AAPCC), which was issued in 2011, AED poisoning represented 3% of adult drug poisoning (above 20 years of age) **(Bronstein et al. 2012).**

In the 2018 annual report, this percentage increased to be4.23% **(Gummin et al., 2019).** Also, in the 2018 annual report, antiepileptic drugs fall in fourth place among the top 25Substance categories with the greatest rate of exposure increase

(Gummin et al., 2019).

In 1939 phenytoin and Phenobarbital (the first antiepileptics) were first introduced to clinical use. Then the first generation of antiepileptics (FGAEs), such as carbamazepine and valproic acid (VPA) that was followed by gabapentin and lamotrigine; the second generation antiepileptics (SGAEs) **(Günaydın et al.2015)**.

The primary effect of antiepileptics poisoning is on the CNS, so neurological manifestations such as loss of consciousness, pupillary shifts, dizziness, ataxia, seizures, and even death are the most expected manifestations **(Dudra-Jastrzêbska et al., 2007).**

Antiepileptic drugs (AEDs) are considered a potential risk factor for suicidal behavior **(Brent et al., 1987).**

In 2008 FDA issued an advisory to health care professionals about a 2-fold increased risk of experiencing suicidal thoughts and behavior of 11 AEDs **(Mula and Hesdorffer, 2011)**. The warning of the advisory resulted in great concern and confusion about the patients who use antiepileptic drugs, especially the epileptic patients **(Hesdorffer and Kanner, 2009).**

The percentage of suicidal deaths as a cause of death in patients suffer from epilepsy varies widely in the range of 0.7%–24% in the literature **(Britton and Shih, 2010).**

Around the world, suicide is considered a serious real public health problem. The prevalence rate of suicide in Europe in 2011 was 13.9/100,000 persons per year **(Ferrer et al., 2014).** Although the highest rates were prevalent among older individuals and men, recently, the rates increased among adolescents and young adults **(Wasserman, 2004; Nock et al., 2008).**

These rates are even higher among the patients who suffer from epilepsy, with a rate of 5 and 14.3% of suicide and suicide attempts in their lifetime **(Jones et al., 2003).**

So, the current study was conducted to assess the AEDs – acutely intoxicated cases regarding their Socio-demographic data, the most frequently used drug, clinical presentation, mode of exposure, period of hospitalization, and outcome. Also, to assess the relation between the administration of antiepileptic drugs and committing suicide.

METHODS

Study design and protocol

This is a prospective statistical study done on all acute antiepileptic drugs intoxicated cases that came to the national environmental and clinical toxicology research center (NECTR) during six - months period from the beginning of May to the end of October 2018. The study protocol was authorized and approved by the local research ethics committee of Kasr Alainy faculty of medicine, Cairo University, and conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. The patients were asked for their permission for data collection and their examination.

Subjects

Both sexes and all ages of patients who had a history of either suicidal or accidental intake of antiepileptic drugs were included. However, patients who are treated regularly with antiepileptic drugs and show side effects of these drugs and those with a medical history of chronic debilitating disease (heart, respiratory, renal, and liver failure) were excluded.

Collection of data

Patients were analyzed regarding:

1. Demographic data: including age, sex, residence, marital status, and status of education.

2. Primary data for patients' assessment: including the name of the administered antiepileptic drug, level of the drug taken, name of co-administered drug &

period of delay between the occurrence of toxicity and arrival to NECTR.

3. Data of physical examination on admission: including symptoms (gastrointestinal tract (GIT), respiratory, cardiovascular, and central nervous system (CNS) symptoms), signs (pulse, blood pressure, conscious level, and pupil size) & severity and mortality rate of the overdosed drug detected by poison severity scoring (PSS) **(Sam et al. 2009)** where cases are classified into None, Minor, Moderate, Severe grades and Fatal.

4. Manner of overdose intake among the studied cases, presence of previous suicidal attempt, previous suicide with the same drug or other drugs, and causes of drug intake.

5. If the patient was admitted or not.

6. Duration of hospitalization.

7. Outcome of the case (cured, discharge by own, death).

Statistical analysis

The statistical package SPSS (Statistical Package for the Social Sciences) version 24 was used. Data were summarized using frequency (count) and categorized using relative frequency (%). For comparing categorical data, Chi-square ($\chi 2$) test was performed. Exact test was used when the expected frequency was < 5 **(Chan 2003)**. P-value **< 0.05** was considered statistically significant. During the six-month duration (from the beginning of May to the end of October 2018) of the present study, 127 acute antiepileptic drug intoxicated cases were presented at and NECTR with the following results.

RESULTS

Regarding age, most cases, 53 (41.7%), were from 20 to 40 years, followed by 41 cases (32.3%) who were from 10 to 20 years, followed by 26 cases (20.5%) who were below five years. The minority of cases, 5 (3.9%) & 2 (1.6%), were from 5 to 10 years & more than 40 years, respectively. Regarding sex, 96 cases (75.60%) were females, and 31 cases (24.4%) were males. Regarding residence, 64 cases (50.4%) were from urban areas, while 63 cases (49.6%) were from rural areas. Regarding marital status, 82 cases (64.6%) were single (about half of those are in a relationship), 30 cases (23.6%) were married, 14 cases (11%) were engaged, and 1 case (0.8%) was divorced. Regarding the status of education, 80 cases (63%) were educated, and 47 cases (37%) were non-educated **(Table 1**).

Table (1): Age, sex, residence, marital status and level of education distribution among the studied cases

		Count	%
Age (years)	**Less than5 years**	26	20.5%
	5 to 10	5	3.9%
	10 to 20	41	32.3%
	20 to 40	53	41.7%
	More than 40	2	1.6%
Sex	**Male**	31	24.4%
	Female	96	75.6%
Residence	**Urban**	64	50.4%
	Rural	63	49.6%
5+Marital status	**Single**	82	64.6%
	Married	30	23.6%
	Divorced	1	0.8%
	Engaged	14	11.0%
Status of education	**Yes**	80	63.0%
	No	47	37.0%

Regarding the overdosed drug, Carbamazepine overdose represented 93 cases (73.2%), followed by sodium valproate overdose, which represented 18 cases (14.2%). Both carbamazepine and sodium valproate overdose represented 5 cases (3.9%), gabapentin overdose represented 4 cases (3.1%), phenytoin overdose represented 3 cases (2.4%) & levetiracetam overdose represented 2 cases (1.6%). Each lamotrigine and zonisamide represented 1 case of overdosed cases. Regarding the level of the overdosed drugs, carbamazepine level was sub-therapeutic in 14 (11%) cases, therapeutic in 4 (3.1%) cases, and toxic in 75 (59.1%) cases, while the valproic acid level was sub-therapeutic in 3 (2.4%) cases, and toxic in 15 (11.8%) cases. Both carbamazepine toxic and toxic valproate levels represented 3 (2.4%) cases & both carbamazepine non-toxic and toxic valproate levels represented 2 (1.6%) cases. Phenytoin level was toxic in 3 (2.4%) cases, while drug level was not measured in 8 (6.3%) cases. It was noted that 69 (54.3%) of the cases took their own drug and 58 (45.7%) of the cases took the drug of others. Regarding the co-administered drugs, 98 cases (77.2%) were with no co-ingestions, 16 cases (12.6%) co-ingested antipsychotics, 10 cases (7.9%) ingested other drugs (antibiotics, analgesics, and antihistaminics), and 3 cases (2.4%) co-ingested both antipsychotics and other drugs **(Table 2).**

Table (2): data concerning antiepileptics intoxication; drug names, drug levels, the overdosed drug is the patient's prescribed drug or not & type of co-administered drugs.

		Count	%
Drug name	**Carbamazepine**	93	73.2%
	Sodium valproate	18	14.2%
	Phenytoin	3	2.4%
	Levetiracetam	2	1.6%
	Lamotrigine	1	0.8%
	Gabapentin	4	3.1%
	Carbamazepine+valproic	5	3.9%
	Zonisamide	1	0.8%
Drug level	**Subtherapeutic Carbamazepine**	14	11.0%
	Therapeutic Carbamazepine	4	3.1%
	toxic Carbamazepine	75	59.1%
	Subtherapeutic Valproate	3	2.4%
	toxic Valproate	15	11.8%
	carba nontoxic+val toxic	2	1.6%
	carba toxic +valptoxic	3	2.4%
	not measured	8	6.3%
	phenytoin toxic	3	2.4%
The overdosed drug is the patient's prescribed drug or not	**Yes**	69	54.3%
	No	58	45.7%
Type of co-ingested drug	**No**	98	77.2%
	Antipsychotics	16	12.6%
	Others	10	7.9%
	Antipsychotics +others	3	2.4%

Cases presented within the first 6 hours were 46 (36.2%), while those with a period of 6-12 hours delay were 45 (35.4%), those of 12-24 hours delay was 35 (27.6%), and only 1 case (0.8%) came to the hospital with 24 hours delay. Regarding presented clinical manifestations, 80 (63.0%) cases were non-conscious, 67 (52.8%) showed normal blood pressure, 120(94.5%) cases showed normal pupil size, 90 (70.9%) cases had their heart rates within normal range, 96 (75.6%) & 108 (85.0%) cases had no GIT & no respiratory manifestation, respectively. According to the Poison severity score, 34 cases (26.8%) had no findings, 61 cases (48.8%) got a minor score, 25 cases (19.7%) got a moderate score, while 6 cases (4.7%) got a severe score. Regarding cases admission, 113 cases (89%) were admitted, while 14 cases (11%) were managed without being admitted. Regarding the period of hospitalization, the majority of cases, 92 (72.4%), were hospitalized from 24 hours to 48 hours, whereas 25 (19.7%) of cases were hospitalized for the period less than 24 hours, whereas and 10 (7.9%) of cases were hospitalized for more than 48 hours. Regarding patients' outcomes, 107 cases (84.3%) were cured, 19 cases (15.1%) were discharged on their request, and only 1 case (0.8%) died **(Table 3).**

Table (3): Data of the cases according to Period of delay between exposure to toxicity and presentation, Clinical picture, PSS, admission, period of hospitalization and Outcome

		Count	%
Number of hours delay before coming to NECTR	**Less than 6 hours**	46	36.2%
	6 to 12 hours	45	35.4%
	12 to24 hours	35	27.6%
	More than 24 hours	1	0.8%
Clinical picture			
conscious or not	**Yes**	47	37.0%
	No	80	63.0%
blood pressure	**Normal**	67	52.8%
	Hypotension	59	46.5%
	Hypertension	1	0.8%
Pupil size	**Normal**	120	94.5%
	Constricted	6	4.7%
	Dilated	1	0.8%
Pulse	**Normal**	90	70.9%
	Tachycardia	37	29.1%
GIT manifestation	**Yes**	31	24.4%
	No	96	75.6%
Respiratory	**Aspiration**	6	4.7%
	Wheezes and cough	13	10.2%
	No	108	85.0%
Poison severity score	**No finding**	34	26.8%
	Minor	61	48%
	Moderate	25	19.7%
	Severe	6	4.7%
	Fatal	1	0.8%
Admitted or not	**Yes**	113	89.0%
	No	14	11.0%

Period of hospitalization	**Less than 24 hours**	25	19.7%
	From 24 to 48 hours	92	72.4%
	More than 48 hours	10	7.9%
Outcome	**Cured**	107	84.3%
	Discharge by own	19	15.0%
	Death	1	0.8%

Regarding the manner of overdose intake, 93 (73.2%) cases were suicidal, and 34 cases (26.8%) were accidental. Regarding previous suicide attempts, 43 cases (46.2%) had no previous suicide attempts, but 50 cases (53.7%) had previous suicide attempts. It was noted that 73 cases (78.4%) did not use the same drug for suicide, but 20 cases (21.5%) used the same drug for suicide. Regarding causes of drug intake, 51 cases (54.8%) were due to emotional problems, 36 cases (38.7%) were due to family problems, 5 cases were (5.37%) due to `educational problems, and only 1 case (1.07%) was due to negligence **(Table 4).**

Table (4): Manner of overdose intake among the studied cases, presence of previous suicidal attempt, previous suicide with same drug or other drugs and causes of drug intake.

		Count	**%**
Manner ofoverdose intake	**Accidental**	34	26.8%
	Suicidal	93	73.2%
Previous suicidal attempts	**Yes**	50	53.7%
	No	43	46.2
Previous Suicide with same drug or other drug	**Yes**	20	21.5%
	No	73	78.4%
Causes of drug intake	**Family problem**	36	38.7%
	Emotional problem	51	54.8%
	Negligence problem	1	1.07%
	Education problem	5	5.37%

There was significant statistical relation (P = 0.008) regarding mode of exposure and sex as the suicidal mode was higher in females (79.2%) than in males (54.8%) while the accidental mode was higher in males (45.2%) than in females (20.8%). Also, there was a statistically high significant relation (P < 0.001) regarding age and manner of overdose intake, where accidental mode was higher at age group less than or equal to 5 years (100%) and at age group 5 to 10 years (80.0%) while the suicidal mode was higher at age groups > 40 years (100%), 20 to 40 years (98.1%) and 10 to 20 years (90.2%) **(Table 5).**

Table (5): Relation between manner of overdose intake & each of sex and age among studied cases

		Mode of overdose intake				
		Accidental		**Suicidal**		
		Count	**%**	**Count**	**%**	**P value**
Sex	**Male**	14	45.2%	17	54.8%	0.008
	Female	20	20.8%	76	79.2%	
Age	**Less than 5 years**	26	100.0%	0	0.0%	< 0.001
	5 to 10	4	80.0%	1	20.0%	
	10 to 20	3	7.3%	37	90.2%	
	20 to 40	1	1.9%	52	98.1%	
	More than 40 years	0	0.0%	2	100.0%	

Pearson chi-square test. (*) P < 0.05 is statistically significant. P value>0.05 is statistically insignificant.

There was significant statistical relation (P< 0.001) regarding the period of hospitalization and severity grades of the studied cases where cases who developed severe & moderate grades represented 100% of cases who were hospitalized for more than 48 hours while cases that developed minor grades represented 59.8% of cases who were hospitalized from 24 to 48 hours and cases with none grade represented 60.0% of cases hospitalized for less than 24 hours **(Table 6).**

Table (6): Relation between period of hospitalization and PSS among the studied cases

		period of hospitalization						P value
		Less than 24 hours		From 24 to 48 hours		More than 48 hours		
		Count	%	Count	%	Count	%	
Poisoning severity score (PSS)	None	15	60.0%	19	20.7%	0	0.0%	<0.001
	Minor	6	24.0%	55	59.8%	0	0.0%	
	Moderate	4	16.0%	16	17.4%	5	50.0%	
	Severe	0	0.0%	1	1.1%	5	50.0%	
	Fatal	0	0.0%	1	1.1%	0	0.0%	

Pearson chi-square test. (*) P < 0.05 is statistically significant

There was a highly significant statistical relation (P <0.001) between drug level and period of hospitalization, where cases with toxic carbamazepine level represented 70.7 % of cases who were hospitalized for 24 to 48 hours and represented 70% of cases who were hospitalized for more than 48 hours while cases with sub-therapeutic carbamazepine level represented 52% of cases who were hospitalized for less than 24 hours. Also, cases with toxic valproate levels represented 14.1% of cases who were hospitalized for 24 to 48 hours, while cases with sub-therapeutic valproate levels represented 12% of cases who were hospitalized for less than 24 hours **(Table 7).**

Table (7): Relation between drug level and period of hospitalization among the studied cases

		period of hospitalization						P value
		Less than 24hours		From 24 to 48 hours		More than 48 hours		
		Count	%	Count	%	Count	%	
Drug level	Sub therapeutic Carbamazepine level	13	52.0%	1	1.1%	0	0.0%	<0.001
	Therapeutic Carbamazepinelevel	2	8.0%	2	2.2%	0	0.0%	
	Toxic Carbamazepine level	3	12.0%	65	70.7%	7	70.0%	
	Sub therapeutic Valproate level	3	12.0%	0	0.0%	0	0.0%	
	Toxic Valproate level	1	4.0%	13	14.1%	1	10.0%	
	Nontoxic carbamazepine level + Toxic valproate level	0	0.0%	2	2.2%	0	0.0%	
	Toxic carbamazepine level + Toxic valproate level	0	0.0%	2	2.2%	1	10.0%	
	non measuredlevels	3	12.0%	5	5.4%	0	0.0%	
	Toxic phenytoin level	0	0.0%	2	2.2%	1	10.0%	

Pearson chi-square test. (*) P < 0.05 is statistically significant.

There was a highly significant statistical relation ($p<0.001$) between drug level and PSS as cases with toxic carbamazepine level represented 70% of cases with minor PSS, 60% of cases with moderate PSS & 50% of cases with severe PSS while cases with subtherapeutic or therapeutic carbamazepine level represented 26.5%, 9.9% & 12 % of cases with none grade, minor & moderate PSS, respectively **(Table 8).**

Table (8): Relation between drug level and PSS among the studied cases

		Poisoning severity score										P value
		None		Minor		Moderate		Severe		Fatal		
		Count	%	Count	%	Count	%	Count	%	Count	%	
Drug level	Sub therapeutic Carbamazepine level	7	20.6%	4	6.6%	3	12.0%	0	0.0%	0	0%	< 0.001
	Therapeutic Carbamazepine level	2	5.9%	2	3.3%	0	0.0%	0	0.0%	0	0%	
	Toxic Carbamazepine level	13	38.2%	43	70.5%	15	60.0%	3	50.0%	1	100%	
	Sub therapeutic Valproate level	3	8.8%	0	0.0%	0	0.0%	0	0.0%	0	0%	
	Toxic Valproate Level	4	11.8%	7	11.5%	4	16.0%	0	0.0%	0	0%	
	Nontoxic carbam-azepine level + toxic valproate level	0	0.0%	1	1.6%	1	4.0%	0	0.0%	0	0%	
	Toxic carbamazepine level +toxic valproate level	0	0.0%	0	0.0%	2	8.0%	1	16.7%	0	0%	
	Non measured level	5	14.7%	3	4.9%	0	0.0%	0	0.0%	0	0%	
	Toxic phenytoin level	0	0.0%	1	1.6%	0	0.0%	2	33.3%	0	0%	

Pearson chi-square test. (*) P < 0.05 is statistically significant.

DISCUSSION

There has been more widespread use of antiepileptic drugs in patients with underlying psychiatric disorders, often as an unlicensed indication. This patient group is at substantially increased risk of self-poisoning **(Nixon et al., 2008).** Furthermore, The US Food and Drug Administration (FDA) issued an alert that all antiepileptic drugs pose an increased risk of suicidality **(Busco, 2008).**

This prospective study was conducted on cases intoxicated with antiepileptic drugs presented at **NECTR** for six months period from May to October 2018 and included 127 cases (31 males and 96 females).

The current study investigated the intoxicated patients' demographic data and regarding the age, the most affected age groups were those between 20-40 years (41.7%), followed by those more than 10-20 years (32.3%), followed by those below 5 years (20.5%) and the least affected age group was that above 40 years (1.7%).In agreement with the present study, a study was done in Menoufia governorate, Lower Egypt, of 1-year period from February 2014 to January 2015, showed similar findings, as their patients' age ranged from less than five years old to more than 40 years old with the highest incidence was between 20-40 years old **(Amin et al., 2017).** Also, a prospective study was conducted by Sane and Goudarziin at the Shiraz Shoushtari Hospital in Iran, during a 2-year period from 2010 to 2012, and it showed that the mean age of patients was 26.2 years **(Sane and Goudarzi, 2013).**

According to the present study, the admissions of females were greater than males, where female cases represented (75.6%) while male cases represented

(24.4%). Similarly**,** the study done by **Günaydın et al. (2015)** from the period of January 2010 to February 2013 revealed that female cases represented 74.7% and male cases represented 25.3%. In contrast to the present study, a study was done in the United States from 2000 to 2012 where the percentage of male cases (77%) overcame the percentage of the female cases **(Cantrell and Lucas, 2014).**

Regarding residency, patients from urban areas (92.1%) overcame those from rural areas (7.9%). This may be due to the easy accessibility to the center (NECTR), which is being located in Cairo, so it is much closer to most urban areas. These data were consistent with those detected by a study done in Ontario, Canada, from April 2002 to December 2011, where cases from urban areas (86.4%) overcame cases from rural areas (13.6%) **(Finkelstein et al., 2015)**. However, this was in contrast to the study of **Amin et al. (2017)** at Menoufia University, where cases were mostly from rural areas; this is mainly due to the fact that the majority of residents in Menoufia governorate live in rural areas with an urbanization rate with only 20.6%.

As regards education, the educated cases (63%) overcame illiterate cases (37%). This was similar to the study done in the Poison Control Center of Ain Shams University Hospitals (PCCA), during the period from June 2007 until the end of July 2008, where most of the cases were educated **(Ghanem et al., 2015).**

The present study demonstrated the following regarding marital status, the single cases represented 64.6%, the married cases represented 23.6%, the engaged cases represented 11%, and the divorced represented 0.8%. This was in accordance with the study of **Ghanem et al. (2015)** at Ain Shams University Hospitals (PCCA), where the majority of cases were single (58%), and it was in contrast to the study of **Ahmad et al. (2015)**, where the rate of suicide was higher among married cases (66%).

In the current study, the commonest used AED was carbamazepine (73.2%), followed by sodium valproate (14.2%) then phenytoin (2.4%). This could be because carbamazepine is more frequently prescribed. This was in agreement with the study of **Amin et al. (2017)** and the study of **Nixon et al. (2008),** whereas the study of **Amin et al. (2017)** showed that the commonest AED was carbamazepine (49%). **Moreover, Nixon et al. (2008)** showed that the first three used AED were CMZ, VPA, and Phenytoin. On the other hand, in the study from Iran**,** the first three AED were CMZ, Phenobarbital, and VPA **(Islambulchilar et al., 2009).** This difference might result from differences in population samples where the study of **Nixon et al. (2008)** included only the adult population, while the study of **Islambulchilar et al. (2009)** included child population, for which Phenobarbital was usually prescribed**.**

Regarding co-administration, 77.2% of cases administrated only AED drug, whereas (22.9%) of cases administrated AED with another group of drugs. This was in agreement with **the 2015 annual report of the AAPCC and national poison data system (NPDS)**, which stated that single substance cases reflect the majority (75.9%) of all exposures**(Mowry et al., 2015).** Contrary to the present study, **Nixon et al. (2008)** showed that cases who ingested AED together with other agent groups were higher and represented 65.4%.

Concerning the time interval between drug consumption and presentation to the toxicology center, we reported that 36.2% of cases were presented within the first 6 hours from exposure. This was consistent with the results obtained from the study done by **Akbaba et al. (2007)**, where 34.6% of cases

presented in less than 2 hours and 65.3% of cases presented between 2 to 3 hours from exposure.

According to Poisoning Severity Score, in the present study, 26.8% of cases were classified as none grade cases, 48% of cases were classified as minor grade cases, 19.7% of cases were classified as a moderate grade, 4.7% of cases were classified as a severe grade, and one case was fatal (0.8%). Comparable with the present study, the study done at Menoufia University showed that cases of none grade were 34.7% of cases followed by 50% of cases were of minor grade, moderate grade cases represented 13.3%, and the least were cases of severe grade, which represented 2% **(Amin et al., 2017)**.

Regarding the period of hospital admission, 72.4% of studied cases were hospitalized from 24 hours to 48 hours, while only 7.9% of cases were hospitalized for more than 48h. In line with the present study, the study that was done by **Islambulchilar et al. (2009)** showed the median hospitalization period of the case groups who were poisoned with non-benzodiazepine antiepileptic drugs (NBDAED) was 24 hours.

In the present study, 84.3% of cases improved, 15% of cases discharged on their request, so their outcome could not be determined, and one case (0.8%) died (carbamazepine overdose case with toxic serum blood level and developed aspiration). This result coincides with the result from **Sane and Goudarzi (2013**), who stated that two patients (1%) died in their study (one carbamazepine overdose case and one sodium valproate overdose case), and they explained that the death was owing to status epilepticus and aspiration pneumonia.

Concerning the mode of exposure, in the current study, 73.2% were suicidal cases, and 26.8% were accidental intoxication. Causes of suicide included economic problems, love failure, quarrels, unemployment, examination failure, and chronic illness.

In agreement with the above result, the prospective study that was done by **Lee et al. (2008)** at Tainan City from the period January 2001 to December 2002 showed that suicidal cases represented 66.1%. On the contrary, according to **the 2015 Annual Report of the American Association of Poison Control Centers (AAPCC)** National Poison Data System (NPDS), accidental exposures accounted for 79.4%, and suicidal exposures accounted for 16.7% of human exposures **(Mowry et al., 2015).**

The present study demonstrated that 53.7% of suicidal cases had previous suicide attempts. This result was consistent with the result from a large majority of studies done at the period from **2000 to 2012**, which showed that the percentage of repeated previous suicide attempts was 82.5% **(Mendez-Bustos et al., 2013).**

In the present study, there was a significant relationship ($p=0.008$) between sex and manner of overdose intake, where suicidal cases were more common in females. The predominance of females over males and the higher percentage of suicidal attempts in females can be explained by a lower rate of employment and suppression of personal freedom by parents. The same results were observed by **Aslan et al. (2011) and Sane and Goudarzi (2013).**

In the present study, there was high significant statistical relation ($p<0.001$) between age and manner of overdose intake where suicidal cases were mostly seen in the age group of 10 to 20 years and in the age group of 20 to 40 years, while accidental intoxication was mostly seen in the age group below five years and the age group of 5 to 10 years. This result was consistent with **Aggarwal et al. (2014),** who collected the data from a tertiary care teaching hospital at Dehradun, in Uttarakhand, India, where

most cases of accidental toxicity occurred in children below 12 years (97%), while most of the suicidal toxicity occurred in adolescent (80.4%) and it is also consistent with **Dnyanesh et al. (2014)** and **Gupta et al. (2003).** This may be explained as toddlers have over curiosity and explore their world by their mouth **(Singh, 2007),** while adolescents experience stressful life conditions and have many physiological and emotional troubles during this period of their life **(Trangadia et al., 2016)**.

In the present study, there was a significant relationship ($p<0.001$) between drug level and period of hospital admission, where cases with toxic serum levels that stayed from 24 to 48 hours were more than those with non-toxic serum levels and cases with unmeasured levels. Regarding this, **Celenk et al. (2013)** showed insignificant ($p> 0.05$) relation.

In the present study, there was a significant relationship ($p<0.001$) between drug level and poisoning severity score as in the case group that developed moderate and severe clinical signs and symptoms, their serum drug level was toxic, while the case group whose serum drug level was non-toxic and the group whose serum drug level was not measured, developed any or mild signs and symptoms. Also, the results of the study done by **Çelenk et al. (2013)** were within the same range as the present result ($p=0.04$).

CONCLUSION

It was concluded that female cases outnumbered male cases, carbamazepine followed by valproic acid and then phenytoin were the most common drugs taken, and most of the cases were presented with carbamazepine toxic serum levels. The overdosed antiepileptic drug was mostly the patient's prescribed drug. According to PSS, most intoxicated cases showed minor grades. Period of hospitalization was from 24 to 48 hours in the majority of cases. Most of the cases were cured, and the mortality rate was 0.8%. Suicidal cases were common than accidental cases and showed a significantly higher frequency among females than males & among the adult age group than other age groups. Most of the suicidal cases had previous suicidal attempts.

ABBREVIATIONS

AAPCC: the American Association of Poison Control Centers
AED : Antiepileptic drug
CBZ: Carbamazepine
CNS: Central nervous system
FDA: Food and Drug Administration
FGAEs: First generation of antiepileptics
GIT: Gastrointestinal tract
NBDAED: Non-benzodiazepine antiepileptic drugs
NECTR: National environmental and clinical toxicology research center
NPDS: National poison data system
PCCA: Poison Control Center of Ain Shams University Hospitals
PSS:Poison severity scoring
SGAEs: Second generation antiepileptics
VPA:Valproic acid

REFERENCES

Aggarwal, B., Rana, S.K. & Chhavi, N. (2014). Pattern of poisoning in children, an experience from a teaching hospital in Northern India, JK SCIENCE .16 (4): 174-178

Ahmad, M.; Rahman, F.N.; Islam, M.M.,and Majumder, M. R.U. (2015). Death due to Poisoning-a Medicolegal Study at Dhaka Medical College, Dhaka. Faridpur Medical College Journal, 9(2), 76-79.

Akbaba, M.; Nazlican, E.; Demirhindi, H.; Sütoluk, Z and Gökel, Y. (2007). Etiological and demographical characteristics of acute adult poisoning

in Adana, Turkey. Human & experimental toxicology, 26(5), 401-406.

Amin, S. A., Zanaty, A. W., Kandeel, F. S., and El-Nady, M. S. (2017). Patterns of antiepileptic drugs–poisoned cases arrived at Menoufia University Poison and Dependence Control Center. Menoufia Medical Journal, 30(4), 1178-1185.

ASLAN, Ş., EMET, M., Cakir, Z., AKÖZ, A., and GÜR, S. T. A. (2011). Suicide attempts with amitriptyline in adults: a prospective, demographic, clinical study. Turkish Journal of Medical Sciences, 41(2), 243-249.

Brent, D. A., Crumrine, P. K., Varma, R. R., Allan, M., & AlIman, C. (1987). Phenobarbital treatment and major depressive disorder in children with epilepsy. Pediatrics, 8,0(6), 909-917.

Britton, J. W., & Shih, J. J. (2010). Antiepileptic drugs and suicidality. Drug, healthcare and patient safety, 2, 181-189.

Bronstein, A. C., Spyker, D. A., Cantilena Jr, L. R., Rumack, B. H., & Dart, R. C. (2012). 2011 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th annual report. 50(10):911-1164.

Busco, M. (2008). FDA advisory members agree antiepileptics pose suicidality risk, need for black-box warning. Medscape Medical News. Medscape WebMD, New York.

Cantrell, L., & Lucas, J. (2014). Suicide by non-pharmaceutical poisons in San Diego County. Clinical Toxicology, 52(3), 171-175

Çelenk, Y., Katı, C., Duran, L., Ufuk Akdemir, H., & Balcı, K. (2013). The Evaluation of Patients Admitted to the Emergency Department with Non-Benzodiazepine Antiepileptic Drug Poisoning. Journal of Academic Emergency Medicine/Akademik Acil Tip Olgu Sunumlari Dergisi, 12(4).199-204

Chan, Y. H. (2003). Biostatistics 103: qualitative data-tests of independence. Singapore Med J, 44(10), 498-503.

Dnyanesh, D. K., Dnyanesh, S., & Bellad, R. (2014). Profile of paediatric poisoning at a tertiary care center in Karnataka. International Journal of Applied Sciences and Biotechnology. 2 (2),142-145.

Dudra-Jastrzêbska, M., Andres-Mach, M. M., Luszczki, J. J., & Czuczwar, S. J. (2007). Mood disorders in patients with epilepsy. Pharmacological Reports, 59(4), 369-378.

Even, K. M., Armsby, C. C., & Bateman, S. T. (2014). Poisonings requiring admission to the pediatric intensive care unit: A 5-year review. Clinical Toxicology, 52(5), 519-524.

Ferrer, P., Ballarín, E., Sabaté, M., Vidal, X., Rottenkolber, M., Amelio, J., & Ibáñez, L. (2014). Antiepileptic drugs and suicide: a systematic review of adverse effects. Neuroepidemiology, 42(2), 107-120.

Finkelstein, Y; Macdonald, E.M; Hollands, S.; Sivilotti, M.L.; Hutson, J.R.; Mamdani, M.M. and Juurlink, D.N. (2015). Risk of suicide following deliberate self-poisoning. JAMA Psychiatry, 72(6):570-575.

Gök, Ş. (2006). Antiepileptic Drug Intoxications, Türkiye Klinikleri J. Surg. Med. Sci, 2(46), 112-120.

Gummi, D. D., Mowry, J. B., Spyker, D. A., Brooks, D. E., Beuhler, M. C., Rivers, L. J., ... & Ryan, M. L. (2019). 2018 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS):

36th Annual Report. Clinical Toxicology, 57(12), 1220-1413.

Günaydın, Y. K., Akıllı, N. B., Dündar, Z. D., Köylü, R., Sert, E. T., Çekmen, B., ... & Cander, B. (2015). Antiepileptic drug poisoning: three-year experience. Toxicology Reports, 2, 56-62

Gupta, S.K., Peshin, S.S., Srivastava, A., et al. (2003).A study of childhood poisoning at national poisons information centre, All India Institute of medical sciences, New Delhi. Journal of Occupational Health, 45 (3),191-196.

Hesdorffer, D.C. & Kanner, A.M. (2009). The FDA alert on suicidality and antiepileptic drugs: fire or false alarm?. Epilepsia, 50(5), 978-986.

Islambulchilar, M., Islambulchilar, Z., & Kargar-Maher, M. H. (2009). Acute adult poisoning cases admitted to a university hospital in Tabriz, Iran. Human & Experimental Toxicology, 28(4), 185-190

Jones, J. E., Hermann, B. P., Barry, J. J., Gilliam, F. G., Kanner, A. M., & Meador, K. J. (2003). Rates and risk factors for suicide, suicidal ideation, and suicide attempts in chronic epilepsy. Epilepsy & Behavior, 4, 31-38.

Lee, H. L., Lin, H. J., Yeh, S. T. Y., Chi, C. H., & Guo, H. R. (2008). Presentations of patients of poisoning and predictors of poisoning-related fatality: findings from a hospital-based prospective study. BMC Public health, 8(1), 7-8.

Maedie, F. H., Alhaddad, H., & Hussain, S. A. (2015). Evaluation of poisoning cases in the poisoning consultation center and forensic medicine institute within Baghdad area. Iraqi Journal of Pharmaceutical Sciences (P-ISSN: 1683-3597, E-ISSN: 2521-3512), 24(2), 22-29.

Mendez-Bustos, P., de Leon-Martinez, V., Miret, M., Baca-Garcia, E. & Lopez-Castroman, J. (2013). Suicide attempters: a systematic review. Harvard Review of Psychiatry, 21(6), 281-295.

Mowry, J. B., Spyker, D. A., Brooks, D. E., Zimmerman, A., & Schauben, J. L. (2016). 2015 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd Annual Report. Clinical Toxicology, 54(10), 924-1109.

Mula, M. (2016). Third-generation antiepileptic drug monotherapies in adults with epilepsy. Expert review of Neurotherapeutics, 16(9), 1087-1092.

Mula, M., & Hesdorffer, D. C. (2011). Suicidal behavior and antiepileptic drugs in epilepsy: analysis of the emerging evidence. Drug, Healthcare and Patient Safety, 3, 15-20.

Ngugi, A. K., Bottomley, C., Kleinschmidt, I., Sander, J. W., & Newton, C. R. (2010). Estimation of the burden of active and lifetime epilepsy: a meta-analytic approach. Epilepsia**,** 51(5), 883-890.

Nixon, A. C., Doak, M. W., Crozier, H., Crooks, D. P., & Waring, W. S. (2008). Patterns of antiepileptic drug overdose differ between men and women: admissions to the Edinburgh Poisons Unit, 2000–2007. QJM: An International Journal of Medicine, 102(1), 51-56.

Nock, M. K., Borges, G., Bromet, E. J., Cha, C. B., Kessler, R. C., & Lee, S. (2008). Suicide and suicidal behavior. Epidemiological Review, 30, 133-154.

Rezaie, L.; Khazaie, H.; Soleimani, A. and Schwebel, D.C. (2011). Is self-immolation a distinct method for suicide? A comparison of Iranian patients attempting suicide by self-immolation and by poisoning. Burns, 37(1), 159-163.

Sam, K. G., Kondabolu, K., Pati, D.,

Kamath, A., Kumar, G. P., & Rao, P. G. (2009). Poisoning severity score, APACHE II and GCS: effective clinical indices for estimating severity and predicting outcome of acute organophosphorus and carbamate poisoning. Journal of Forensic and Legal Medicine, 16(5), 239-247.

Sane, N., & Goudarzi, F. (2013). Seizure in Patients with Antiepileptic Drug Overdose: Study on Patients Admitted To Shoushtari Hospital in Shiraz. Asia Pacific Journal of Medical Toxicology, 2(3), 101-104.

Singh M. (2007). Medical emergencies in children.4thed. New Delhi: Sagar 128-134.

Trangadia M, Kharadi R & Gupta BD (2016). Epidemiologic Study of Fatal and Non-Fatal Poisoning Case in Pediatric Around Jamnagar, Region, Gujarat in India (January-December 2013) International Journal of Medical Toxicology and Forensic Medicine.6 (3), 128-134.

Wasserman, D. (2004). Aggarwal, B., Rana, S.K. & Chhavi, N. (2014): Pattern of Poisoning in Children, an Experience From a Teaching Hospital in Northern India, JK SCIENCE .16 (4): 174-178.

الملخص العربي

التسمم و الميول الانتحاريه المرتبطه بالادويه المضاده للصرع

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المقدمة يتم استخدام الادوية المضادة للصرع بشكل متزايد، عاده كاستخدام غير مرخص , في المرضي الذين يعانون من اضطرابات نفسيه و الذين هم اكثر عرضه لخطر ايذاء النفس. ومن المتوقع أن يؤدي ذلك إلى زيادة احتمالية استخدام هذه الأدوية كوسيلة للجرعة الزائدة. **الاهداف**: أجريت الدراسة الحالية لتقييم حالات التسمم الحاد بمضادات الصرع, على وجه الخصوص العلاقة بين اعطاء الادويه المضاده للصرع و الانتحار. **الطريقة**: اشتملت الدراسة على 127 حالة تسمم بأدوية الصرع تم دخولهم الي المركزالقومي للسموم و ذلك لمدة ستة أشهر في الفتره من مايو إلى أكتوبر2018. تم تحليل البيانات فيما يتعلق بالبيانات الاجتماعية والديموغرافية ، والبيانات الأولية لتقييم المرضى ، والبيانات المتعلقة بالفحص البدني ، وطريقة تناول الجرعة الزائدة ، وحالة المريض عند الدخول ، وفترة الاستشفاء والنتيجة. **النتائج**: كانت الفئه العمريه الاكثر شيوعا هي 20-40 سنه بنسبه(75.6%) للاناث. و قد كان الكاربامازين هو الاكثر تناولا (73.2%). كانت الطريقه الاكثر شيوعا للتسمم بالجرعات الزائده هي الانتحار (73.2%) و تم شفاء اغلب الحالات.**الخلاصه**: يشكل الانتحار بالادويه المضاده للصرع نسبه عاليه بين الاناث و الفئه العمريه البالغه. لذلك يوصي باجراء تقييم نفسي و متابعه لهولاء المرضي.