Pregnancy Outcomes of Serotonin-Norepinephrine Reuptake Inhibitors (SNRI): Analysis of FDA Adverse Event Reporting System (FAERS) Database (2012-2021)

Fatimah Alyami [1], BPharm, MS, PhD Candidate, Jeff Jianfei Guo [2], BPharm, PhD
[1] Graduate Assistant, James L. Winkle College of Pharmacy, University of Cincinnati, OH.
[2] Professor of Pharmacoeconomics and Pharmacoepidemiology, James L. Winkle College of Pharmacy, University of Cincinnati, OH.

University of CINCINNATI

Presentation ID: 117752

Background

The use of Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) during pregnancy is a controversial issue as SNRIs can affect the development of the fetus negatively. In the United States, the Food and Drug Administration (FDA) had issued several warnings regarding the use of SNRI during late pregnancy and increased risk of newborn persistent pulmonary hypertension syndrome, also, they have issued warnings of increased risk of congenital malformation. Moreover, is relatively limited information regarding the impact of SNRIs among women during their pregnancy.

Objective

The objective of the study was to describe the most commonly reported pregnancy adverse events (AEs) related to SNRIs as reported in the FDA Adverse Event Reporting System (FAERS) database.

Methods

- The primary data source was the publicly available FAERS database. The study design was a retrospective descriptive study from Quarter 1, 2012 to Quarter 1, 2021.
- Adverse event (AE) reports extracted using index of study SNRI drug either brand-name or generic names listed. Reported AEs are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA). AEs were separated based on the preferred term, or PT. There are multiple PTs for each case.
- Number of pregnancy related adverse events AEs was calculated for each SNRI medication.
- Analysis was performed for six groups of MedDRA Preferred Terms (PTs) - Spontaneous Abortion, Induced Abortion, Stillbirth, Congenital Malformation, Ectopic Pregnancy, and Low Birth Weight.
- Descriptive statistics was used to describe number of pregnancy adverse events AE reports and most frequently reported pregnancy adverse events.

Results

- The total number of pregnancy related adverse events for all SNRI included in the study was (3618); Venlafaxine (2514), Duloxetine (1064), Desvenlafaxine (36), Milnacipran (4) and Levo-milnacipran (2).
- The most commonly reported pregnancy related AEs was congenital malformation (2377, [65%]) followed by spontaneous abortion (920, [25%]) and low birth weight (140, [3.9%]).
- The least common pregnancy related AE was stillbirth followed (82, [2.3%]) by ectopic pregnancy (20, [0.5%]).
- There were 613 patients outcomes associated with pregnancy related AEs, including 110 (18%) deaths, 60 (9.8%) disability, 274 (44.7%) hospitalizations and 169 (27.6%) life-threatening events.
- Out of 613 outcomes , 80% (496) outcomes were represented by congenital malformation AEs involving the usage of Venlafaxine, Duloxetine and Desvenlafaxine.

Figure 1: Number of Patients by Gender (2012-2021)

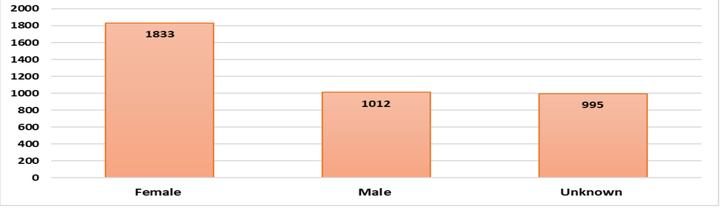


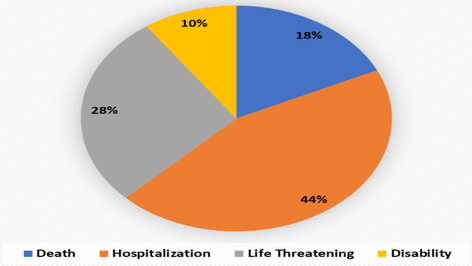
Table 1 : List of Serotonin-norepinephrine reuptake inhibitors (SNRIs) included in the study.

Drug Name	FDA Approval Date	Indications	Generic Availability
Venlafaxine (Effexor XR)	1993 (IR), 1997 (XR).	Major depression Generalized anxiety disorder Panic disorder Social phobia	Yes
Duloxetine (Cymbalta, Irenka)	2004	Major depression Generalized anxiety disorder Diabetic peripheral neuropathy Fibromyalgia Musculoskeletal pain Osteoarthritis	Yes
Desvenlafaxine (Pristiq, Khedezla)	2008	Major depression	Estimated to be available in 2022
Milnacipran (Savella)	2009	Fibromyalgia	No
Levomilnacipran (Fetzima)	2013	Major depression	No

Table 2: Pregnancy Related Adverse Events Associated with Serotonin-Norepinephrine Reuptake Inhibitors (SNRI). Using FAERS Databases 2012-2021.

SNRI Antidepressant	Reported Pregnancy Adverse Event						
	Abortion Induced	Abortion Spontaneous	Congenital Malformation	Ectopic Pregnancy	Still Birth	Low Birth Weight	Total
Desvenlafax	0	15	18	1	0	2	36
Duloxetine	5	289	716	5	3	45	1063
Levomilnacipran	0	1	0	0	1	0	2
Milnacipran	2	2	0	0	0	0	4
Venlafaxine	72	613	1643	14	79	93	2514
Total	79	920	2377	20	83	140	3619

Figure 2: Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) Patients Outcomes Associated with Pregnancy Related AEs



Discussion

- In this study, Venlafaxine (2514, [69.46%]) had the largest number of pregnancy related AEs.
- About 80% (496) patient outcomes were represented by congenital malformation AEs involving the usage of Venlafaxine, Duloxetine and Desvenlafaxine.
- According to Lexi-comp Pregnancy Considerations section, exposure to SNRIs late in the third trimester is associated with neonate adverse events, such as hypo- or hypertonia, hyper-reflexia, jitteriness, irritability, constant crying, and tremor.
- The risk of bleeding, including postpartum hemorrhage may increase with the maternal use of venlafaxine.
- FARES database has several limitations, such as duplicate reports, unable to establish causality and lack of verification.

Conclusion

Therapeutic risk management is crucial for SNRI use during pregnancy since they are considered as high-risk population. Further studies are warranted to establish a causal relationship between SNRI use and pregnancy related AEs.

References

- Zoega H, Kieler H, Nørgaard M, et al. Use of SSRI and SNRI Antidepressants during Pregnancy: A Population-Based Study from Denmark, Iceland, Norway and Sweden. PLOS ONE. 2015;10(12). doi:10.1371/journal.pone.0144474
- Kieler H, Malm H, Artama M, et al. Use of antidepressants and association with elective termination of pregnancy: population based case–control study. BJOG: An International Journal of Obstetrics & Gynaecology. 2014;122(12):1618-1624. doi:10.1111/1471-0528.13164
- Kornum. Use of selective serotonin-reuptake inhibitors during early pregnancy and risk of congenital malformations: updated analysis. Clinical Epidemiology. 2010:29. doi:10.2147/clep.s9256
- Ornoy A, Koren G. SSRIs and SNRIs (SRI) in Pregnancy: Effects on the Course of Pregnancy and the Offspring: How Far Are We from Having All the Answers? International Journal of Molecular Sciences. 2019;20(10):2370. doi:10.3390/ijms20102370
- Center for Drug Evaluation and Research. FDA Adverse Event Reporting System (FAERS) Public Dashboard. U.S. Food and Drug Administration. https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard. Accessed March 16, 2021.

Contact the Presenting Author

Fatimah Alyami
Email : alyamifh@mail.uc.edu

James L. Winkle College of Pharmacy, University of Cincinnati.
3255 Eden Ave.
161 Kowalewski Hall
Cincinnati, Ohio 45229