

# Sex-based differences in the predisposing factors of overdose: A retrospective study

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**Abstract.** Drug overdose is one of the common events encountered in the emergency department (ED). The aim of the present study was to investigate the sex difference and predisposing factors of overdose in the ED. Data of 299 patients with self-poisoning reported at our poison center from January 2018 to August 2019 were retrospectively analyzed. Study cases categorized using the International Classification of Diseases, Tenth Revision coding system, which include codes T36 to T50, were selected. Data were collected including Glasgow Coma Scale scores and vital signs upon arrival (including body temperature, heart rate, systolic blood pressure, and diastolic blood pressure, sex, age, marital status, arrival time, season on admission, previous suicide attempts, psychiatric history, related comorbidities, recent arguments, categories of overdose with or without concurrent ethanol use, length of hospital stay, and survival to discharge) were analyzed. The top three types of substances that were frequently involved in drug overdose were benzodiazepine (42.9%), mixed medications (32.1%), and acetaminophen (6.1%). The 196 enrolled patients were aged 14 to 92 years (mean  $\pm$  standard deviation, 39.2 $\pm$ 18.3), and of these patients, male intentional overdose patients were 8.1 years older than their female counterparts (45.3 $\pm$ 19.5 vs. 37.2 $\pm$ 17.5, respectively;  $P < 0.05$ ). Most intentional overdose cases occurred during the spring season ( $n = 63$ , 32.1%), especially in male patients ( $n = 28$ , 57.1%;  $P < 0.001$ ). Approximately 11.2% (22/196) and 2% (4/196) of the total patients were admitted to the Toxicology ward and intensive care units, respectively. The length of hospital stay was 2 $\pm$ 4.1 days. In summary, it is suggested that physicians notify the suicide prevention centers to be on alert for middle-aged men who are facing conflicts, especially during the spring season.

## Introduction

Drug overdose is one of the common events encountered in the emergency department (ED). In 2018, 67,367 drug overdose-related deaths were reported in the United States, and the age-adjusted rate of drug overdose deaths was 20.7 per 100,000 population according to the data from the United States Centre for Disease Control and Prevention. The rates were higher in men than in women. In 2018, the age-adjusted rate of drug overdose deaths was 27.9 in men, while that in women was 13.6 (1).

The incidence of overdose in Taiwan is 0.16-0.22 per 1,000 population according to the Taiwan National Poison Centre (2). In addition, the mortality rate associated with poisoning is relatively high, which ranks fourth among unintentional injuries, of which the top three causes are automobile injuries, unintentional falls, and drowning (3). Even though drug overdose-related deaths have garnered considerable public attention, the complications of nonfatal overdose including cognitive impairment, cardiac and muscular problems, renal failure, hearing loss, and other injuries should also be taken into consideration (4,5). The average hospital cost of overdosed patients who were treated and admitted is also notably high (6).

Qin *et al* reported that although several studies have sought to interpret the sex gap in suicidal behavior, where unemployment, retirement, being single, and interpersonal conflicts were all significant risk factors for suicide in men, no significant risk factors other than mental illness were reported in women (7,8). However, having a child aged  $< 2$  years was a significant protective factor against suicide in women (8).

Therefore, the predisposing factors for drug overdose should be recognized. In addition, the sex difference and predisposing factors of overdose occurring in the ED should be investigated.

## Materials and methods

**Patients and drugs.** Data of patients with self-poisoning admitted to the ED from January 2018 to August 2019 were retrospectively analyzed. This project was approved by the Ethics Committee of Mackay Memorial Hospital (Taipei, Taiwan), while the study was approved (approval no. 19MMHIS288e) by the Institutional

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Review Board of Mackay Memorial Hospital. The study cases were selected using the following International Statistical Classification of Diseases and Related Health Problems, 10th Revision, (ICD-10) coding system (9): poisoning by, adverse effect of and underdosing of systemic antibiotics (T36); other systemic anti-infectives and antiparasitics (T37); hormones and their synthetic substitutes and antagonists (T38); nonopioid analgesics, antipyretics, and antirheumatics (T39); narcotics and psychodysleptics (hallucinogens) (T40); anesthetics and therapeutic gases (T41), antiepileptic, sedative-hypnotics, and antiparkinsonism drugs (T42); psychotropic drugs (T43); drugs primarily affecting the autonomic nervous system (T44); primarily systemic and hematological agents (T45); agents primarily affecting the cardiovascular system (T46); agents primarily affecting the gastrointestinal system (T47); agents primarily acting on the smooth and skeletal muscles and the respiratory system (T48); topical agents primarily affecting the skin and mucous membrane and ophthalmological, otorhinolaryngological, and dental drugs (T49); and diuretics and other and unspecified drugs, medicaments, and biological substances (T50).

Data of 299 patients with self-poisoning were collected from January 2018 to August 2019. A total of 196 intentional overdose patients were enrolled, while 103 patients were excluded (Fig. 1). The exclusion criteria were as follows: Patients who had unintentional overdose, experienced mis-swallowing, developed an accidental adverse drug reaction (ADR), were discharged from the ED without complete treatment, and with incomplete data (Fig. 1). The following data were collected and analyzed: Glasgow Coma Scale (GCS) scores and vital signs upon arrival (including body temperature, heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP), sex, age, marital status, arrival time, season on admission, previous suicide attempts, psychiatric history, related comorbidities, recent arguments, categories of overdose with or without concurrent ethanol use, length of hospital stay, and survival to discharge.

**Statistical analysis.** A statistical software (IBM SPSS Statistics for Windows, version 20.0; IBM Corp.) was used to perform all data analyses. Both unpaired Student's *t*-test and chi-square test were used in the statistical analyses, and a *P*-value of <0.05 was considered to indicate a statistically significant difference.

## Results

The 196 enrolled patients were aged 14-92 years [mean  $\pm$  standard deviation (SD)]: 39.2 $\pm$ 18.3), and the male to female ratio was 1:3 (men, *n*=49; women, *n*=147). The data revealed that male intentional overdose patients were 8.1 years older than their female counterparts (45.3 $\pm$ 19.5 vs. 37.2 $\pm$ 17.5, respectively; *P*=0.009) (Fig. 2 and Table I). In comparison with female patients, 6.1% (3/49) of the male patients tended to have premeditated drug overdose after arguing with a girlfriend, which had a significant difference (*P*<0.05). Moreover, more than half of the overdose patients were single (*n*=117, 59.2%; Table I), which was considered as one of the risk factors of overdose.

Most intentional overdose cases occurred during the spring season (*n*=63, 32.1%), especially in male patients (*n*=28, 57.1%; *P*<0.001). The majority of patients (*n*=78, 39.8%) were sent to our ED in the evening (from 15:00 to 23:00 p.m.). In 31.6% (62/196) of

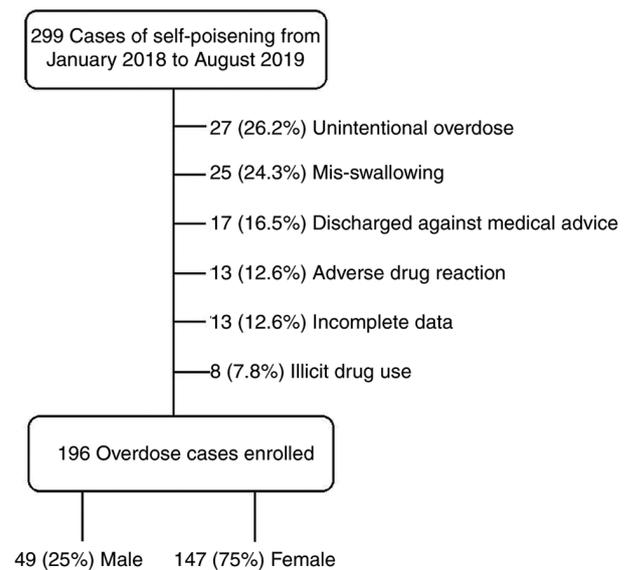


Figure 1. Enrolment of 196 overdose cases along with exclusion criteria.

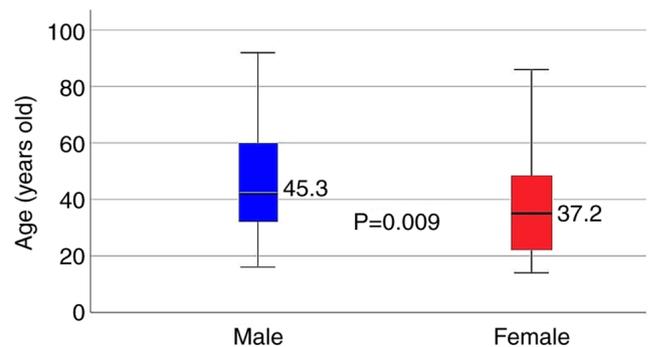


Figure 2. Comparison of the mean age of drug overdose between male and female patients. The mean age of drug overdose of male patients was 8.1 years older than that of female patients using an unpaired *t*-test (*P*=0.009).

overdose patients, an argument with a family member motivated them to commit a premeditated drug suicide attempt (Table I).

Benzodiazepines (*n*=96, 49%; *P*=0.004) were the most common drugs used in intentional overdose. In addition, approximately 8.2% of female patients (12/147) committed self-poisoning using acetaminophen (Table II). A great number of intentional overdose patients had a history of depression (*n*=96, 49%) and insomnia problems (*n*=79, 40.3%) (Table I). Only 27.6% of the patients (54/196) reported concurrent use of alcohol (Table I).

Body temperature (in °C) was slightly higher in female patients than in male patients (mean  $\pm$  SD, 36.7 $\pm$ 0.6 vs. 36.5 $\pm$ 0.5, respectively; *P*=0.026). Our study also revealed significantly higher levels of systolic and diastolic blood pressure in male patients compared with female patients. No significant differences were found in the marital status, comorbidities, and concurrent psychiatric diseases between the two sex groups (Table I).

Approximately 11.2% (22/196) and 2% (4/196) of total patients were admitted to the Toxicology ward and intensive care units, respectively (Table I). The length of hospital stay was 2 $\pm$ 4.1 days, and none of the patients in our study succumbed to intentional drug overdose.

Table I. Differences between male and females patients in 196 cases of intentional overdose from January 2018 to August 2019.

Intentional overdose	All	Male	Female	P-value (two-tailed)
n (%)	196 (100)	49 (25)	147 (75)	
Age (years old)	39.2±18.3	45.3±19.5	37.2±17.5	0.009 <sup>a</sup>
Times of overdose	1.2±0.7	1.1±0.3	1.2±0.8	0.339
Seasons (n, %)				<0.001 <sup>a</sup>
Spring	63 (32.1)	28 (57.1)	35 (23.8)	
Summer	43 (21.9)	5 (10.2)	38 (25.9)	
Autumn	45 (23.0)	6 (12.2)	39 (26.5)	
Winter	45 (32.0)	10 (20.5)	35 (23.8)	
Arrival time				0.127
Day	55 (28.1)	16 (32.7)	39 (26.5)	
Evening	78 (39.8)	23 (46.9)	55 (37.4)	
Night	63 (32.1)	10 (20.4)	53 (36.5)	
History of prior overdose	63 (32.1)	13 (26.5)	50 (34)	0.331
Marriage status				
Single	117 (59.2)	27 (55.1)	90 (61.2)	0.507
Marriage	60 (30.6)	19 (38.8)	41 (27.9)	0.157
Divorced	19 (9.7)	3 (6.1)	16 (10.9)	0.329
Alcohol-drinking	54 (27.6)	19 (38.8)	35 (23.8)	0.113
Body temperature (°C)	36.6±0.6	36.5±0.5	36.7±0.6	0.026 <sup>a</sup>
Heart rate (beats per min)	88.9±19.9	89.1±16.9	88.9±20.9	0.583
Systolic blood pressure (mmHg)	116.9±21.2	123.1±20.1	114.9±21.3	0.014 <sup>a</sup>
Diastolic blood pressure (mmHg)	68.7±14.4	75.1±15.6	66.6±13.4	0.001 <sup>a</sup>
Glasgow Coma Scale	12.9±3.6	13.1±3.4	12.8±3.7	0.676
Hypertension	21 (10.7)	6 (12.2)	15 (10.2)	0.689
Diabetes mellitus	14 (7.1)	5 (10.2)	9 (6.1)	0.337
Uremia	3 (1.5)	1 (2)	2 (1.4)	0.737
Depression	96 (50)	23 (46.9)	73 (49.7)	0.741
Personality disorder	75 (38.3)	23 (46.9)	52 (35.4)	0.149
Bipolar affective disorder	25 (12.8)	4 (8.2)	21 (14.3)	0.266
Schizophrenia	10 (5.1)	1 (2)	9 (6.1)	0.261
Argument with family members	62 (31.6)	17 (34.7)	45 (30.6)	0.595
Argument with father	10 (5.1)	4 (8.2)	6 (4.1)	0.261
Argument with mother	13 (6.6)	1 (2.0)	12 (8.2)	0.136
Argument with friends	43 (21.9)	8 (16.3)	35 (23.8)	0.273
Argument with boyfriend	4 (2.0)	0 (0)	4 (2.7)	0.243
Argument with girlfriend	3 (1.5)	3 (6.1)	0 (0)	0.003 <sup>a</sup>
Conflict with co-workers	10 (5.1)	4 (8.2)	6 (4.1)	0.454
Suffering from insomnia	79 (40.3)	20 (40.8)	59 (40.1)	0.933
Hospitalization in the Toxicology ward	22 (11.2)	4 (8.2)	18 (12.2)	0.433
Intensive care unit admission	4 (2)	1 (2)	3 (2)	1.000
Length of stay (days)	2.0±4.1	2.1±4.2	2.0±4.1	0.183

<sup>a</sup>Indicates a statistically significant difference (P<0.05).

## Discussion

Comparison in the rate of drug overdose between men and women during the spring season. One of our interesting results indicated that intentional drug overdose mostly occurred during the spring season. Numerous studies also revealed that

suicide rates peaked during the spring season (10). The sudden increase in the duration and amount of sunlight is a conceivable reason for these phenomena. Hakko *et al* reported a 9% increase in the suicide rates in spring and an 8% increase in fall within the non-violent (i.e., ingestion of poisons, drugs, gases, or vapors) subgroup (11). This finding is compatible with the

Table II. Substances involved in intentional overdose.

Substance of overdose n, (%)	N=196, (100%)	Males, n=49 (25%)	Females, n=147 (75%)
Benzodiazepines <sup>a</sup>	62 (31.6)	20 (41.0)	42 (28.5)
Flunitrazepam	10 (5.1)	3 (6.2)	7 (4.7)
Estazolam	7 (3.6)	2 (4)	5 (3.4)
Alprazolam	4 (2.1)	1 (2)	3 (2)
Lorazepam	3 (1.6)	2 (4)	1 (0.7)
Bromazepam	1 (0.5)	0 (0)	1 (0.7)
Clonazepam	1 (0.5)	1 (2)	0 (0)
Mixed medications	63 (32.1)	9 (18.8)	54 (36.6)
Acetaminophen	12 (6.1)	0 (0)	12 (8.2)
Non-benzodiazepine hypnotics	6 (3.1)	2 (4)	4 (2.7)
Zolpidem	5 (2.6)	0 (0)	5 (3.4)
Stilnox	4 (2.1)	2 (4)	2 (1.4)
Anti-depressants	2 (1)	0 (0)	2 (1.4)
Diphenhydramine	2 (1)	0 (0)	2 (1.4)
Amphetamine	2 (1)	2 (4)	0 (0)
Baclofen	1 (0.5)	0 (0)	1 (0.7)
Bromadiolone	1 (0.5)	0 (0)	1 (0.7)
Bupropion	1 (0.5)	0 (0)	1 (0.7)
Gasoline	1 (0.5)	1 (2)	0 (0)
Humalog Mix (Insulin)	1 (0.5)	1 (2)	0 (0)
Iron	1 (0.5)	1 (2)	0 (0)
Ketamine	1 (0.5)	0 (0)	1 (0.7)
Norvasc	1 (0.5)	0 (0)	1 (0.7)
Quetiapine (anti-psychotics)	1 (0.5)	1 (2)	0 (0)
Sertraline	1 (0.5)	0 (0)	1 (0.7)
Valsartan	1 (0.5)	0 (0)	1 (0.7)
Zolpiclone	1 (0.5)	1 (2)	0 (0)
Total	196	49	147

<sup>a</sup>P=0.004, obtained using Chi-squared test in substance overdose analysis between benzodiazepine use and other substances.

present data; notably, the overdose rate increased during the spring season, in both sex groups (32.1%) and particularly in men (57.1%) with statistical significance. A study conducted in Iran revealed that seasonal peaks and troughs were also observed in medication use and self-poisoning rates during spring and winter (12). In the present study, 57.1% of male patients tended to commit suicide by drug overdose during the spring season. Rocchi *et al* indicated that suicide cases had a seasonal peak distribution in both men and women during the spring season (13). A study conducted in Greece revealed that suicide attempts in men increased during spring and summer and significantly decreased in September (14). A previous study reported that the rates of suicide attempts among men only peaked during spring, while cases in women peaked during spring and fall (15). A study by Mann reported that seasonal variance in suicide rates depends on an underlying seasonal biological variance, which affects the control of impulses. Such variance was mostly related to the serotonergic (5-HT) circuits since the brain levels of serotonin are sensitive to climate change; a clear seasonal rhythm is evident in serotonergic functions. Abnormalities in the number of serotonergic

neurons, serotonin transportation, receptor binding, and serotonin levels in key brain areas have all been linked to suicide (16). Functional imaging studies have demonstrated decreased serotonin transporter binding in patients who attempted suicide (17). Thus, low levels of serotonin are often associated with impulsive and aggressive behavior.

*Sex difference in overdose by physiology.* The body temperatures of self-poisoned women were slightly higher (0.2°C) than those of male patients. Several factors cause variations in body temperature including sex-based variation, thus indicating that women have a higher body temperature than men (18). Body temperature is also sensitive to changes in hormone levels, and women exhibit elevation in body temperature of ~0.9° Fahrenheit (F) during ovulation (19). By contrast, the blood pressure of overdosed male patients was higher than that of female patients. A previous study reported that the blood pressure, measured through 24-h ambulatory blood pressure monitoring, is higher in men than in women at similar ages (20). Increased body temperature and blood pressure mostly related to overdose from stimulants (i.e., cocaine,

amphetamine, and methamphetamine). In our study, most patients were intentionally overdosed with benzodiazepines, which would not significantly increase the body temperature and blood pressure. Therefore, the elevated body temperature in women and blood pressure in men might be a physiological effect rather than a manifestation of a drug overdose.

*Age distribution between drug overdose male and female patients.* Notably, in the present study, women had a three-fold increased risk for premeditated drug overdose than men. Veisani *et al* indicated that the majority of non-violent suicide victims were women (21). Another study showed that poisoning was the most common non-violent suicidal method of women (22). In addition, the WHO/EURO Multicenter study on parasuicides indicated that the seasonal pattern of suicide attempts in women showed a peak in spring and nadir in winter (23). However, no significant difference was noted in the incidence of self-poisoning among the four seasons. In the present study, older male patients had a greater tendency to self-poison compared with older women ( $P \leq 0.009$ , for the pooled sample and men and women) despite the increased risk of intentional overdose among women. A study in Taiwan revealed that the mean age of suicidal victims was 49.4 ( $\pm 18.3$ ) years, and more than half of non-violent (54.9%) suicidal victims were aged between 35 to 64 years (24). In the present study, the mean age of male overdose patients was 8.1 years older than that of female overdose patients with statistical significance.

*Comparison of the drug overdose rate between men and women facing conflicts.* Male patients had an obvious tendency to have premeditated drug overdose after arguing with their girlfriends. Although relationship breakdown is a known risk factor for suicide, men and women may not be equally susceptible (25,26). In a previous study by Kposowa, it was reported that divorced men had an 8-fold increased risk of committing suicide than divorced women (27). A study in Korea indicated that interpersonal conflict is the most common precipitating factor for committing suicide in adolescents, whereas family conflict is one of main risk factors in older people (28). People with unsettled conflicts have a higher level of suicidal ideation, hopelessness, and depression than those who could deal with their partner harmoniously (29). Furthermore, men have been taught to live independent lives and act decisively without approaching others in time of need (30). The expression of suicidal ideation in men may be deemed as a sign of weakness. Thus, men are particularly vulnerable and avoid seeking help as an impact of hegemonic masculinity (31), whereas women are more likely to seek help (32). A study by Pollack in 2006, implied that boys are imbued with hiding their emotions between the ages of 3 and 5 years by enforcing a 'boy code', which rewards toughness and enforces prohibition against emotional expression or vulnerability (33). Although depression is a well-known risk factor for suicide (34), men do not realize this when they are depressed because men are expected to be in control at all times of their emotions and actions (35). This explains in part how the dynamics of male suicide continue to be underestimated and poorly understood.

Overdose is commonly observed in daily emergency practice. To prevent patients from engaging in intentional

overdose, determining the epidemiology and predisposing factors is of utmost importance. The top three types of substances commonly ingested in overdose amounts are benzodiazepine (42.9%), mixed medications (32.1%), and acetaminophen (6.1%). In the present study, 11.2% of overdosed patients required hospitalization, while 2% were admitted to the intensive care unit. The length of stay was  $2 \pm 4.1$  days.

Male drug overdose patients were 8.1 years older than female patients, and drug overdose was 2.4-fold higher in men than in women during the spring season. Men had a 2.3-fold increased risk of drug overdose while facing conflicts than women. Hence, physicians should notify the suicide prevention centers to be on alert for middle-aged men, facing conflicts, especially during the spring season.

At present, drug overdose is a frequent occurrence in clinical practice. Investigations, such as the present study, with the potential to reduce the risk of death due to a drug overdose, are invaluable.

In addition, although various factors can influence the drug overdose rate, the tendency to engage in such act varies. In addition, men and women may overdose on drugs depending on the factors such as age and season; hence, in the future, continuous and strengthened follow-up investigations are expected to be undertaken from the authors of the present study.

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#### **Availability of data and materials**

The datasets used during the present study are available from the corresponding author upon reasonable request.

#### **Authors' contributions**

STT collected the data, wrote the draft, and discussed the manuscript. CHLo and CHLi collected the data and wrote the draft. YJS designed the study, collected the data, performed the statistical analyses, and discussed the manuscript. All authors confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript to be published.

#### **Ethics approval and consent to participate**

The present study was approved (approval no. 19MMHIS288e) by the Institutional Review Board of Mackay Memorial Hospital (Taipei, Taiwan).

#### **Patient consent for publication**

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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