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# Incidence of Antipsychotic Drugs Intoxication in Damietta Governorate

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ORIGINAL ARTICLE

# Incidence of Antipsychotic Drugs Intoxication in Damietta Governorate

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**Abstract**

*Background*: **Antipsychotic drugs (APs) are the base for the pharmacological therapy of schizophrenia (SZ) and other psychotic disorders. Antipsychotics intoxication side effects are commonly including decrease level of consciousness, seizures and extra pyramidal symptoms.**

*Objective*: **To shed light on the incidence of APs intoxication in Al-Azhar University Hospital (New Damietta) from the December 1, 2020 to the end of November 2022.**

*Patients and methods*: **It involved 146 cases who admitted to toxicology unit and after arrival to the hospital, 10 ml of blood was separated and the serum was used for detection of APs by using a high-performance liquid chromatography (HPLC) and other blood samples were stored at −8 °C for random blood sugar, hemoglobin levels, kidney function tests, arterial blood gases, creatine kinase, myoglobin blood levels and liver enzymes. Urine drugs screen and echocardiographic (ECG) changes were recorded then treatment to all cases were done.**

*Results*: **Adult young, females, singles, students cases were the most frequently affected. The majority of cases were had a history of mental illness. Clozapine drug was the most commonly used. Suicidal manner was the most common. Decreased level of consciousness was the most common clinical presentation followed by extra pyramidal symptoms.**

*Conclusions*: **No correlation between ingested APs doses and serum APs blood levels, neuroleptic malignant syndrome occurred with normal drug doses in old ages and recovery outcome was the most common result.**

*Keywords:* Antipsychotic drugs, Detection, High-performance liquid chromatography, Intoxication

## 1. Introduction

Antipsychotic drugs were classified into two main groups; typical: haloperidol (HAL) and chlorpromazine (CPZ)) and atypical: antipsychotic drugs (AAPDs): (i.e., clozapine (CLZ), risperidone (RSP), aripiprazole (ARP), quetiapine (QUE) and olanzapine (OLA)).[1] APs have a long history of being used extensively for the management of psychotic disorders such as SZ and other psychiatric disorders like bipolar disorder, obsessive compulsive disorder, tic disorders and disruptive behavioral disorders.[2] AAPDs characterized by less extra pyramidal symptoms (EPS) at therapeutic doses.[3] Drugs with high relative alpha$_1$ ($\alpha_1$) adrenergic antagonism (e.g., CLZ, OLA and RSP) are likely to cause dizziness, orthostatic hypotension, reflex tachycardia and miosis. Drugs with high relative ($\alpha_2$) adrenergic receptor antagonism (e.g., CLZ and RSP) may cause sympathomimetic effects (i.e., tachycardia). High relative histaminic ($H_1$) receptor blockade (e.g., CLZ, OLA and QUE) will cause CNS depression and hypotension. Drugs with high relative muscarinic ($M_1$) receptor binding (e.g., CLZ and OLA) will cause peripheral and central anti-cholinergic symptoms.[4,5] Seizures and neuroleptic

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malignant syndrome (NMS) were adverse effects that may be produced with short-term management of APs.[6] Extra pyramidal symptoms such as dystonia, parkinsonism, tardive dyskinesia (TD), and akathisia were more common in cases using typical APs. Acute laryngeal dystonia (ALD) also appeared to develop more commonly in young males taking high potency APs.[7] Oculogyric crisis (OGC) was an uncommon movement disorder due to APs overdose.[8] The present study aimed to shed light on the incidence of APs intoxications or overdose and its pattern.

## 2. Patients and methods

This is an observational cross-sectional study that included 146 cases admitted to toxicology unite or psychiatric department due to APs poisoning or overdose at Al-Azhar university hospital in new Damietta during the period extending from the December 1, 2020 to the end of November 2022. Ethical approval: An approved was obtained from the Ethical Research Board (ERB) of the Faculty of Medicine, Al-Azhar University, Damietta, Egypt. All patients or their relatives assigned informed consent. Inclusion Criteria: history of APs intake given either by the patients themselves or their relatives. Patients who developed decreased level of consciousness or EPS or tachycardia or CNS symptoms. Both sexes (males and females). Any co-ingested drugs were recorded. Exclusion Criteria: patients without a definitive history of APs intake and patients with a history of chronic renal or liver diseases.

### *2.1. Methods*

Socio-Demographic Data: Age, sex, residence, occupation, marital status, and history of mental illness or smoking. Present history: manner and dose of drug intake. Delay time and clinical presentations were recorded. General and systemic examination on admission and the degree of consciousness of patients was graded according to the Glasgow Coma Scale (GCS). Investigations; Complete blood count (CBC), Alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinene, random glucose, creatin phosphokinase blood (CPK) levels, and arterial blood gases (ABGs) were detected. Serum APs detection by HPLC; Sample Preparation: The blood samples were collected from cases and collected into EDTA containing tubes, centrifuged, and the plasma then stored at −20 °C till analysis. Chromatographic System: HPLC YL 9100 (South Korea) with YL-Clarity program and C 18 column (250 mm × 4.6 μm). Mobile Phase Preparation: Acetonitrile (Li Chrolve, Germany) and 62.4 mM phosphate buffer (containing 0.3% triethylamine (Kahira, Egypt), pH 4.5) at ratio of 40:60 (v/v). Standard and Internal Standard (IS) Preparation: in ARP detection; tablets were containing 15 mg of ARP (Hikma Pharma, Egypt) base (used as standard) and clotrimazole (Arab drug company, Egypt) was used as IS. In CPZ detection: tablets containing 25 mg CPZ hydrochloride (Misr Co for Pharma. Egypt) base (used as standard) and levomepromazine hydrochloride was used as IS. In CLZ detection; tablets were containing 25 mg of CLZ (Multi Apex Co., Egypt) base (used as standard) and caffeine (Sigma chemical company, USA) was used as IS. In HAL detection; tablets were containing 5 mg of HAL base (used as standar,d) and loratadine (Sedicobayer, Egypt) was used as IS. In OLA detection; tablets were containing 5 mg of OLA (Eva pharma, Egypt) base (used as standard) and CLZ used as IS. In QUE detection; tablets were containing 25 mg of QUE (Apex Pharma, Egypt) base (used as standard) and CLZ was used as IS. In RSP detection; tablets were containing 1 mg of RSP (Multi apex pharma, Egypt) base (used as standard) and CLZ used as IS. Each Standard was dissolved separately in 15 ml methanol adjusted to pH 2 Hydrochloric acid (HCL) (El Nasr Pharmaceutical Chemicals Company, Egypt). Suspensions were shaken and then the solutions were used for the preparation of calibrator samples. Each IS was dissolved separately in 15 ml methanol, then adjusted to pH 2 with HCL t,hen suspensions were shaken and cleared by centrifugation and the solution was filtered then 1 μg/ml solutions mixed with mobile phase, then used as IS. All solutions were stored at 4 °C till use. Extraction: The first test tube containing 1 ml test serum sample, the second tube containing 1 ml standard solution and the third blank tube containing 1 ml drug free plasma obtained from blothe od of healthy volunteers. Then 50 μl of IS was added to all tubes then 4 ml dichloromethane was added to all tubes. All tubes were vortexed by (Vortex Mixer, Taiwan) for 30 s and centrifuged, and the organic layers were transferred to another conical glass tubes. Organic layers were evaporated an,d the residues were taken in 100 μl of mobile phase then 20 μl was injected into the column of HPLC. Results: APs serum concentrations were calculated by using the formula: area of the analyte/area of the standard x concentration of standard. Treatment that including Gastric lavage, multiple doses activated charcoal (MDAC) administration and any other specific treatment was recorded.

### 2.2. Statistical analysis

Data was analyzed by (SPSS vs. 22). The difference between tthe wo means was statistically analyzed For qualitative data the number and percent distribution was calculated. Chi square ($\chi^2$) or Fisher's exact test were used as a tests of significance. Tests of significance were determined based on a $P$ value <0.05.

## 3. Results

Table 1.

This table shows: the majority of cases were in the age group 21–30 years 53 cases (36.3%) followed by age group 1–10 years 40 cases (27.4%) then age group 11–30 years 31 cases (21.2%), age group >41 years 12 cases (8.2%) and age group 31–40 years were 10 years (6.8%). The majority of cases were students, 62 cases (42.5%) followed by housewives, 30 cases (20.5%) then without jobs, 22 cases (15.1%). Only 29 cases (19.9%) were cigarette smokers Table 2.

This table shows: the mean delay time was 5.1(1–48) hours. The most common used APs was CLZ 40 cases (27.4%) followed by OLA 30 cases (20.5%) then, RSP 22 cases (15.1%) then ARP 22 cases (15.1%) then HAL 14 cases (9.6%) then QUE 14 cases (9.6%) then CPZ 4 cases (2.7%). The majority of cases had no co-ingested drugs, 82 cases (56.2%). The mean dose of APs was 1800.2 mg, the maximum dose was 20,000 mg and the minimum dose was 0.25 mg Table 3.

This table shows: there were 60 cases (41.1%) presented with a decreased level of consciousness, 28 cases (19.6%) with EPS; (14 cases (9.6%) up-rolling of the eye balls and blurring of vision, 4 cases (2.7%) unilateral deviation of the neck and protrusion of tongue, 4 cases (2.7%) inability to talk, 2 cases (1.4%) sudden jerky movement of limbs, 2 cases (1.4%) protruded tongue and up-rolling of eyes, 2 cases (1.4%) protruded tongue and 2 cases (1.4%) difficulty opening his mouth and involuntarily twisted neck), 16 cases (11%) with seizures, 6 cases (4.1%) with agitation, 4 cases (2.7%) with sever

*Table 1. Socio-demographic data of studied cases.*

| Variable | *N* (Percentage) |
|---|---|
| Age group | |
| 1–10 Years | 40 (27.4%) |
| 11–20 Years | 31 (21.2%) |
| 21–30 Years | 53 (36.3%) |
| 31–40 Years | 10 (6.8%) |
| >41 Years | 12 (8.2%) |
| Job | |
| Students | 62 (42.5%) |
| Housewives | 30 (20.5%) |
| No jobs | 22 (15.1%) |
| Manual workers | 10 (6.8%) |
| Farmers | 6 (4.1%) |
| Skilled workers | 4 (2.7%) |
| Employees | 4 (2.7%) |
| Teachers | 4 (2.7%) |
| Retired | 2 (1.4%) |
| Engineers | 2 (1.4%) |
| Smoking | |
| No | 117 (80.1%) |
| Yes | 29 (19.9%) |

*Table 2. Toxicological findings in studied cases (N = 146).*

| | *N* (Percentage) |
|---|---|
| Delay time (hours) | |
| Mean ± S.D. | 5.10 ± 7.42 |
| Minimum-Maximum | 1–48 |
| Antipsychotic drugs | |
| Clozapine | 40 (27.4%) |
| Olanzapine | 30 (20.5%) |
| Risperidone | 22 (15.1%) |
| Aripiprazole | 22 (15.1%) |
| Haloperidol | 14 (9.6%) |
| Quatiapine | 14 (9.6%) |
| Chlorpromazine | 4 (2.7%) |
| Co-ingested drugs | |
| No | 82 (56.2%) |
| Yes | 64 (43.8) |
| Doses of antipsychotic drugs (mg) | |
| Mean ± S.D. | 1800.2 ± 4649.7 |
| Minimum-Maximum | 0.25–20000 |

*Table 3. Main complain in studied cases (N = 146).*

| | *N* (Percentage) |
|---|---|
| Complain | |
| Decreased level of consciousness | 60 (41.1%) |
| Seizures | 16 (11%) |
| Up-rolling of the eye balls and blurring of vision | 14 (9.6%) |
| Agitation | 6 (4.1%) |
| Vomiting | 4 (2.7%) |
| Unilateral deviation of the neck and tongue protrusion | 4 (2.7%) |
| Unbalanced walking | 4 (2.7%) |
| Somnolence interrupted by agitation | 4 (2.7%) |
| Inability to talk | 4 (2.7%) |
| Difficulty breathing and talking | 4 (2.7%) |
| Delirium | 4 (2.7%) |
| Auditory hallucinations | 4 (2.7%) |
| Sudden jerky movement of limbs | 2 (1.4%) |
| Protruded tongue and up-rolling of eyes | 2 (1.4%) |
| Protruded tongue | 2 (1.4%) |
| Palpitations | 2 (1.4%) |
| Lethargy | 2 (1.4%) |
| Hand tremor | 2 (1.4%) |
| Dizziness on standing | 2 (1.4%) |
| Difficulty opening mouth and twisted neck | 2 (1.4%) |
| Confusion | 2 (1.4%) |

vomiting, 4 cases (2.7%) with unbalanced walking, 4 cases (2.7%) with somnolence repeatedly interrupted by spontaneous agitation, 4 cases (2.7%) with delirium, 4 cases (2.7%) with auditory hallucinations, 2 cases (1.4%) with palpitations, 2 cases (1.4%) with lethargy, 2 cases (1.4%) with hand tremor, 2 cases (1.4%) with dizziness on standing and 2 cases (1.4%) with confusion Table 4.

This table shows: cases presented by tachycardia were 94 (64.4%). Hypotension was recorded in 77 cases (52.7%). There were 18 cases (12.3%) with upward deviated eye. There were 78 cases (53.4%) with GCS >12, 49 cases (33.6%) 9–11 GCS and 19 cases (13%) < 8 GCS. Neck deviation and rigidity reported in 12 cases (8.2%). Difficulty in swallowing food particles recorded in 30 cases (20.5%) Table 5.

This table shows: 39 cases (26.7%) drowsy, 34 cases (23.3%) in coma, 20 cases (13.7%) with anxiety, 16 cases (11%) confused, 16 cases (11%) with tonic clonic seizures, 10 cases (6.8%) agitated, 6 cases (4.1%) had tremor, 4 cases (2.7%) were lethargic and 1 case (0.7%) with dizziness. Urinary retention had recorded in 19 cases (13%) and incontinence in 4 cases (2.7%) Table 6.

This table shows: Positive urine screen 6 cases (4.1%) with hashish, 2 cases (1.4%) tramadol and 1 case (0.7%) benzodiazepine. 26 cases (17.8%) with metabolic acidosis, 6 cases (4.1%) respiratory acidosis, 2 cases (2.7%) metabolic alkalosis and 2 cases (1.4%) respiratory alkalosis. Creatine phosphokinase mainly increased in 12 cases (8.2%). Regarding ECG there were 78 cases (53.4%) with sinus tachycardia. There were 20 cases (13.7%) with prolonged QT interval Table 7.

This table shows: liver functions tests were increased in 24 cases (16.4%), renal functions tests were increased in 4 cases (2.7%). Hyperglycemia was detected in 10 cases (6.8%), myoglobin blood level increased in 4 cases (2.7%) and CPK blood level increased in 12 cases (8.2%) Table 8.

This table shows: the mean CLZ serum blood level was 889 (192–3177) ng/ml. The mean OLA serum blood level was 275 (11–1503) ng/ml. The mean RIS serum blood level was 54 (10–110) ng/ml. The mean ARP serum blood was 394 (170–1420) ng/ml. The

*Table 4. General examination of the studied cases (N = 146).*

| | *N* (Percentage) |
|---|---|
| Pulse rate (beat/minute) | |
| Mean ± S.D. | 117.2 ± 28.2 |
| Minimum-Maximum | 40–170 |
| Systolic blood pressure (mm Hg) | |
| Mean ± S.D. | 113.7 ± 29.3 |
| Minimum-Maximum | 80–160 |
| Diastolic blood pressure (mm Hg) | |
| Mean ± S.D. | 65 ± 19.4 |
| Minimum-Maximum | 30–110 |
| Respiratory rate (breaths/minute) | |
| Mean ± S.D. | 16.2 ± 6.2 |
| Minimum-Maximum | 7–34 |
| Temperature (°C) | |
| Mean ± S.D. | 36.6 ± 0.7 |
| Minimum-Maximum | 35–40 |
| Eye examination | |
| Normal | 128 (87.7%) |
| Upward deviated | 18 (12.3%) |
| Coma degree (GCS) | |
| >12 | 78 (53.4%) |
| 9–11 | 49 (33.6%) |
| <8 | 19 (13%) |
| Head and neck examination | |
| Normal | 134 (91.8%) |
| Neck deviation and rigidity | 12 (8.2%) |
| Difficulties in swallowing | |
| No | 116 (79.5%) |
| Yes | 30 (20.5%) |

*Table 5. Systemic manifestations of studied cases (N = 146).*

| | *N* (Percentage) |
|---|---|
| CNS examination | |
| Drowsy | 39 (26.7%) |
| Coma | 34 (23.3%) |
| Anxiety | 20 (13.7%) |
| Confusion | 16 (11%) |
| Generalized tonic clonic seizures | 16 (11%) |
| Agitation | 10 (6.8%) |
| Tremor | 6 (4.1%) |
| Lethargy | 4 (2.7%) |
| Dizziness | 1 (0.7%) |
| Urinary system examination | |
| Normal | 123 (84.2%) |
| Urinary retention | 19 (13%) |
| Urinary incontinence | 4 (2.7%) |

*Table 6. Laboratory finding and ECG changes in studied cases (N = 146).*

| | *N* (Percentage) |
|---|---|
| Urine drugs screen | |
| Negative | 137 (93.8%) |
| Hashish | 6 (4.1%) |
| Tramadol | 2 (1.4%) |
| Benzodiazepine | 1 (0.7%) |
| Metabolic changes | |
| Normal | 108 (74%) |
| Metabolic acidosis | 26 (17.8%) |
| Respiratory acidosis | 6 (4.1%) |
| Metabolic alkalosis | 4 (2.7%) |
| Respiratory alkalosis | 2 (1.4%) |
| ECG changes | |
| Sinus tachycardia | 78 (53.4%) |
| Normal | 66 (45.2%) |
| Sinus brdycardia | 2 (1.4%) |
| QT interval | |
| Normal | 126 (86.3%) |
| Prolonged | 20 (13.7%) |

*Table 7. Investigation of the studied cases (n = 146).*

| | |
|---|---|
| Alanine aminotransferase (U/L) | |
| Mean ± S.D. | 27.8 ± 14.4 |
| Minimum-Maximum | 15–120 |
| Aspartate aminotransferase (U/L) | |
| Mean ± S.D. | 45 ± 37.3 |
| Minimum-Maximum | 10–305 |
| Creatinine (mg/dl) | |
| Mean ± S.D. | 0.97 ± 0.210 |
| Minimum-Maximum | 1–2 |
| Blood Urea Nitrogen (mg/dl) | |
| Mean ± S.D. | 15.8 ± 11.9 |
| Minimum-Maximum | 10–110 |
| Myoglobin (ng/ml) | |
| Mean ± S.D. | 39.3 ± 23.01 |
| Minimum-Maximum | 20–200 |
| Hemoglobin (gm/dl) | |
| Mean ± S.D. | 12.05 ± 1.11 |
| Minimum-Maximum | 9–14 |
| White Blood Cells (/$mm^3$) | |
| Mean ± S.D. | 7674 ± 2440.7 |
| Minimum-Maximum | 4000–19436 |
| Random blood sugar (mg/dl) | |
| Mean ± S.D. | 177.6 ± 32.67 |
| Minimum-Maximum | 136–350 |
| CPK (U/l) | |
| Mean ± S.D. | 270.5 ± 1157.3 |
| Minimum-Maximum | 60–9899 |

mean HAL serum blood level was 50 (6–215) ng/ml. The mean QUE serum blood was 4290 (100–6520) ng/ml. The mean CPZ serum blood level was 625(570–680) Table 9.

This table shows: gastric lavage was done to 54 cases (37%) and MDAC were given to 114 cases (78.1%). Na $HCO_3$ prescriped to 142 cases (97.3%). Cold compresses and paracetamol IV were prescriped to 4 cases (2.7%). Diphenhydramine was prescriped to 50 cases (34.2%). Biperiden was prescriped to 18 cases (12.3%). Benztropine was used in 12 cases (8.2%). Diazepam was used in 20 cases (13.7%). Oral dantrolene by ryle tube was used in 4 cases (2.7%). Amantadine was used in 2 cases (1.4%). N-acetyl cysteine was prescriped to 4 cases (2.7%), oral contraceptive pills (OCP) were discontinued in 2 cases (1.4%) due to drug interaction, CLZ dose was increased due to smoking interaction in 2 cases (1.4%) and physostigmine was prescriped to 2 cases

*Table 8. Serum blood level of antipsychotic drugs in studied cases.*

| | Mean | Minimum-Maximum | Standard Deviation |
|---|---|---|---|
| Clozapine (N = 40) | 889 | 192–3177 | 757 |
| Olanzapine (N = 30) | 275 | 11–1503 | 355 |
| Risperidone (no = 22) | 54 | 10–110 | 37 |
| Aripiprazole (N = 22) | 394 | 170–1420 | 353 |
| Haloperidol (N = 14) | 50 | 6–215 | 72 |
| Quatiapine (N = 14) | 4290 | 100–6520 | 2217 |
| Chlorpromazine (N = 4) | 625 | 570–680 | 64 |
| Total (N = 146) | 800.9 | 6–6520 | 1427.69 |

*Table 9. Descriptive data of the studied cases according to treatment (N = 146).*

| | N (Percentage) |
|---|---|
| Gastric lavage | |
| No | 92 (63%) |
| Yes | 54 (37%) |
| MDAC | |
| Yes | 114 (78.1%) |
| No | 32 (21.9%) |
| Na $HCO_3$ | |
| Yes | 142 (97.3%) |
| No | 4 (2.7%) |
| Cold compresses | |
| No | 142 (97.3%) |
| Yes | 4 (2.7%) |
| Anti-pyretic | |
| No | 142 (97.3%) |
| Yes | 4 (2.7%) |
| Diphenhydramine | |
| No | 96 (65.8%) |
| Yes | 50 (34.2%) |
| Biperiden | |
| No | 128 (87.7%) |
| Yes | 18 (12.3%) |
| Benztropine | |
| No | 134 (91.8%) |
| Yes | 12 (8.2%) |
| Diazepam | |
| No | 126 (86.3%) |
| Yes | 20 (13.7%) |
| Dantrolene | |
| No | 142 (97.3%) |
| Yes | 4 (2.7%) |
| Other specific treatment | |
| No | 120 (86.3%) |
| Drug dose reduction | 6 (4.1%) |
| N-Acetyl Cysteine | 4 (2.7%) |
| OCPs discontinuation | 2 (1.4%) |
| Amantadine | 2 (1.4%) |
| Clozapine dosage increase | 2 (1.4%) |
| Physostigmine | 2 (1.4%) |
| Time staying (days) | |
| Mean ± S.D. | 2.6 ± 1.31 |
| Minimum-Maximum | 1–7 |

(1.4%). The mean time staying was 2.6 (1–7) days. Recovery outcome was in 144 cases (98.6%) and death in 2 cases (1.4%) Table 10.

There were statistically significant difference ($P$ value < 0.05) between age groups and gender as female cases were more common than male cases and statistically significant difference between age groups and residence as urban residence cases were more common than rural residence cases, statistically significant difference between age groups and marital status as single cases were more common than married, divorced and widow cases, significant relation between age groups and manner of poisoning as the most of cases (54.1%) were suicidal mode, statistically significant difference between

*Table 10. Comparison of studied groups according to residence, marital status, manner of poisoning, extra pyramidal symptoms, pupil finding, mechanical ventilation and outcome.*

| | Age groups. | | | | | Test of significance | *P* value |
|---|---|---|---|---|---|---|---|
| | 1 −10 Years *N* (%) | 11 −20 Years *N* (%) | 21 −30 Years *N* (%) | 31 −40 Years *N* (%) | >41 Years *N* (%) | | |
| Gender | | | | | | | |
| Male | 22 (55%) | 4 (12.9%) | 16 (30.2%) | 6 (60%) | 8 (66.7%) | $\chi^2$ 20.72 | 0.001 S |
| Female | 18 (45%) | 27 (87.1%) | 37 (69.8%) | 4 (40%) | 4 (33.3%) | | |
| Residence | | | | | | | |
| Urban | 22 (55%) | 27 (87.1%) | 30 (56.6%) | 7 (70%) | 8 (66.7%) | $\chi^2$ 10.07 | 0.039 S |
| Rural | 18 (45%) | 4 (12.9%) | 23 (43.3%) | 3 (30%) | 4 (33.3%) | | |
| Marital status | | | | | | | |
| Single | 40 (100%) | 31 (100%) | 30 (56.6%) | 0 (0.0%) | 0 (0.0%) | Fisher's Exact 103.25 | 0.001 S |
| Married | 0 (0.0%) | 0 (0.0%) | 21 (39.6%) | 8 (80%) | 6 (50%) | | |
| Divorced | 0 (0.0%) | 0 (0.0%) | 2 (3.8%) | 2 (20%) | 2 (16.7%) | | |
| Widow | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 4 (33.3%) | | |
| Manner of poisoning | | | | | | | |
| Accidental | 39 (97.5%) | 8 (25.8%) | 12 (22.6%) | 2 (20%) | 6 (50%) | Fisher's Exact 70.27 | 0.001 S |
| Suicidal | 1 (2.5%) | 23 (74.2%) | 41 (77.4%) | 8 (80%) | 6 (50%) | | |
| Mental illness | | | | | | | |
| Yes | 8 (20%) | 25 (80.6%) | 53 (100%) | 10 (100%) | 12 (100%) | $\chi^2$ 87.244 | 0.001 S |
| No | 32 (80%) | 6 (19.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | | |
| EPS | | | | | | | |
| Yes | 16 (40%) | 6 (19.4%) | 8 (15.1%) | 4 (40%) | 0 (0.0%) | $\chi^2$ 13.72 | 0.008 S |
| No | 24 (60%) | 25 (80.6%) | 45 (84.9%) | 6 (60%) | 12 (100%) | | |
| Pupils | | | | | | | |
| Constricted | 6 (15%) | 0 (0.0%) | 8 (15.1%) | 0 (0.0%) | 6 (50%) | $\chi^2$ 69.38 | 0.001 S |
| Dilated reactive | 0 (0.0%) | 11 (35.5%) | 21 (39.6%) | 2 (20%) | 4 (33.3%) | | |
| Miosis | 4 (10%) | 0 (0.0%) | 0 (0.0%) | 4 (40%) | 0 (0.0%) | | |
| Normal | 30 (75%) | 20 (64.5%) | 24 (45.3%) | 4 (40%) | 2 (16.7%) | | |
| Mechanical ventilation | | | | | | | |
| Yes | 4 (10%) | 11 (35.5%) | 11 (20.8%) | 2 (20%) | 4 (33.3%) | $\chi^2$ 7.631 | 0.102 NS |
| No | 36 (90%) | 20 (64.5%) | 42 (79.2%) | 8 (80%) | 8 (66.7%) | | |
| Outcome | | | | | | | |
| Recovery | 40 (100%) | 31 (100%) | 53 (100%) | 10 (100%) | 10 (83.3%) | $\chi^2$ 22.64 | 0.010 S |
| Death | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (16.7%) | | |

(S)=$P < 0.05$: Significant, (NS)=$P > 0.05$: Non significant and $\chi^2$ = Chi square test.

age groups and history of mental illness in studied cases as the most of cases were with history of mental disease and statistically significant difference between age groups and EPS as the young age were more affected and there were significant relation between age groups and pupil examination as the pupil was normal in most cases but, miosis was recorded in age group <10 years and age group 30–40 years also, dilated reactive pupil was recorded in age >10 years and statistically significant difference between age groups and outcome result as most cases (98.6%) were recovered but, cases who died were >40 years. There were no statistically significant difference (*P*-value >0.05) between age groups and mechanical ventilation.

## 4. Discussion

Childhood and adolescence <30 years of age represented the majority of cases (84.9%) which could be due to the rapid increase in the use of APs for children and adolescent in the last 20 years for treatment of sleep disorders, anxiety and mood disorders and this in agreement with Mubarak et al.[9] The age of cases suffering from QUE-NMS was 60 years and this is in accordance with Randolph,[10] who reported that the average age of cases presented by QUE-NMS was high. The higher female ratio (61.6%) could be due to females are psychologically more vulnerable to drug poisoning than males and this in agreement with Mubarak et al.[9] who reported that higher female ratio (65%). NMS was in male (100%) and this in accordance with Gurrera,[11] who reported that NMS occurred in male more commonly than female by a ratio of 2 to 1. The majority of the studied cases with both accidental and suicidal poisoning were from urban areas (64.4%) while (35.6%) were from rural areas and this also reported by Anthony and Kulkarni.[12] The majority of cases were students (42.5%) due to accidental poisoning or failure in love or educational challenge followed by housewives (20.5%) due to separation or psychological problems,

unemployed (15.1%) due to economic or psychological problems and this was in accordance with Milner et al.[13] who reported that the high rate of suicide among unemployed was due to their socioeconomic and psychological problems. Cases with history of mental illness were (74%), this may be due to presence of delusions and/or auditory hallucinations and this coincided with Hammad et al.[14] who reported that significant relation between severity of toxicity and patients who were on psychic diseases. The most common APs taken was CLZ (27.4%) and this coincided with Mubarak et al.[9] who reported that CLZ was the drug used in (35%) of cases. Cases presented by NMS were caused by HAL (typical antipsychotic drug) and QUE-AAPDs and this is in accordance with Murri et al.[15] who reported that NMS is caused mostly by typical APs, but reports of AAPDs causes NMS are well documented. In this study NMS is not a dose-dependent phenomenon. Rather, it is an idiosyncratic reaction to APs that may happen after a single normal dose and this was in agreement with Wijdicks,.[16] The mean delay time was 5.1 h which could be attributed to the site of Damietta Toxicology Unite in new Damietta with easy availability of transportation for it and this in agreement with Mubarak et al.[9] who declared that (75%) of cases admitted to the hospital within 5 h from intake. Symptoms of NMS delayed beyond 48 h and this was in accordance with Schneider et al.[17] who reported that symptoms of NMS usually start within 2 weeks of APs therapy. Cases with GCS <8 were (13%) and cases with GCS 9–11 were (33.6%) and this was in close with Hammad et al.[14] who reported that coma was severe and fatal grades in (100%) followed by (28%) of moderate severity grade. ECG changes presented by tachycardia were (53.4%) and QT interval prolongation in (13.7%) and this was in accordance with Hammad et al.[14] who reported that the frequency of ECG changes of studied cases were sinus tachycardia (20%) followed by wide QT interval prolongation. Cases with hypotension were (52.7%) and this may be due to antagonism of $\alpha_1$-receptors and this in accordance with Pepersack et al.[18] who demonstrated that hypotension is a common adverse effect with AAPDs. Cases presented with tachypnea were (16.4%) and this in agreement with Mubarak et al.[9] who reported that tachypnea was observed in (46.67%) of cases. There were (54.8%) of cases with normal pupil, (26%) with dilated reactive pupil and this in agreement with Fareha *et* al.[4] who reported that peripheral anti-cholinergic stigmata. (5.5%) of cases with miosis and this in accordance with Stahl,[19] who demonstrated that miosis was due to the $\alpha_1$-adrenergic receptor antagonism effect of APs. Cases presented by decreased level of consciousness were (41.1%), cases with somnolence repeatedly interrupted by spontaneous agitation (2.7%), cases with lethargy (1.4%) and cases with confusion (1.4%) this may be owing to the centrally mediated sedation and decreased cerebral perfusion secondary to systemic hypotension and anti-cholinergic action contributed to CNS depression caused by APs and also antagonism action on peripheral $\alpha_1$-adrenergic leads to decreased vasomotor tone and accounts for it and this in accordance with Kwiatkowsk,[20] who reported that the mental state changes were the most frequent manifestation in APs overdose, impaired consciousness is a frequent and dose-dependent feature of APs overdose, ranging from somnolence to coma and evident dizziness. There were 4 cases (2.7%) diagnosed as NMS presented with altered mental state and decreased level of consciousness and this was in accordance with Shah et al.[21] who reported that in >80% of patients altered mental status precede the beginning of signs of NMS. Seizures were present in (11%) and this in agreement with Hammad et al.[14] who reported that convulsions were found in severe cases. Extra pyramidal symptoms reported in (19.6%) manifested by up-rolling of the eye balls and blurring of vision or unilateral deviation of the neck and protrusion of tongue or difficulty breathing and talking due to ALD or protruded tongue and these sings occurred with either typical or AAPDs and occurred in normal doses or overdoses this was in accordance with Levine and Ruha,[22] whose stated that EPS can occur with either typical or AAPDs. There were (13%) of cases with urinary retention this may be due to anti-cholinergic stigmata side effect and this was in agreement with Fareha et al.[4] and (2.7%) with urinary incontinence and this was due to NMS and this in agreement with Ana et al.[23] who reported that the features of NMS were including; urinary incontinence. Liver enzymes were increased in (16.4%) this was may be due to co-ingested drugs and this was in agreement with Marwick et al.[24] who demonstrated that APs-induced hepatotoxicity is infrequent. Renal functions tests (RFTs) were increased in (2.7%) this was may be due to elder cases on APs were susceptible to decreased renal functions, thus having elevated intoxication risk and this is in agreement with Hammad et al.[14] who demonstrated that RFTs were increased in (10%) of cases. Normal ABGs were (74%) and this coincided with Mubarak et al.[9] who demonstrated that the majority of cases in his study had normal ABGs (66.7%). Creatine phosphokinase increased in 12 cases (8.2%) in severe poisoned and cases with NMS and this in agreement with Hammad et al.[14] who reported that increased CPK level in all cases of severe and lethal toxicity grades. There were no correlation between duration or dosage of APs

therapy and NMS and this is in agreement with Zou et al.[25] Gastric lavage was done to (37%) due to attendance to the hospital within 2 h or ingestion of multiple drugs and this was in agreement with Chan,[26] who demonstrated that gastric decontamination is frequently done within 2 h. MDAC were given to (78.1%) and this was in accordance with Hammad et al.[14] who reported that all cases received MDAC. Mechanical ventilation were needed in (21.9%) and this was due to severe hypoxia or CNS depression or metabolic disturbances or large overdoses of APs and this in close with Hoffman et al.[27] who stated that mechanical ventilation was necessary for cases with large overdoses of APs or ingestion of other CNS depressant drugs. Benzodiazepines were given to (13.7%) presented by seizures or agitation and this in accordance with Hammad et al.[14] who stated that benzodiazepines were used in (28.3%) of cases to management convulsions. Diphenhydramine was prescriped to (34.2%), biperiden to (12.3%) and benztropine to (8.2%) of cases with EPS and this in agreement with Slow et al.[28] who reported that anti-cholinergic, including diphenhydramine and benztropine remain the base of management of EPS because of their fast onset and resolution of distressing symptoms. Cold compresses and IV paracetamol were prescriped to (2.7%) as an anti-pyretic to manage fever in NMS. Oral dantrolene was prescriped to (2.7%) presented by NMS and this in accordance with Vivian et al.[29] who demonstrated that dantrolene is a peripheral muscle relaxant which inhibits calcium release from the sarcoplasmic reticulum and decreases the available calcium for ongoing muscle contraction. Amantadine was prescriped to (1.4%) complaining NMS and this in agreement with Leah et al.[30] who reported that it has been used as adjunctive treatment in NMS for moderate and severe cases. Clozapine daily dose were increase in (1.4%) due to interacting with smoking due to cigarette smoking induces cytochrome P450 CYP1A2 and CYP2B6 enzyme action and lead to decrease CLZ blood level and this in agreement with Bolu et al.[31] OCP were stopped taking with CLZ as it leaded to increase CLZ serum blood level and this was in agreement with Karjalainen et al.[32]

### 4.1. Conclusions

Predominance of age <30 years and adult young females, single and students cases were the most frequently affected. Majority of cases were had a history of mental illness. AAPDs were the most common used. Suicidal manner was the most common. Toxicity occurred with overdoses and with normal doses as an idiosyncratic reaction. Decreased level of consciousness was the most common clinical presentation followed by EPS and seizures. Age of NMS cases were >40 years with normal APs dose. There was no correlation between ingested APs doses and serum APs blood levels and symptoms.

## Conflicts of interest

All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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