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ORIGINAL RESEARCH

Urinary and gynecologic adverse events associated with SSRI use

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Background

Selective Serotonin Receptor Inhibitors (SSRIs) are the most prescribed psychiatric drug in the United States. However, the adverse effects of SSRIs related to the genitourinary and reproductive systems in real-world settings remains unclear. The aim of this study is to identify a comprehensive profile of adverse events (AEs) associated with SSRIs in females using data from the FDA Adverse Events Reporting System (FAERS) and variability of adverse events across individual SSRIs.

Methods

A software designed to analyze adverse drug events, OpenVigil 2.1, was used to query the FAERS data. We defined 445 genitourinary and reproductive system related adverse events related to genitourinary and reproductive systems. Proportional reporting ratio (PRR) was utilized to assess the strength of association between adverse events and SSRIs. Subgroup analysis was conducted to stratify adverse events by age.

Results

The majority of AEs were related to sexual dysfunction, such as issues of arousal, libido, and orgasm. Additional significant findings were related to gynecologic bleeding, urinary retention and incontinence, and hypersexuality. Citalopram exhibited the strongest signal strengths, as evidenced by the highest proportional reporting ratios (PRRs), particularly in relation to sexual dysfunction. The strongest signals related to sexual dysfunction were found in the 40-59 years age group. Urinary symptoms were most prevalent in the over 60 years age group.

Conclusion

According to our findings, the potential for genitourinary and reproductive system related AEs of SSRIs warrants further investigation of underlying mechanisms and monitoring in clinical practice. AEs are important considerations for clinical practice as side effects of SSRIs can impact treatment compliance and patient quality of life.

Introduction

Selective Serotonin Receptor Inhibitors (SSRIs) increase serotonin (5-HT) transmission by inhibiting 5-HT uptake in the synaptic cleft and increasing the availability of activity of 5-HT in chemical transmission.[1] While used in the treatment of depression, off-label uses of SSRIs have grown to include migraine prophylaxis, antiviral therapy, bulimia, fibromyalgia, treatment of vasomotor symptoms and premature ejaculation.[2-5] The five most common SSRIs available are citalopram, fluoxetine, paroxetine, sertraline, and escitalopram. Citalopram has been found to be the most selective of the SSRIs, affecting only the 5-HT receptors, versus other SSRIs, which affect both norepinephrine and 5-HT receptors.[1] Paroxetine was identified as the most potent.[5]

Adverse events (AEs) are harmful, unintentional effects that occur due to pharmacologic therapy. AEs may include fatigue, sexual dysfunction, insomnia, dizziness, lightheadedness, tremors, dry mouth, and weight gain.[1, 6] Currently, these medications are the most prescribed psychiatric drug in the United States and are primarily used in the treatment of major depressive disorder.[7,8] Approximately 40% of patients reported AEs to their provider.[2] Increased and widespread usage of these drugs requires a deeper understanding of their AE profile. The impact of such AEs on the genitourinary and reproductive systems may have significant implications for patient compliance and quality of life. These concerns may also be under-addressed in clinical practice due to embarrassment around discussing sexual difficulty and related topics.

Since the early 2000s, studies have identified SSRI-related AEs on sexual dysfunction and urinary incontinence.[9-11] A study found that 14/1000 more patients treated with SSRIs developed urinary incontinence, with this increasing to 60 additional cases developing in elderly patients.[9] This is a substantial number of additional patients affected, warranting our investigation of GU AEs in addition to only AEs related to sexual dysfunction. Delayed ejaculation, anorgasmia, and/or decreased libido may affect up to 80% of patients.[2,3] However, there are only a few studies detailing other effects on the genitourinary and reproductive systems in females.[11, 12] While there is acknowledgement of sexual AEs, there is limited research on specific forms of sexual dysfunction (anorgasmia, premature ejaculation, libido, hypersexuality, arousal disorders). The Food and Drug Administration Adverse Events Reporting System (FAERS) database collects granular adverse event (AE) reports from healthcare professionals, manufacturers, and patients, providing a comprehensive resource for pharmacovigilance studies. As such, we aim to utilize the database to assess reported AEs in females from 2003 to 2022 to better characterize the breadth of AEs associated with SSRIs.

Methods

This was a retrospective study using data collected from the FAERS database, which contains public de-identified information regarding AEs submitted for drugs and therapeutic biological products reported to the Food and Drug Administration (FDA) by healthcare providers, patients, and pharmaceutical companies.[13] Institutional Review Board approval was waived. The goal of the database is to promote drug safety and surveillance for approved products in the US. The database contains demographics, drug information, report sources, and AEs from over 17 million submitted AEs OpenVigil 2.1 is a pharmacovigilance tool used for data extraction, cleaning, and analysis of the FAERS database. However, this large, public database lacks granularity as to other medications and relevant patient characteristics and is unable to establish causal relationship between drug and AE. Data from Q4/2003-Q3/2022 are included in the database.[14] We constructed queries on OpenVigil 2.1 using generic drug names. We included the five most prescribed antidepressants (fluoxetine, sertraline, paroxetine, escitalopram, citalopram) as well as SSRIs as a class in this analysis.[2,15] A total of 147,314 AE reports from females were included for SSRIs as a class. We used the advanced search function to include only females and to stratify data by age group.

The FAERS database codes AEs as Preferred Terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA) hierarchical classification system. We defined ovary, uterus, and urinary system-related AEs using 445 PTs from the MedDRA dictionary (Table S1). According to MedDRA, these PTs could be classified into 13 categories: bladder and urethral disorder, urinary tract signs and symptoms, renal lithiasis, ovarian cysts and neoplasms, cervix neoplasms, cervix disorders (excluding neoplasms), ovarian disorders (excluding cysts and neoplasms), menstrual cycle and uterine bleeding disorders, sexual function disorders, uterine disorders (excluding neoplasms), endocrine disorders of gonadal function, uterine neoplasms, and menopause related conditions. Methodology was adapted from Jiao et al., (2020).[16]

OpenVigil 2.1 was used to conduct disproportionality analyses. Proportionality reporting ratio (PRR) was used to determine association between AE and SSRIs. A higher PRR indicates a stronger association. A PRR=2 indicates that the AE is twice as frequent in consumers of the drug compared to the background population. According to the criteria of Evans et al. (2001), a positive signal of disproportionality must feature a PRR greater than or equal to two, Chi-square of four or more, and include three or more cases.[17] As we defined AEs by 445 PTs, we first conducted 445 disproportionality analyses to assess the associations between these 445 PTs and SSRIs as a Class (Table S1). Next, we performed 2,225 disproportionality analyses to assess the associations between these PTs and each of the five SSRIs across all ages of females. To investigate variability in AEs across age

groups, we conducted 10,680 subgroup analyses by age group. Age groups were 0-18, 19-39, 40-59, and over 60 years, which were chosen to represent different physiologic phases of the female lifespan (Table S2).[18,19]

Results

AE reports submitted for SSRIs. Table 1 shows an overview of AEs reports submitted for SSRIs in females. The majority of AEs occurred in the 19-39 and 40-59 age groups for fluoxetine, sertraline, and citalopram. For escitalopram, the most AE reports occurred from 19-39 and ≥60. The number of positive signals related to GU and reproductive system AEs for SSRIs as a class, fluoxetine, paroxetine, sertraline, escitalopram, and citalopram were 37, 17, 15, 31, 15, and 23, respectively.

SSRIs as a class. Significant GU and reproductive related signals were found for 37 PTs, the majority of which were related to bladder and urethral symptoms (9/37, 24%) and sexual function disorders (14/37, 38%) for all age groups. Across all age groups, the most AEs were found for sexual dysfunction (328/2158, 15.2%), anorgasmia (326/2158, 15.1%), decreased libido (319/2158, 14.7%), loss of libido (240/2158, 11.1%), and urinary retention (212/2158, 9.8%). Oligomenorrhea and renal colic emerged as statistically significant signals in the 0-18 age group. Hot flush and menopausal symptoms became statistically significant in the 19-39 and 40-59 age groups, respectively. Uterine hemorrhage was noticeably significant in the above 60 years age group (Table 2).

Fluoxetine. Across all females, there were 17 statistically significant signals related to GU/reproductive AEs. 10/17 (59%) of these were related to sexual function disorders and included female orgasmic disorder, libido decreased, libido increased, orgasm abnormal, decreased orgasmic sensation, sexual dysfunction, anorgasmia, disturbance in sexual arousal, hypersexuality, and loss of libido. Other significant PTs included urinary retention, renal pain, ovarian enlargement, endometrial hyperplasia, cervical incompetence, polycystic ovaries, and menopausal symptoms. Urinary incontinence became significant in the 19-39 years age group. Micturition urgency, pollakiuria, and ovarian cysts emerged as statistically significant in females above 60 years (Table S3).

Paroxetine. For paroxetine, statistically significant signals emerged for 15 GU/reproductive related PTs for all females. The strongest signals were found for decreased libido (PRR=2187), anorgasmia (PRR=1251), loss of libido (PRR=1132), libido increased (249), and hot flush (169). Other statistically significant signals emerged for incontinence, abnormal uterine contractions, precocious puberty, premenstrual syndrome, female orgasmic disorder, female sexual dysfunction, libido disorder, orgasm abnormal, and disturbance in sexual arousal. For the 19-39 age group, significant signals emerged for

Table 1. Overview of Adverse Events Submitted to FAERS for SSRIs Between 2004 and the Third Quarter of 2022.

	No.					
	SSRIs as a class	**Fluoxetine**	**Paroxetine**	**Sertraline**	**Escitalopram**	**Citalopram**
No. of female adverse event reports						
Overall	147314	37282	71604	72556	33225	39753
By age group, y						
0-18	13739	5290	4976	7365	2477	2590
19-39	38778	9199	14012	21053	9100	11022
40-59	30903	8199	14003	14947	8091	11220
≥60	19436	5411	7546	11736	6279	7895
No. of genitourinary events with positive signals						
Overall	37	17	15	31	15	23
By age group, y						
0-18	10	0	2	7	0	2
19-39	28	10	11	20	12	15
40-59	22	10	8	16	5	13
≥60	12	5	8	6	7	3
Total No. of unique events	49	22	20	38	22	24

Abbreviations: FAERS, Food and Drug Administration's Adverse Events Reporting System; SSRIs, selective serotonin reuptake inhibitors.

urinary retention and sexual dysfunction. For the 40-59 years age group, significant signals emerged for amenorrhea and menstrual disorders. Above 60 years, urinary incontinence became statistically significant (Table S4).

Sertraline. Of 31 statistically significant GU and reproductive related AEs across all females for sertraline, 11 were related to bladder and urethral symptoms and 12 fell under sexual function disorders. Bladder and urethral symptoms included bladder discomfort, bladder pain, bladder irritation, dysuria, enuresis, micturition urgency, pollakiuria, urge incontinence, urinary hesitation, urinary retention, and urinary incontinence. Sexual dysfunction disorders included female sexual arousal disorder, female sexual dysfunction, infertility, decreased libido, increased libido, abnormal orgasm, decreased orgasmic sensation, sexual dysfunction, anorgasmia, disturbance in sexual arousal, and loss of libido. Amenorrhea and oligomenorrhea emerged as statistically significant signals in the 0-18 years age group, while nocturia was significant in the 19-39 years age group. Bladder spasm and dyspareunia became significant in the 40-59 years age group and uterine hemorrhage was significant above 60 years (Table S5).

Escitalopram. There were 15 statistically significant GU and reproductive relevant AEs in females for escitalopram. 10/15 (66%) of these AEs were related to sexual function disorders. Others included enuresis, urinary

Table 2. Genitourinary and Ovary/Uterus-Related Adverse Events With Positive Signals for SSRIs as a Class

Classification	Adverse event	Overall			Age 0-18 y			Age 19-39 y		
		No.	PRR	χ^{2a}	No.	PRR	χ^{2a}	No.	PRR	χ
Bladder and urethral symptoms	Bladder discomfort	15	3.58	24.36	-	-	-	14	11.32	
	Bladder irritation	14	8.20	74.43	-	-	-	18	7.81	
	Bladder pain	27	2.77	27.85	-	-	-	-	-	-
	Dysuria	-	-	-	-	-	-	46	2.03	
	Enuresis	26	3.05	32.56	-	-	-	7	3.24	
	Micturition disorder	20	2.36	13.98	5	7.81	18.47	-	-	-
	Micturition urgency	61	2.05	30.98	-	-	-	30	3.89	
	Pollakiuria	-	-	-	-	-	-	61	3.21	
	Nocturia	-	-	-	-	-	-	8	3.54	
	Urge incontinence	10	3.87	17.70	-	-	-	-	-	-
	Urinary hesitation	12	2.85	12.20	-	-	-	-	-	-
	Urinary retention	212	3.48	358.10	38	5.23	107.90	61	3.82	1
	Urinary incontinence	-	-	-	18	2.63	15.26	15	2.48	
Urinary tract signs and symptoms	Urinary tract discomfort	4	3.99	5.93	-	-	-	4	28.04	
	Kidney pain	-	-	-	10	18.38	92.52	-	-	-
	Renal colic	-	-	-	-	-	-	-	-	-
Ovarian cysts and neoplasms	Ovulation pain	4	4.13	6.30	-	-	-	-	-	-
Uterine disorders (excluding neoplasms)	Endometrial hyperplasia	9	2.18	4.53	-	-	-	5	3.05	
	Uterine atony	5	4.62	10.23	-	-	-	-	-	-
	Abnormal uterine contractions	6	3.82	9.39	-	-	-	-	-	-
	Uterine pain	-	-	-	-	-	-	-	-	-
	Uterine hemorrhage	-	-	-	-	-	-	-	-	-
Cervix disorders (excluding neoplasms)	Cervical incompetence	15	7.89	76.56	-	-	-	130	3.24	
	Cervix hematoma uterine	4	117.10	150.30	-	-	-	4	168.20	
Endocrine	Precocious	6	3.07	6.17	-	-	-	-	-	-

Classification	Adverse event	Overall			Age 0-18 y			Age 19-39 y		
		No.	PRR	χ^{2a}	No.	PRR	χ^{2a}	No.	PRR	χ
disorders of gonadal function	puberty									
	Adrenogenital syndrome	4	9.25	19.61	-	-	-	-	-	-
	Anovulatory cycle	5	3.96	7.91	-	-	-	-	-	-
Menstrual cycle and uterine bleeding disorders	Menstrual disorder	87	2.12	49.33	-	-	-	-	-	-
	Premenstrual dysphoric disorder	7	9.92	42.67	-	-	-	7	10.52	
	Oligomenorrhea	-	-	-	6	2.80	4.78	-	-	-
	Premenstrual syndrome	27	3.66	47.45	-	-	-	14	2.52	
Menopause-related conditions	Premature menopause	16	3.41	23.97	-	-	-	8	2.32	
	Hot flush	-	-	-	-	-	-	121	2.35	
	Menopausal symptoms	-	-	-	-	-	-	-	-	-
	Postmenopausal hemorrhage	-	-	-	-	-	-	-	-	-
Sexual function disorders	Female orgasmic disorder	68	60.96	2332	-	-	-	40	67.29	9
	Female sexual arousal disorder	16	42.60	409.80	-	-	-	-	-	-
	Female sexual dysfunction	40	45.05	1110	-	-	-	27	34.41	4
	Decreased libido	319	15.02	3554	12	11.72	77.73	118	7.18	5
	Libido disorder	15	9.76	98.34	-	-	-	-	-	-
	Increased libido	50	10.93	392.2	3	9.38	11.26	73	16.13	2
	Abnormal orgasm	47	37.20	1138	-	-	-	35	58.88	8
	Decreased orgasmic sensation	12	42.17	298.4	-	-	-	8	48.07	1
	Sexual dysfunction	328	27.44	6350	13	36.93	191.70	157	12.90	
	Anorgasmia	326	72.69	12576	8	41.67	118.70	194	65.27	
	Disturbance in sexual arousal	78	63.45	2747	4	62.50	60.92	35	50.76	7
	Sexual inhibition	5	36.61	98.14	-	-	-	-	-	-
	Hypersexuality	18	7.03	80.63	-	-	-	8	8.21	
	Loss of libido	240	13.54	2405	-	-	-	107	6.22	4

Abbreviations: PRR, proportional rate ratio; SSRIs, selective serotonin reuptake inhibitors.
[a]χ^2 indicates not a positive signal (no significant association between SSRI and AE).

retention, polycystic ovaries, oligomenorrhea, and premature menopause. Decreased estradiol became statistically significant in the 19-39 age group and uterine hemorrhage became significant in the 40-59 age group. Hematuria, pollakiuria, urinary incontinence, micturition incontinence, and incontinence emerged as significant in the ≥60 years age group. The strongest signals were related to sexual function disorders for escitalopram (Table S6).

Citalopram. Citalopram had 23 statistically significant AEs related to GU/reproductive PTs, with 18/23 (78%) events related to bladder and urethral symptoms and sexual function disorders across all females. Bladder and urethral symptoms included bladder irritation, bladder pain, enuresis, micturition disorder, micturition urgency, pollakiuria, and urinary retention. Sexual dysfunction disorders included female orgasmic disorder, female sexual arousal disorder, female sexual dysfunction, libido decreased, orgasm abnormal, sexual dysfunction, anorgasmia, disturbance in sexual arousal, sexual inhibition, hypersexuality, and loss of libido. The strongest signal strengths with regard to urinary symptoms were for bladder irritation. The most AE reports were for pollakiuria and urinary retention. In the 40-59 age group, urinary incontinence emerged as a statistically significant AE (Table S7).

Comparison of signal strength across SSRIs. There were 49 AEs that were common across one or more SSRI. There was variability in signal strength for AEs across individual SSRIs. Across all age groups, citalopram had the strongest signal for all AEs related to sexual dysfunction: anorgasmia (PRR= 56.455), disturbance in sexual arousal (PRR=56.455), female orgasmic disorder (PRR=65.574), female sexual dysfunction (PRR=43.152), hypersexuality (PRR=18.821), orgasm abnormal (PRR=59.162), and sexual dysfunction (PRR=18.751). When stratified by age group, citalopram continued to have the strongest signals with regard to sexual dysfunction (Table 3).

Discussion

In this study, we identified AEs related to the GU and reproductive system associated with SSRIs use. The most associations between SSRIs occurred in the categories of urinary and bladder symptoms and sexual dysfunction. 49 unique positive signals were found for SSRIs as a class, 22 for fluoxetine, 20 for paroxetine, 38 for sertraline, 22 for escitalopram, and 24 for citalopram. AEs most often occurred in the 19-39 and 40-59 age groups.

AEs related to bladder and urethral symptoms emerged as positive signals across all SSRIs and SSRIs as a class. Disorders of urinary incontinence, urinary retention, and bladder discomfort/irritation comprised the strongest signals in this category across SSRIs. While the association between urinary

Table 3. Comparison of Adverse Events Across the 5 SSRIs

Age group	Adverse event	Fluoxetine	Paroxetine	Sertraline	Escitalopram	Citalopram
		PRR	PRR	PRR	PRR	PRR
Overall	Anorgasmia	42.66	27.50	145	19.68	56.45
	Disturbance in sexual arousal	26.41	13.26	35	21.72	56.45
	Bladder irritation	-	-	15.85	-	14.12
	Enuresis	-	-	3.56	3.29	4.39
	Endometrial hyperplasia	6.27	-	3.73	-	-
	Female orgasmic disorder	22.91	17.17	32	37.29	65.57
	Female sexual dysfunction	-	18.17	21	23.49	43.15
	Hypersexuality	14.73	-	-	-	18.82
	Decreased libido	10.61	20.58	96	6.14	9.42
	Increased libido	14.47	15.70	15	7.44	-
	Loss of libido	8.40	16.43	85	8.24	7.66
	Libido disorder	-	9.29	6	-	-
	Abnormal orgasm	14.27	18.09	13	46.32	59.16
	Decreased orgasmic sensation	90.25	-	4	-	-
	Micturition urgency	-	-	2.89	-	3.57
	Premenstrual syndrome	-	6.65	3.68	-	-
	Pollakiuria	-	-	2.44	-	-
	Polycystic ovaries	3.37	-	-	4.22	-
	Postmenopausal hemorrhage	-	-	2.25	9.09	-
	Premature menopause	-	-	-	7.69	5.46
	Sexual dysfunction	15.74	-	18.75	18.75	18.75
	Urinary retention	4.14	-	-	3.74	2.54
19-39 y	Anorgasmia	18.60	13	-	9.63	34.03
	Bladder pain	-	-	14.18	-	8.60
	Disturbance in sexual arousal	-	12.07	-	-	43.69

Age group	Adverse event	Fluoxetine	Paroxetine	Sertraline	Escitalopram	Citalopram
		PRR	PRR	PRR	PRR	PRR
	Female orgasmic disorder	19.79	-	-	23.61	
	Female sexual dysfunction	-	-	-	16.26	22.59
	Decreased libido	5.14	6.98	-	-	4.01
	Increased libido	7.99	32.54	-	-	-
	Loss of libido	6.82	8.02	-	4.21	4.65
	Micturition urgency	-	-	6.73	-	5.74
	Abnormal orgasm	-	-	-	62.37	62.71
	Sexual dysfunction	8.07	12.45	-	12.62	9.77
	Premature menopause	-	-	-	10.08	4.82
	Urinary retention	5.76	2.46	4.54	2.80	-
40-59 y	Anorgasmia	64.88	36.08	22.65	-	42.18
	Bladder irritation	-	-	76.11	-	44.31
	Disturbance in sexual arousal	40.36	-	53.98	-	152.79
	Decreased libido	13.43	35.81	7.08	6.89	6.78
	Loss of libido	3.96	18.29	19.52	8.29	5.41
	Female orgasmic disorder	-	-	39.03	-	169.37
	Increased libido	23.85	10.45	-	-	-
	Menstrual disorder	3.73	3.28	4.99	-	-
	Pollakiuria	-	-	2.71	-	3.98
	Sexual dysfunction	11.34	36.31	13.40	15.47	-
	Urinary incontinence	2.06	-	-	-	3.38
	Urinary retention	2.81	-	-	2.98	-
≥60 y	Urinary retention	4.52	4.58	6.33	3.19	2.51
	Urinary incontinence	-	2.31	2.46	2.92	-

Abbreviations: PRR, proportional rate ratio; SSRIs, selective serotonin reuptake inhibitors.
PRR proportional reporting ratio, – not a positive signal (no significant association between SSRI and AE).

symptoms and SSRIs has been established, our study offers detailed insight into the specific forms of urinary symptoms (e.g., urgency, nocturia, pollakiuria) associated with SSRIs.[20,21] It is thought that urinary incontinence may mediated by the 5HT4 receptors found on the bladder.[9, 22-24] Activation of this enteric serotonin receptors is thought to stimulate gastrointestinal smooth muscle and induce a prokinetic effect. It is believed that activation of serotonin receptors in the bladder can have similar effects in both men and women.[9] However, we also saw contradictory emergence of urinary retention as statistically significant with signals for each SSRI and SSRIs as a class. Further research is needed to understand the relationship between urinary retention and SSRI use.

AEs of SSRIs are known to involve sexual dysfunction.[2,3,25-27] An unexpected finding was the emergence of increased libido for all SSRIs except citalopram. There is limited literature which references a disinhibition of libido occurring in a select population of SSRI users occurring after starting an SSRI or changing dosage.[4,28] This draws attention to the unpredictable impact that SSRIs may have on libido. Of all SSRIs, paroxetine is generally accepted as having the greatest risk of sexual dysfunction of SSRIs.[4,7,27] Paroxetine is also approved for the treatment of vasomotor symptoms such as hot flashes and low libido in postmenopausal women.[29] Our results showed that citalopram had the strongest association with sexual AEs related to sexual dysfunction of all SSRIs, with multiple measures of association (PRRs) found to have a signal strength upwards of 3,000. While paroxetine was associated with AEs related to sexual dysfunction, the maximum signal strength was a PRR of 2,187 for decreased libido. While more studies are needed for clarification of these conflicting findings, as this finding may influence optimal SSRI choice for patients regarding AE profile.

Unlike manifestations of hyposexuality, hypersexuality is a difficult phenomenon for providers to identify and manage, as it may be difficult to distinguish from acute mania.[30] One study suggests that hypersexual AEs may be a product to abnormal elevations of serotonergic activity in the central nervous system.[31] Further research is necessary investigate the molecular mechanism and strengthen this hypothesis. It is critical for physicians to be aware of the variety of symptoms that may develop SSRI use and to effectively distinguish AEs from a mood switch triggered by SSRI use. A thorough discussion of possible AEs with patients is recommended when initiating an SSRI. At follow up visits, providers should intentionally inquire about urinary and AEs related to sexual function as patients may not bring up these concerns themselves. They may experience embarrassment around these AEs or think that these findings are not related to medication use. If

an AE were to develop, providers should consider the risks and benefits of continuing the medication. If symptoms are severe, discontinuation should be considered.

Other surprising findings included the frequency of AEs related to menstrual and uterine bleeding disorders. These AEs included uterine hemorrhage, cervical hematomas, hematuria, and postmenopausal hemorrhage. At least one bleeding related complication was found for all SSRIs and SSRIs as a class. One study links postpartum bleeding with dose-dependent SSRI use and advocates for therapeutic drug monitoring in pregnancy.[32] Other studies found an association between upper GI bleeds and SSRI use, thought to be due to the role of serotonin in potentiating the coagulation cascade.[31-34] SSRI-associated bleeding is thought to be due to blocking of serotonin uptake into platelets leading to an impaired response.[35] Increased awareness of and investigation into this phenomenon is necessary to optimize treatment tolerability and safety.[36] These effects could put patients at risk for anemia or bleeding, which could be life-threatening.

Variability of AEs emerged across the female lifespan. Statistically significant AEs related to sexual dysfunction were present up to age 60. The strongest signals were found in the 40-59 years age group, which can be explained by the decrease in estrogen levels that occur in females as they age.[37] Unsurprisingly, urinary symptoms were most prevalent in the 0-18 years and over 60 years age group, but occurred at increased rates compared to the background population. These are important considerations for clinical practice as AEs of SSRIs can impact treatment compliance and patient quality of life.

A limitation of this study is that the FAERS database cannot provide evidence as to causal relationship between product exposure and reported event. As FAERS is a voluntary and unverified reporting system, it is impossible to calculate the true incidence of AEs from the database. The voluntary reporting structure makes assessing the clinical significance of a high PRR difficult. Furthermore, this analysis excluded data entered into FAERS without associated gender and age information. Additionally, granular patient characteristics and situational details regarding AEs are also unknown. For example, it is impossible to know the exact situation that led to the reporting of postmenopausal hemorrhage as a significant AE. Therefore, it is unclear if there are any confounding factors that impact the AEs reported. It is important to note that patients are frequently counseled on AE profiles and that reporting bias may be present due to the subjective and voluntary nature of the reporting system. Additional studies are needed to verify our findings and determine the underlying mechanisms between SSRIs and AEs.

Our study features a number of strengths. Over 1 million AE reports are submitted to the FDA each year, allowing for detection of rare adverse reactions associated with SSRIs. Furthermore, our study offers a profile of all 445 AEs related to the genitourinary and reproductive systems allowing for a comprehensive view of common and rare AEs associated with SSRIs. Lastly, stratification of AEs by age group provided detailed insight into variability in AEs of SSRIs over the female lifespan.

Conclusions

This study offers a comprehensive profile of GU and reproductive system related AEs associated with SSRI use among females. AEs were most often related to sexual dysfunction and urinary symptoms, but also were frequently related to bleeding disorders, ovarian cysts, uterine disorders, endocrine conditions, menstrual cycle abnormalities, and menopause related conditions. While the pathophysiology of each AE remains unclear, an understanding of potential risks of these drugs is valuable in the management of patients taking SSRIs, particularly in the event of rare AEs that are often not associated with SSRI use. Further work is needed to establish causal relationships and understand underlying mechanisms between SSRIs and associated AEs.

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SUPPLEMENTARY MATERIALS

Supplemental Tables

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