American Journal of Emergency Medicine 38 (2020) 333–338

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Sex differences in patients with suicidal intent that are managed by toxicologists
An analysis of the Toxicology Investigators' Consortium (ToxIC) Registry

Gillian A. Beauchamp [a,b], Jacob Fishbein [a], Gregory A. Makar [a], Rita M. Pechulis [c], Matthew D. Cook [a,b], Robert D. Cannon [a,b], Kenneth D. Katz [a,b], Hope Kincaid [d], Jennifer L. Carey [e], Marna Rayl Greenberg [a,*], On behalf of Toxicology Investigators' Consortium (ToxIC)

[a] Lehigh Valley Health Network, Department of Emergency and Hospital Medicine/USF Morsani College of Medicine, Cedar Crest Boulevard & I-78, Allentown, PA 18103, USA
[b] Lehigh Valley Health Network, Department of Emergency and Hospital Medicine, Section of Medical Toxicology/USF Morsani College of Medicine, Cedar Crest Boulevard & I-78, Allentown, PA 18103, USA
[c] Lehigh Valley Health Network, Department of Medicine, Division of Critical Care Medicine/USF Morsani College of Medicine, Cedar Crest Boulevard & I-78, Allentown, PA 18103, USA
[d] Lehigh Valley Health Network, Network Office of Research and Innovation/USF Morsani College of Medicine, Cedar Crest Boulevard & I-78, Allentown, PA 18103, USA
[e] University of Massachusetts Medical School, Department of Emergency Medicine, Division of Medical Toxicology, 55 Lake Avenue North, Worcester, MA 01655, USA

ARTICLE INFO

Article history:
Received 26 August 2019
Accepted 14 September 2019

Keywords:
ToxIC
Sex
Suicide

ABSTRACT

Introduction: The Toxicology Investigator's Consortium (ToxIC) maintains a prospective case registry of all patients that have been managed at the bedside by medical toxicologists. We set out to characterize the differences in toxicological suicide attempts between men and women among adult patients with poisonings managed by medical toxicologists.

Methods: ToxIC database consults for adults aged 19–65 whose primary reasons for encounter were classified as suicide attempt were used for this study (1/2010–12/2016). Data used for analysis included primary agents of toxic exposure, routes of administration, and complications. The statistical analysis was limited to descriptive methods.

Results: Out of 51,440 registry cases, 33,259 cases remained for analysis after applying the ages 19–65 and removing those without complete data. Of these, there were 4827 suicide attempts (14.5% of toxicological exposures) which were sub classified by gender.

There were more females (F) than males (M) whose toxicology consults were due to suicidal attempts (57.6% versus 42.4%). We also found that more males used alcohol as their primary agent (2.8%M v 1.5%F) or a nonpharmaceutical (%7.4 M v %2.3 F).

Conclusions: In our study, we found that there were more females than males who attempted suicide by self-poisoning; and more of them used pharmaceuticals than males. In contrast, a greater number of males used nonpharmaceuticals such as alcohol. We did not find large sex-differences in suicide completion rates, routes of administration, or subsequent symptomologies. In summary, sex-based differences were observed between adult patients with suicidal-intent exposures/ingestions managed at the bedside by medical toxicologists.

1. Introduction

One of the commonly repeated statistics about suicide is that females attempt suicide more frequently than males, but that males complete it more frequently [1–3]. Part of the explanation for this phenomenon is that women tend to use less lethal methods of suicide attempts, such as toxic ingestion, while men who complete suicides tend to have used firearms [1,2,4].

Many patients die each year from accidental or intentional medication or drug overdoses, and many more go to the emergency department (ED) for accidental or intentional overdoses [5,6]. There are a growing number of Americans who acknowledge the impact of these suicide attempts since the opioid crisis has resulted in deaths and destruction of lives [7]. It is imperative that the scientific community gather data to help inform

* Corresponding author at: 1909 Earls Court, Allentown, PA 18103, USA.
E-mail address: mrgdo@ptd.net (M.R. Greenberg).

https://doi.org/10.1016/j.ajem.2019.158450
0735-6757/

providers regarding the management of at-risk populations, helping those who have suffered from overdoses to recover from underlying risk factors such as substance use disorder or mental illness, and/or negative physical and psychosocial health consequences.

While acute management is a large part of the management of an intentional overdose, many patients have a history of harmful use of medications or other substances, and underlying life stressors that led to substance use and suicidality [8,9]. Psychosocial stressors may differ markedly between the sexes due to different perspectives, identities, and the structural inequalities/differences built into the societal framework that affect their different tendencies toward different potential toxic exposures [10]. These sex differences may be amplified during the adult years—as the differing roles and social expectations imposed on men and women are observed [11–13].

Moreover, it is reasonable to expect sex differences in these toxicological incidences when directly comparing males with females because, as previous studies have shown, men and women process drugs differently [14]. They have different metabolic enzyme and transport protein concentrations, different volumes of distribution, and different excretion capabilities for different drugs [15,16]. Beyond purely biochemical differences, men and women have different psychological factors governing their intake and exposure to potential poisons [17–19]. They also tolerate different forms/levels of risks [20,21]. These abovementioned differences may make for substantially different longitudinal profiles in the clinical timeline between the sexes.

We sought to taxonomize the causes, treatments and outcomes of the toxicology consults for suicide attempts reported in the ToxIC registry; and to additionally elucidate clinically meaningful sex differences.

2. Methods

After the hospital's IRB reviewed the study and waived oversight due to the nature of the study, the data in this study was gathered through the ToxIC (Toxicology Investigator's Consortium) registry, containing information from toxicology consults reported by toxicologists. The data was supplied after an online request from the Toxic consortium. The data source had content including but not limited to patient demographic and background information; past medical history; the source, nature, and reason of the encounter; ADR (Adverse Drug Reaction) information when applicable; clinical presentation including symptoms and lab results; treatment(s) administered; and other information the attending toxicologist deemed pertinent. The Toxic Datasheet can be found in Appendix A.

All consultations between January 2010 and December 2016 for patients in the age range of 19–65 years of age in ToxIC were included in this study—and missing or incomplete information was cause for exclusion from analysis. Data was reported exclusively as frequencies assessed from the database. Frequencies of suicide attempts, (with "at least some intent to die," as defined on the ToxIC encounter form), were reported as numbers of male versus female patients who had attempted suicide, as well as the proportion of overall toxicological exposures comprised by suicide attempts for each sex. Analysis included category assignment of "non-pharmaceutical" such as alcohol or street drugs and "pharmaceutical" such as prescription medications. Furthermore, among the suicide attempts, the proportions of different drugs and how these proportions varied between the sexes were observed. The statistical analysis was limited to descriptive methods only, due to the elective nature, by participating physicians and facilities, of data entry in the database

3. Results

After exclusion for missing data or incomplete information (Fig. 1 Flow Diagram), there were 33,259 cases between the ages of 19 and 65 years old with data available regarding the reason for the toxicology consult, and 4827 (14.5%) of them were classified as suicide attempts. Of the 4827 suicide attempts, 2782 were females (57.6%), and 2045 were males (42.4%). The demographics for the total number of suicide attempts of patients aged 19–65 overall and classified by sex can be found in Table 1.

The breakdown of suicide attempts overall and by sex and defined by pharmaceutical vs nonpharmaceutical, single vs multiple exposure, type of exposure, drug class of primary agent of toxicity and route of administration can be found in Table 2. Males had a much greater frequency of nonpharmaceutical suicide attempts than females (7.4% vs. 2.3%).

A breakdown of suicide by symptomologies, completion, and lifesaving measures taken can be found in Table 3. Among deaths, whether life support was withdrawn is also included.

4. Discussion

In our study, males had a greater frequency of nonpharmaceutical suicide attempts. However, both sexes had high percentages

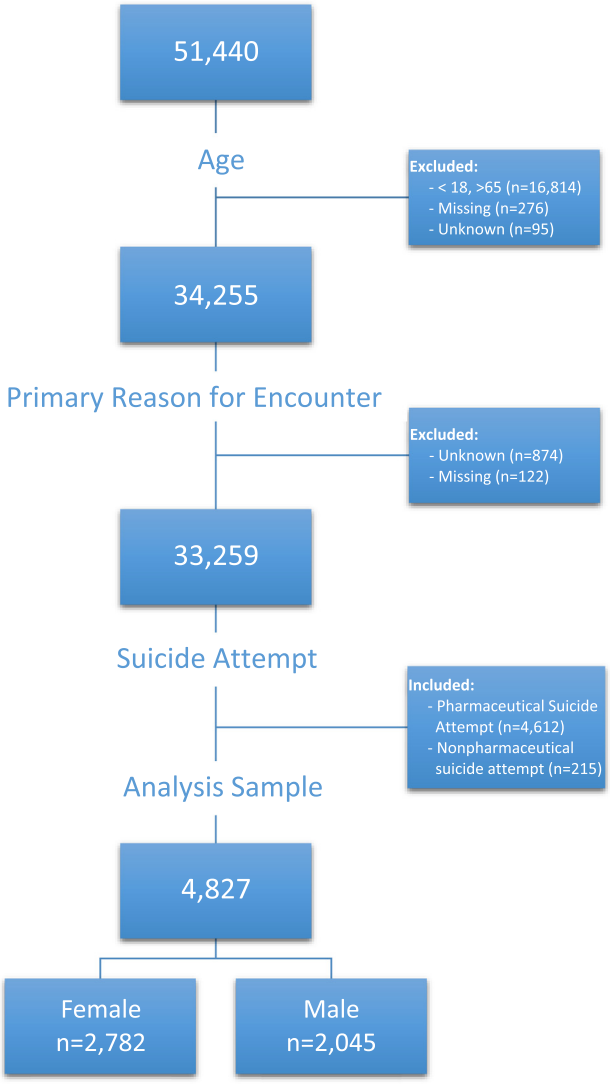

Fig. 1. Flow diagram.

Table 1
Demographics.*

Variable	Total N	Entire Sample (N = 4827)	Female (N = 2782)	Male (N = 2045)
Pregnancy Status	2782			
Pregnant			40 (1.4)	–
Not Pregnant			2742 (98.6)	–
Race	4178			
American Indian/Alaska Native		41 (1.0)	16 (0.7)	25 (1.4)
Asian		93 (2.2)	65 (2.7)	28 (1.6)
Australian Aboriginal		0	0	0
Black/African		500 (12.0)	273 (11.3)	227 (12.8)
Caucasian		2385 (57.1)	1387 (57.6)	998 (56.3)
Native Hawaiian or Pacific Islander		9 (0.2)	6 (0.2)	3 (0.2)
Mixed		24 (0.6)	15 (0.6)	9 (0.5)
Other		155 (3.7)	78 (3.2)	77 (4.3)
Unknown/Uncertain		970 (23.2)	565 (23.5)	405 (22.9)
Multiple Races		1 (0.02)	1 (0.04)	0
Hispanic/Latino	4178			
Yes		356 (8.5)	196 (8.1)	160 (9.0)
No		2820 (67.5)	1636 (68.0)	1184 (66.8)
Unknown		1002 (24.0)	574 (23.9)	428 (24.2)

* *Note:* Total N is not 4827 for some categories as some of the responses were unknown or not applicable, and percentages in these categories were calculated based on included N.

of pharmaceuticals being used for toxicological suicide attempts (97.7% of toxicological suicide attempts in females and 92.6% in males). This finding reinforces that physicians should consider the mental health status of their patient before prescribing pharmaceuticals that could be used for this purpose. In particular our findings suggest that interventions such as prescribing smaller quantities of analgesics, sedative-hypnotics/muscle relaxants, and antidepressants may have advantage for at risk females.

Not unexpectedly, females made up a majority of the suicide attempts reported in ToxIC. In context, US Census Bureau Data from 2010 was used to estimate the make-up of the population between 20 and 64 years was 49.6% male and 50.4% female [22]. Among 19–65-year-olds included in this study, females made up 57.6%, and males just 42.4%, of the cases whose toxic exposures were classified as suicide attempts. As compared to census rates, females were found to be disproportionately represented, which is in line with previous research regarding females' greater predilection towards poisoning suicide attempts, and towards attempting suicide overall [1,2].

The similarity in completion rates of toxicological suicide attempts between the sexes (1.4% in females and 1.3% in males) may appear to contradict the established literature saying that men complete suicides more often than women despite women attempting more frequently [1,2].Our findings are limited by the fact that the database only reports on toxicological related attempts that are evaluated by a toxicologist (e.g. does not include pre-hospital deaths or those who attempted and didn't go to the hospital for care). Recognizing that the group this study examines only comprises a subset of all suicide attempts; and in large measure it may be the difference in method choices that is responsible for the different rates of completion overall.

The result that males are more likely to attempt suicide using alcohol as the primary agent of toxicity (2.8% in males vs. 1.5% in females) is consistent with previous research findings that alcohol consumption and alcoholism rates are significantly higher in adult males than in adult females [23–26]. Nonetheless, the greater rates of suicide attempts using nonpharmaceuticals such as alcohol in men may be more of a product of availability than susceptibility [19], as it has been previously observed—in research regarding the differences in substance use disorders overall between men women—that despite men having a significantly greater likelihood of having or developing a substance use disorder (two to three times more likely), women show greater escalation rates in drug use once having become dependent [19,26,27].

We found that females were more likely to use pharmaceuticals to attempt suicide than males. Only a small minority of females who used self-intoxication to attempt suicide used a nonpharmaceutical. It would be informative for efforts in suicide prevention strategies to learn more about why this is. Since the data gathered in the ToxIC database is geared towards gathering information about consults in general, rather than specifically about suicide attempts, we did not obtain more in-depth survey-style information from suicide attempt victims about their motives and histories of mental illness/suicidality. This would be an interesting topic to explore further in assessing how to better target efforts against the root causes of self-poisonings and suicide attempts. Because that is all that was available from the database, the data during the time period studied captured only dichotomous (male/female) outcomes. Future research evaluating these parameters for suicide in patients that are not in the dichotomous spectrum (e.g. transgender) is indicated.

Future research could include further delineation of the sex differences in withdrawal of life support among completed toxicological suicides (58.3% in females and 40.0% in males)—to determine if this was a result of Do Not Resuscitate (DNR) orders, family or physician/institutional decisions, clinical manifestations due to physiologic differences, severity of illness or poor prognosis for functional recovery, social norms or expectations, or a statistical artifact of our small sample size in this subgroup due to the relative rarity of completed suicide attempts in the database.

5. Limitations

Cases included in the ToxIC database were not necessarily comprehensive of all the toxicological consults at all the facilities participating with the registry, as completion of the data forms was elective on the basis of time constraints pertaining to particular physicians and healthcare teams working on the cases. As such, some higher order and potentially meaningful statistical analyses were excluded from consideration for our results.

Many cases were also excluded due to missing, incomplete, or contradictory information in the data forms. In these instances, and those mentioned above, it cannot be determined with absolute certainty that there were no statistically relevant distinguishing factors differentiating the excluded cases from those for which data was obtained and deemed suitable for analysis. Examples of such factors could include severity and urgency of the cases,

Table 2
Suicide Attempt Info* N(%).

Variable	Total N	Entire Sample (N = 4827)	Female (N = 2782)	Male (N = 2045)
Pharmaceutical Suicide Attempt		4612 (95.5)	2718 (97.7)	1894 (92.6)
Nonpharmaceutical Suicide Attempt		215 (4.5)	64 (2.3)	151 (7.4)
Single or Multiple Exposure?	4692			
Single Exposure		2304 (49.1)	1326 (48.9)	978 (49.4)
Multiple Exposure		2388 (50.9)	1385 (51.1)	1003 (50.6)
Type of Exposure	4760			
Acute		3860 (81.1)	2211 (80.9)	1649 (81.4)
Chronic		22 (0.5)	10 (0.4)	12 (0.6)
Acute-on-chronic		809 (17.0)	473 (17.3)	336 (16.6)
Unknown		69 (1.4)	39 (1.4)	30 (1.5)
Agent #1 Class	4672			
Alcohol Ethanol		96 (2.1)	40 (1.5)	56 (2.8)
Alcohol Toxic		85 (1.8)	27 (1.0)	58 (2.9)
Amphetamine-like Hallucinogen		1 (0.02)	0	1 (0.1)
Analgesic		912 (19.5)	587 (21.7)	325 (16.5)
Anesthetic		2 (0.04)	2 (0.1)	0
Anticholinergic/Antihistamine		306 (6.5)	182 (6.7)	124 (6.3)
Anticoagulant		38 (0.8)	17 (0.6)	21 (1.1)
Anticonvulsant		253 (5.4)	135 (5.0)	118 (6.0)
Antidepressant		743 (15.9)	446 (16.5)	297 (15.1)
Antimicrobials		8 (0.2)	4 (0.1)	4 (0.2)
Antipsychotic		412 (8.8)	225 (8.3)	187 (9.5)
Cardiovascular		317 (6.8)	182 (6.7)	135 (6.9)
Caustic		17 (0.4)	5 (0.2)	12 (0.6)
Chelator		0	0	0
Chemotherapeutic & Immune		17 (0.4)	13 (0.5)	4 (0.2)
Cholinergic/Parasympathomimetic		0	0	0
Cough & Cold		20 (0.4)	9 (0.3)	11 (0.6)
Diabetic Med		106 (2.3)	55 (2.0)	51 (2.6)
Endocrine		5 (0.1)	2 (0.1)	3 (0.2)
Envenomation		0	0	0
Foreign Objects		0	0	0
Fungicide		0	0	0
Gases/Vapors/Irritants/Dust		11 (0.2)	1 (0.04)	10 (0.5)
GI		4 (0.1)	2 (0.1)	2 (0.1)
Herbals/Dietary Supps/Vitamins		22 (0.5)	15 (0.6)	7 (0.4)
Herbicide		1 (0.02)	0	1 (0.1)
Household		24 (0.5)	10 (0.4)	14 (0.7)
Hydrocarbon		8 (0.2)	2 (0.1)	6 (0.3)
Insecticide		8 (0.2)	2 (0.1)	6 (0.3)
Lithium		100 (2.1)	55 (2.0)	45 (2.3)
Marine Toxin		0	0	0
Metals		19 (0.4)	16 (0.6)	3 (0.2)
Opioid		245 (5.2)	131 (4.8)	114 (5.8)
Other Non-pharmaceutical		4 (0.1)	1 (0.04)	3 (0.2)
Other Pharmaceutical		5 (0.1)	4 (0.1)	1 (0.1)
Parkinson's Med		0	0	0
Photosensitizing Agents		0	0	0
Plants & Fungi		4 (0.1)	2 (0.1)	2 (0.1)
Psychoactive		11 (0.2)	4 (0.1)	7 (0.4)
Pulmonary		0	0	0
Rodenticide		15 (0.3)	2 (0.1)	13 (0.7)
Sed-Hypnotic/Muscle Relaxant		729 (15.6)	467 (17.3)	262 (13.3)
Sympathomimetic		99 (2.1)	42 (1.6)	57 (2.9)
WMD/NBC/Riot		1 (0.02)	0	1 (0.1)
Unknown Agent		24 (0.5)	15 (0.6)	9 (0.5)
Route of Administration	4364			
Oral		4034 (92.4)	2326 (93.1)	1708 (91.5)
Inhalation		22 (0.5)	7 (0.3)	15 (0.8)
Parenteral		56 (1.3)	24 (1.0)	32 (1.7)
Intranasal		12 (0.3)	4 (0.2)	8 (0.4)
Dermal		3 (0.1)	2 (0.1)	1 (0.1)
Unknown		219 (5.0)	123 (4.9)	96 (5.1)
Rectal		2 (0.05)	1 (0.04)	1 (0.1)
Other		16 (0.4)	11 (0.4)	5 (0.3)

* *Note:* Total N is not 4827 for some categories as some of the responses were unknown or not applicable, and percentages in these categories were calculated based on included N.

availability/time-constraints for facilities, etc., all of which may reflect a better or worse (more likely) prognosis for excluded cases in comparison to included cases.

Furthermore, analyses were performed based only on the primary agent deemed responsible for the toxicological encounter. For example, if a patient had taken heroin, alcohol and benzodiazepines but the heroin was classified by the attending as the primary agent, then only heroin was included in the final data set and used for the analysis. Thus, we were not able to assess the impacts of drug interactions or multiple drugs contributing to

Table 3
Complications* N(%).

Variable	Total N	Entire Sample (N = 4827)	Female (N = 2782)	Male (N = 2045)
Major Vital Sign Abnormalities	3105			
Hypotension		273 (8.8)	152 (8.6)	121 (9.0)
Hypertension		27 (0.9)	11 (0.6)	16 (1.2)
Bradycardia		89 (2.9)	47 (2.7)	42 (3.1)
Tachycardia		409 (13.2)	239 (13.5)	170 (12.7)
Tachypnea		0	0	0
Bradypnea		67 (2.2)	34 (1.9)	33 (2.5)
Hyperthermia		0	0	0
Hypothermia		0	0	0
None		2009 (64.7)	1145 (64.8)	864 (64.5)
Multiple Symptoms		231 (7.4)	138 (7.8)	93 (6.9)
Death	4489			
Yes		60 (1.3)	35 (1.4)	25 (1.3)
No		4429 (98.7)	2548 (98.6)	1881 (98.7)
Life Support Withdrawn	61			
Yes		31 (50.8)	21 (58.3)	10 (40.0)
No		22 (36.1)	11 (30.6)	11 (44.0)
Unknown		8 (13.1)	4 (11.1)	4 (16.0)
CPR	4827			
Yes		47 (1.0)	29 (1.0)	18 (0.9)
No		4780 (99.0)	2753 (99.0)	2027 (99.1)
ECMO	4827			
Yes		4 (0.1)	2 (0.1)	2 (0.1)
No		4823 (99.9)	2780 (99.9)	2043 (99.9)
Intubation/Ventilation	4827			
Yes		843 (17.5)	446 (16.0)	397 (19.4)
No		3984 (82.5)	2336 (84.0)	1648 (80.6)

* *Note:* Total N is not 4827 for some categories as some of the responses were unknown or not applicable, and percentages in these categories were calculated based on included N.

the overall toxicological picture, which may be a subject for future research.

Nonetheless, if the included cases span the breadth of variety and severity of toxicological consults we intended to study, the sex-differences may persist across the excluded vs. included and secondary-agent subgroups.

6. Conclusion

We found among adults aged 19–65 categorized by suicide attempt in the ToxIC database, more females used pharmaceutical agents, while more males used nonpharmaceutical agents (such as alcohol) in self-harm attempts. We did not find large sex-differences in rates of suicide completion, routes of administration, or subsequent symptomologies. In a small sample of those that completed suicides, more females than males had life support withdrawn. In summary, sex-based differences were observed between adult patients with suicidal-intent exposures/ingestions managed at the bedside by medical toxicologists. These differences have potential implications for sex-specific prevention and management of suicidal patients with toxicologic exposure.

Funding

The authors have no outside support information, conflicts or financial interest to disclose. This study, in part, was funded by an unrestricted grant, The Dorothy Rider Pool Trust for Health Research and Education community foundation grant (20121573-015), and an abstract was presented at SAEM Annual Meeting and PACEP18 Annual Scientific Assembly.

Author contributions

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data. HK and SD performed the analysis. JF drafted the article and all authors equally contributed to its revision for important intellectual content. All authors gave final approval of the version of the article to be published.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Acknowledgement

Authors would like to acknowledge Samantha Esposito, BS for formatting and editing this report and Shae Duka, BS for her statistical analysis assistance.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2019.158450.

References

[1] Centers for Disease Control and Prevention. National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS); 2017. www.cdc.gov/injury/wisqars.
[2] Suicide Statistics. American Foundation for Suicide Prevention; 2019. https://afsp.org/about-suicide/suicide-statistics/.
[3] Suicide in America: Frequently Asked Questions. NIH, National Institute of Mental Health. https://www.nimh.nih.gov/health/publications/suicide-faq/index.shtml.
[4] Schrijvers DL, Bollen J, Sabbe BG. The gender paradox in suicidal behavior and its impact on the suicidal process. J Affect Disord 2012;138(1–2):19–26. https://doi.org/10.1016/j.jad.2011.03.050.
[5] Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999–2017. National Center for Health Statistics. Data Brief 329; 2018., https://www.cdc.gov/nchs/products/databriefs/db329.htm.
[6] Centers for Disease Control and Prevention. National Center for Injury Prevention and Control, Division of Unintentional Injury Prevention. Data Overview, Overview of the Drug Overdose Epidemic: Behind the Numbers

(Drug Overdose Deaths & Nonfatal Drug Overdoses); 2018. https://www.cdc.gov/drugoverdose/data/index.html.
[7] Americans Recognize the Growing Problem of Opioid Addiction. The Associated Press—NORC Center for Public Affairs Research at the University of Chicago; 2018. http://www.apnorc.org/PDFs/Opioids%202018/APNORC_Opioids_Report_2018.pdf.
[8] Sinha R. Chronic stress, drug use, and vulnerability to addiction. Ann N Y Acad Sci 2008;1141:105–30. https://doi.org/10.1196/annals.1441.030.
[9] Conner KR, Houston RJ, Swogger MT, Conwell Y, You S, He H, et al. Stressful life events and suicidal behavior in adults with alcohol use disorders: role of event severity, timing, and type. Drug Alcohol Depend 2012;120(1–3):155–61. https://doi.org/10.1016/j.drugalcdep.2011.07.013.
[10] Denney JT, Rogers RG, Krueger PM, Wadsworth T. Adult suicide mortality in the United States: marital status, family size, socioeconomic status, and differences by sex. Soc Sci Quart 2009;90(5):1167–85. https://doi.org/10.1111/j.1540-6237.2009.00652.x.
[11] Vijayakumar L. Suicide in women. Ind J Psych 2015;57(Suppl 2):S233–8. https://doi.org/10.4103/0019-5545.161484.
[12] Nowotny KM, Peterson RL, Boardman JD. Gendered contexts: variation in suicidal ideation by female and male youth across U.S. states. J Health Soc Behav 2015;56(1):114–30. https://doi.org/10.1177/0022146514568350.
[13] Eccles JS, Jacobs JE, Harold RD. Gender role stereotypes, expectancy effects, and parents' socialization of gender differences. J Soc Iss 1990;46:183–201. https://doi.org/10.1111/j.1540-4560.1990.tb01929.x.
[14] Vahter M, Gochfeld M, Casati B, Thiruchelvam M, Falk-Filippson A, Kavlock R, et al. Implications of gender differences for human health risk assessment and toxicology. Environ Res 2007;104(1):70–84. https://doi.org/10.1016/j.envres.2006.10.001.
[15] Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and. pharmacodynamicsAnnu Rev Pharmacol Toxicol 2004;44:499–523. https://doi.org/10.1146/annurev.pharmtox.44.101802.121453.
[16] Rademaker M. Do women have more adverse drug reactions? Am J Clin Dermatol 2001;2:349–51. https://doi.org/10.2165/00128071-200102060-00001.
[17] Verma R, Balhara YP, Gupta CS. Gender differences in stress response: role of developmental and biological determinants. Ind Psych J 2011;20(1):4–10. https://doi.org/10.4103/0972-6748.98407.
[18] Kajantie E, Phillips DIW. The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology 2006;31(2):151–78. https://doi.org/10.1016/j.psyneuen.2005.07.002.
[19] Becker JB, Hu M. Sex differences in drug abuse. Front Neuroendocrinol 2008;29(1):36–47. https://doi.org/10.1016/j.yfrne.2007.07.003.
[20] Charness G, Gneezy U. Strong evidence for gender differences in risk taking. J Econ Behav Organ 2012;83(1):50–8. https://doi.org/10.1016/j.jebo.2011.06.007.
[21] Pawlowski B, Atwal R, Dunbar RIM. Sex differences in everyday risk-taking behavior in humans. Evol Psych 2008;6(1):29–42. https://doi.org/10.1177/147470490800600104.
[22] Howden LM, Meyer JA. Age and Sex Composition: 2010. United States Census Bureau Table 2; 2011. , https://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf.
[23] Wilsnack RW, Wilsnack SC, Kristjanson AF, Vogeltanz-Holm ND, Gmel G. Gender and alcohol consumption: patterns from the multinational GENACIS project. Addiction (Abingdon, England) 2009;104(9):1487–500. https://doi.org/10.1111/j.1360-0443.2009.02696.x.
[24] Walter H, Gutierrez K, Ramskogler K, Hertling I, Dvorak A, Lesch OM. Gender-specific differences in alcoholism: implications for treatment. Arch Women's Ment Health 2003;6(4):253–8. https://doi.org/10.1007/s00737-003-0014-8.
[25] Bronisch T, Wittchen H. Lifetime and 6-month prevalence of abuse and dependence of alcohol in the Munich follow-up study. Eur Arch Psych Clin Neurosci 1992;241(5):273–82. , https://www.ncbi.nlm.nih.gov/pubmed/1606191.
[26] Brady KT, Randall CL. Gender differences in substance use disorders. Psych Clin North Am 1999;22(2):241–52. https://doi.org/10.1016/S0193-953X(05)70074-5.
[27] Hernandez-Avila CA, Rounsaville BJ, Kranzler HR. Opioid-, cannabis-and alcohol-dependent women show more rapid progression to substance abuse treatment. Drug Alcohol Depend 2004;74(3):265–72. https://doi.org/10.1016/j.drugalcdep.2004.02.001.