PHARMACOTHERAPY

Medications Most Commonly Associated With Erectile Dysfunction: Evaluation of the Food and Drug Administration National Pharmacovigilance Database

Elie Kaplan-Marans, MD, Arshia Sandozi, DO, MPH, Mariela Martinez, MD, Jeffrey Lee, MD, Ariel Schulman, MD, and Jacob Khurgin, DO

ABSTRACT

Background: Erectile dysfunction (ED) is an adverse effect of many medications.

Aim: We used a national pharmacovigilance database to assess which medications had the highest reported frequency of ED.

Methods: The Food and Drug Administration Adverse Event Reporting System (FAERS) was queried to identify medications with the highest frequency of ED adverse event reports from 2010 to 2020. Phosphodiesterase-5 inhibitors and testosterone were excluded because these medications are often used as treatments for men with ED. The 20 medications with the highest frequency of ED were included in the disproportionality analysis.

Outcomes: Proportional Reporting Ratios (PRRs) and their 95% confidence intervals were calculated.

Results: The 20 medications accounted for 6,142 reports of ED. 5-α reductase inhibitors (5-ARIs) and neuropsychiatric medications accounted for 2,823 (46%) and 2,442 (40%) of these reports respectively. Seven medications showed significant levels of disproportionate reporting with finasteride and dutasteride having the highest PRRs: 110.03 (103.14−117.39) and 9.40 (7.83−11.05) respectively. The other medications are used in a wide variety of medical fields such as cardiology, dermatology, and immunology.

Clinical Implications: Physicians should be familiar with these medications and understand their respective mechanisms of action, so that they may counsel patients appropriately and improve their quality of life.

Strengths and Limitations: The strength of the study is its large sample size and that it captures pharmacologic trends on a national level. Quantitative and comparative "real-world" data is lacking for the most common medications associated with ED. The limitation is that the number of reported events does not establish causality and cannot be used to calculate ED incidence rates.

Conclusion: In a national pharmacovigilance database, 5-ARIs and neuropsychiatric medications had the highest reports of ED adverse effects. There were many other medications used in a variety of medical fields that were also associated with ED. **Kaplan-Marans E, Sandozi A, Martinez M, et al. Medications Most Commonly Associated With Erectile Dysfunction: Evaluation of the Food and Drug Administration National Pharmacovigilance Database. Sex Med 2022;10:100543.**

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Key Words: Erectile Dysfunction; Medications; Side Effects; Sexual Function

INTRODUCTION

Erectile dysfunction (ED) is described in the annals of history as early as 2000 BCE on Egyptian papyrus.[1] Despite advances in modern medicine, ED continues to plague men across all cultures and regions of the world. Incidence increases with age; in men over 70 years old, prevalence is estimated at 50−100%.[2,3] By the year 2025, the worldwide prevalence of ED is predicted to be 322 million.[2,3]

Received March 2, 2022. Accepted May 29, 2022.

Division of Urology, Maimonides Medical Center, New York, NY, USA

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https://doi.org/10.1016/j.esxm.2022.100543

$$PRR = \frac{\text{Number of ED Adverse Events for Medication "X"}}{\text{Number of Total Adverse Events for Medication "X"}} \div \frac{\text{Number of ED Adverse Events for the Other 19 Medications}}{\text{Number of Total Adverse Events for the Other 19 Medications}}$$

Figure 1. Proportional reporting ratio formula.

The etiology of ED can be classified as organic or psychogenic. In an age when about 60% of the population reports prescription drug use in a given year, medication-induced ED is an important organic cause of ED.[4] It is estimated that up to 25% of all ED is related to medication use and may be reversible.[5] It is incumbent on physicians to be familiar with these medications. However, quantitative and comparative data is lacking for the most common medications associated with ED because many of these medications are from different drug classes and have varying indications and mechanisms of action (MOA).

We, therefore, asked: Which medications had the highest reported frequency of ED in the Food and Drug Administration's (FDA) pharmacovigilance database? We also examined the literature on the association of these medications with ED and reviewed the respective mechanisms of action. This article is intended to aid physicians from all specialties in identifying medication-induced ED with the goal of improving patient outcomes.

METHODS

The FDA Adverse Event Reporting System (FAERS) contains both voluntary and mandatory medication adverse event reports submitted to the FDA. Voluntary reports are submitted by healthcare professionals, consumers (including patients, family members, and lawyers), and manufacturers. Mandatory reports are from manufacturers who are required by regulations to send a report to the FDA if they receive a report from a healthcare professional or consumer. The database is designed for post-marketing safety surveillance of products that have already been approved by the FDA. The database is unique in that it offers pharmaceutical insight on the national level. However, the reported events do not prove a causal relationship and the database is limited by the potential for significant under-reporting. Importantly, the database is not designed to calculate adverse event rates.[6]

FAERS was queried to identify the 20 medications with the highest frequency of ED adverse event reports from 2010 to 2020. Phosphodiesterase-5 inhibitors and testosterone were excluded because these medications are often used as treatments for men with ED. Proportional Reporting Ratios (PRRs) and their 95% confidence intervals were calculated. PRR was defined as the ratio between the frequency of ED for a medication relative to all adverse events for that medication divided by the frequency of ED for the other 19 medications relative to all adverse events for those medications (Figure 1). The disproportionality analysis was limited to the top 20 drugs for the practicality of statistical analysis. The number 20 was chosen arbitrarily but it is notable that by the 20th medication, the number of ED reports dropped from 2,650 (finasteride) to 123 (aripiprazole).

The study was exempt from institutional review board ethics approval due to the anonymously coded design of the FAERS database. The patient de-identified FAERS data were exported to Microsoft Excel for Mac, version 16.54, which was also used for statistical analysis.

RESULTS

The top 20 medications accounted for 6,142 reports of ED. 5-α reductase inhibitors (5-ARIs) and neuropsychiatric medications accounted for 2,823 (46%) and 2,442 (40%) of these reports respectively (Figure 2). The other medications are used in a wide variety of medical fields such as cardiology (553 reports, 9%), dermatology (181 reports, 3%), and immunology (143 reports, 2%). Seven medications showed significant levels of disproportionate reporting with finasteride and dutasteride having the highest PRRs: 110.03 (103.14−117.39) and 9.40 (7.83−11.05) respectively (Table 1).

Age was specified in 49% of reports. Of these reports, 62 (1%) were between 12 and 17 years old, 2,629 (43%) were between ages 18 and 64 years, 289 (5%) were between ages 65 and 85 years old, and only 6 (0.1%) were older than 85 years old. There were 4 reports for patients less than 11 years old. A reporting source was specified in 89% of reports. There were

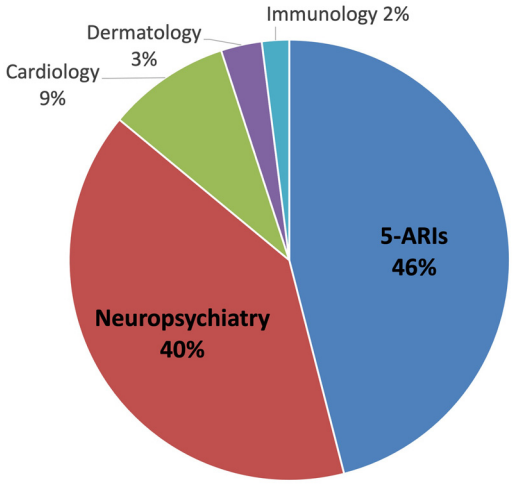

Figure 2. Percentage of ED adverse event reports by medication class.

Table 1. Medical specialty and PRR of medications with the highest frequency of ED adverse event reports.

Medication	Medical Specialty	Class	Mechanism of Action	Number of ED Reports	PRR
Finasteride	Urology	BPH	5-ARI	2,650	**110.03 (103.14-117.39)**
Dutasteride	Urology	BPH	5-ARI	173	**9.40 (7.83-11.05)**
Amlodipine	Cardiology	Antihypertensive	Calcium channel blocker	253	**1.99 (1.71-2.30)**
Paliperidone	Neuropsychiatry	Antipsychotic	Dopamine and serotonin receptor antagonism	190	**1.75 (1.46-2.05)**
Citalopram	Neuropsychiatry	Antidepressant	SSRI	236	**1.59 (1.36-1.84)**
Sertraline	Neuropsychiatry	Antidepressant	SSRI	318	**1.30 (1.13-1.48)**
Isotretinoin	Dermatology	Acne	Retinoid	181	**1.24 (1.03-1.45)**
Escitalopram	Neuropsychiatry	Antidepressant	SSRI	141	1.22 (0.99-1.46)
Quetiapine	Neuropsychiatry	Antipsychotic	Dopamine and serotonin receptor antagonism	211	1.01 (0.85-1.17)
Simvastatin	Cardiology	Antihyperlipidemic	HMG-CoA reductase inhibitors	152	0.99 (0.82-1.18)
Olanzapine	Neuropsychiatry	Antipsychotic	Serotonin, dopamine, histamine, and α-adrenergic receptor antagonism	169	0.93 (0.77-1.10)
Fluoxetine	Neuropsychiatry	SSRI	Inhibits re-uptake of serotonin	123	0.93 (0.74-1.12)
Venlafaxine	Neuropsychiatry	SNRI	Inhibits re-uptake of serotonin and norepinephrine	193	0.91 (0.76-1.07)
Risperidone	Neuropsychiatry	Antipsychotic	Serotonin, dopamine, histamine, and α-adrenergic receptor antagonism	282	0.81 (0.70-0.93)
Atorvastatin	Cardiology	Antihyperlipidemic	HMG-CoA reductase inhibitors	148	0.52 (0.42-0.61)
Aripiprazole	Neuropsychiatry	Antipsychotic	Serotonin, dopamine, histamine, and α-adrenergic receptor antagonism	123	0.45 (0.36-0.55)
Gabapentin	Neuropsychiatry	Antiepileptic	Binds to voltage-gated calcium channels in central nervous system	139	0.43 (0.35-0.51)
Pregabalin	Neuropsychiatry	Antiepileptic	Binds to voltage-gated calcium channels in central nervous system	192	0.33 (0.28-0.39)
Oxycodone	Neuropsychiatry	Pain Reliever	μ opioid receptor agonist	125	0.32 (0.26-0.38)
Adalimumab	Immunology	Disease-modifying antirheumatic drug	TNF-α blocker	143	0.04 (0.04-0.05)

2,526 (41%) reports from healthcare professionals and 2,977 (48%) reports from consumers. The remaining 11% of reports did not specify reporter type.

DISCUSSION

In this study, 5-α reductase inhibitors (5-ARIs) and neuropsychiatric medications accounted for 2,823 (46%) and 2,442 (40%) of ED reports respectively. These results show the potential influence these medications may have on erectile function. The statistically significant elevated PRRs of these drugs are listed in Table 1. The other medications that are used in cardiology (553 reports, 9%), dermatology (181 reports, 3%), and immunology (143 reports, 2%), highlight the need for physicians from all specialties of medicine to be familiar with medication-induced ED.

5-α Reductase Inhibitors

5-ARIs accounted for 2,823 (46%) of ED reports. Finasteride and dutasteride had the highest PRRs of the medications analyzed: 110.03 (103.14−117.39) and 9.40 (7.83−11.05) respectively. This data is consistent with the medical literature linking 5-ARIs to ED.

Finasteride and dutasteride work by irreversibly binding to 5-α reductase, thereby preventing the conversion of testosterone to dihydrotestosterone (DHT). Finasteride binds to type II 5-α reductase which is found mostly in the prostate and genital tract. Dutasteride binds to both type I (found mostly in extraprostatic tissues) and type II 5-α reductase.[7] DHT is vital for physiologic erections as it activates nitric oxide synthase and increases blood flow in cavernosal tissue. Zhang et al randomly assigned rats to treatment or no treatment groups, and showed that long-term oral 5-ARI treatment is associated with ED. They propose that 5-ARIs lead to decreased autophagy and increased apoptosis in the cavernous smooth muscle cells.[8] Similarly, in a double-blind randomized placebo-controlled study, Gormley et al found that patients on finasteride were statistically more likely to have a loss of libido, ejaculatory disorder, and ED.[9]

In addition, the highly disproportionate PRR of 5-ARIs in our study may be supportive of the controversial Post-finasteride Syndrome (PFS). PFS is a constellation of sexual, physical, and neurologic symptoms associated with 5-ARIs that may persist after discontinuation of the drug.[7,9−15] Traish et al provide a thorough review of the medical literature regarding PFS. They argue that 5-ARIs lead to steroidogenic inhibition which can have profound systemic effects such as: loss of libido, ED, ejaculatory disorders, gynecomastia, muscle atrophy, fatigue, depression, anxiety, cognitive impairment, and suicidal ideation.[10,16] While the highly disproportionate PRR of 5-ARIs is noteworthy and warrants further investigation, our dataset does not include medication start and end dates, so it is not powered to assess for PFS.

At this time, the literature on PFS is limited by low-quality evidence. The question remains: is PFS a chance occurrence of symptoms in a subset of men who suffer from lower urinary tract symptoms and/or hair loss, or is it a true syndrome yet to be proven because of a paucity of data? Given the impact 5-ARIs may have on patients' quality of life, some have suggested the burden is on physicians to discount PFS only with overwhelming evidence.[17] In either case, the data from our study points to a strong correlation between ED and 5-ARIs.

Neuropsychiatry

Neuropsychiatric medications accounted for 2,442 (40%) of ED reports. The antipsychotic paliperidone and the selective serotonin reuptake inhibitors (SSRIs) citalopram and sertraline were found to have elevated PRRs. In addition, there were many neuropsychiatric medications with high frequencies of ED including escitalopram, quetiapine, olanzapine, fluoxetine, venlafaxine, risperidone, aripiprazole, gabapentin, pregabalin, and oxycodone (Table 1).

Neuropsychiatric medication-induced ED is a well-described phenomenon. Patients who discontinue these medications because of adverse effects can experience detrimental psychiatric outcomes.[4] Neuropsychiatric medications have a variety of adverse effects due to the multiple receptors targeted throughout the body. These receptors include central and peripheral serotonergic, adrenergic, dopaminergic, cholinergic, histaminergic, and melanocortin receptors.[4]

Antipsychotics inhibit dopamine receptors with varying potency, which results in both direct and indirect inhibition of erections. Dopamine is known to play an important role in emotional sexual behavior and may also directly facilitate erections.[18] Antipsychotics can cause hyperprolactinemia by inhibiting D_2 receptors in the tuberoinfundibular system. This leads to decreased gonadotropin production and secondary hypogonadism.[4] In a non−randomized survey of male patients on antipsychotics for schizophrenia, sexual dysfunction ranged from 40 to 71%.[19]

The different antipsychotics affect various receptors and this may have varying side effects. For example, the antipsychotics that block α_1-adrenergic receptors may cause retrograde ejaculation but not erectile dysfunction.[20] Sexual function is comprised of many elements; libido and ejaculatory function are important sexual processes that are distinct from erectile function. It is possible patients and even providers confused ejaculatory function, for example, with erectile function, which may have confounded the reporting of ED in this database. This highlights the importance of educating both providers and patients on the different facets of sexual function and how they relate to one another.

SSRIs block presynaptic serotonin reuptake, thereby increasing serotonin levels and producing effects on various 5-HT receptors. In rodents, binding of 5-HT_{1A} and 5-HT_{1B} receptors has been shown to inhibit erections while binding of 5-HT_{2C} receptors has been shown to stimulate erections.[21] It follows that SSRIs will have different selectivity for these receptors and affect sexual function differently. Mirtazapine may avoid the sexual dysfunction present with other SSRIs and trazadone is known to cause priapism, which has been postulated to be due to 5-HT_{1C} upregulation.[1] In a study by Rosen et al, up to 58% of patients on SSRIs reported sexual dysfunction.[22]

Gabapentin, pregabalin, and oxycodone also had a high number of reported ED adverse effects. Together with other antiepileptic medications, gabapentin and pregabalin have been reported to cause ED and sexual dysfunction. Though the mechanism is unclear, sexual dysfunction may be due to increased sex hormone binding globulin and decreased free testosterone. Another potential mechanism is decreased sexual stimulation due to GABAergic inhibition.[23]

Oxycodone is a μ opioid receptor agonist that inhibits ascending pain pathways and has also been shown to be associated with ED. Opioids likely disrupt the hypothalamic-pituitary-gonadal axis by binding to μ receptors in the hypothalamus thereby causing negative feedback. Less gonadotropin-releasing hormone is produced, leading to decreased gonadotropins and subsequent secondary hypogonadism.[24]

Of note, benzodiazepines are not listed in Table 1 but they may cause sexual dysfunction from potentiation of GABA in the reticular and limbic system and by affecting the serotonin and dopaminergic pathways.[1] Due to the prevalence of neuropsychiatric medications, it is imperative that urologists be familiar with their association with ED as well as understand the underlying mechanisms of action.

Cardiology

Cardiological medications accounted for 553 (9%) of all ED reports. Interestingly, amlodipine, simvastatin, and atorvastatin were the medications cited most frequently, although in the literature these medications are not as strongly associated with ED as other cardiologic medications.[25,26]

ß-blockers have been shown to be associated with ED, likely secondary to suppression of central nervous system sympathetic outflow. Non−cardioselective ß-antagonists like propranolol have a higher incidence of ED than cardioselective ß-antagonists which avoid $ß_2$ inhibition resulting in vasoconstriction of the corpora cavernosa.[4] Nebivolol has the greatest selectivity for $ß_1$ receptors as well as endothelial nitric oxide vasodilatory effects, and has been shown to have a positive effect on erections. In a double-blind randomized comparison of metoprolol and nebivolol, metoprolol decreased erectile scores after 8 weeks but nebivolol improved them.[27]

The mechanism of thiazide (diuretic)-induced ED is still unknown. In 1 large study, men taking thiazides were twice as likely to report ED than men taking propranolol or a placebo.[28] In contrast, there is less evidence that loop diuretics such as furosemide cause ED, which should be considered by physicians treating hypertensive men.[4]

In our study, amlodipine had a significant PRR. This is in contrast to studies that have shown no association between calcium channel blockers and ED.[26] However, there is data suggesting ejaculatory dysfunction with calcium channel blockers (from decreased bulbocavernosus muscle force) so it is possible that this phenomenon was inaccurately captured in the database as ED rather than ejaculatory dysfunction.[1,29] It is also possible that men with hypertension are inherently more likely to have arteriogenic ED or that polypharmacy acts as a confounding factor.[30]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are common antihypertensives that may actually improve erectile function. ACE inhibitors prevent the formation of angiotensin II while ARBs block the peripheral vasoconstriction caused by angiotensin II. Without angiotensin IIs effects, there is less penile vasoconstriction and collagen remodeling of the corpora cavernosa.[31] In most studies, ACE inhibitors and ARBs have not been associated with ED and some studies even showed a beneficial effect.[32,33] Notably, ß-blockers, diuretics, ACE inhibitors, and ARBs were absent in our list of the top 20 medications with ED adverse event reports.

Finally, in the FAERS dataset, statins were listed as frequently associated with ED, however, the PRR was low. The literature on the association of statins with ED is mixed. Statins lower cholesterol by inhibiting HMG-CoA reductase, a rate-limiting step in cholesterol synthesis. It is possible that men with hyperlipidemia have ED because of their underlying arterial disease and not necessarily from statins. One meta-analysis found that statins may improve ED vs placebo.[25] As seen above, there are many types of widely used cardiological medications, and some of these medications have significant associations with ED while others may be beneficial.

Dermatology and Immunology

Isotretinoin is a sebum suppressive medication used for acne.[34] Isotretinoin accounted for 181 reports of ED and had a significant PRR of 1.24 (1.03−1.45). The literature on isotretinoin-induced ED is limited to case reports. Healy et al describe 54 cases of sexual dysfunction associated with isotretinoin that were reported on a global adverse event reporting website. Coleman et al reported on over 150 cases received by the drug manufacturer. However, the quality of evidence is extremely limited and mechanisms do not appear to be well-described in the literature.[35,36] It is possible that acne is related to depression, which is a known risk factor for ED.[37]

Adalimumab accounted for 143 reports of ED and did not have a high PRR: 0.04 (0.04−0.05). Adalimumab is a tumor necrosis factor (TNF) α blocker. ED is not widely reported from TNF-α blockers. In fact, increasing levels of TNF have been correlated with worsening ED, and in 1 open-label study without a placebo, men on TNF-α blockers for ankylosing spondylitis reported significantly higher erectile scores after 3 months. Further research may elucidate the role of TNF α in the pathophysiology of erectile dysfunction.[38,39]

Strengths and Limitations

The strength of the study is its large sample size that captures pharmacologic trends on a national level. Quantitative and comparative "real-world" data is lacking for the most common medications associated with ED and this study may help physicians better understand medication-induced ED.

This study has a number of limitations. Most importantly, the number of reported events does not establish causality and cannot be used to calculate ED incidence rates. The database is vulnerable to significant under-reporting since it includes both

voluntary and mandatory medication adverse event reports. Moreover, medications that are prescribed more frequently are also likely to have more adverse event reports; however, the PRR accounts for this discrepancy because it is the proportion of ED adverse events relative to total adverse events.

Some common medications known to cause ED such as ß-blockers and androgen deprivation therapy (ADT) medications, fall lower on the frequency list than the top 20 medications included in this study. Perhaps physicians counsel patients on the association of these medications with ED and so patients are less likely to report their side effects to this database. It is also possible that these patients represent an older demographic that are less technologically savvy and less likely to submit electronic reports.

Another limitation is that the source of the prescription is unknown. It is possible that many of these medications were obtained online or through the black market without a prescription.[40,41] If that is the case, the quality and authenticity of these medications are in question. Patients may also have incorrectly self-treated themselves and falsely associated side effects to certain medications. Finally, the reports do not contain granular patient information such as exact age, co-morbidities, dosage and duration of medications, degree of ED, and whether ED resolved with medication discontinuation.

Strategies for the Future

When evaluating for ED, the American Urological Association (AUA) recommends not only evaluating a patient's medications but also eliciting a thorough medical, sexual, and psychosocial history.[42] Unfortunately, most physicians do not even broach the topic of sex.[43] This paper highlights the variety of medications that are associated with ED and the importance of physicians from all specialties to be familiar with their respective mechanisms of action. Table 1 shows the PRRs of medications with the highest frequency of ED adverse event reports and highlights their associated medical specialty. Future work should focus on educating all types of physicians on taking a sexual history and identifying medication-induced ED.

CONCLUSION

Medication-induced ED is widely prevalent and is caused by medications from a variety of medical fields. In a national pharmacovigilance database, 5-ARIs and neuropsychiatric medications had the highest reports of ED adverse effects. Physicians of all specialties should be familiar with these medications and understand their respective mechanisms of action, so that they may counsel patients appropriately and improve their quality of life.

Corresponding Author: Elie Kaplan-Marans, MD, Division of Urology, Maimonides Medical Center, 745 64th Street, 4th Floor, New York, NY 11220, USA. Tel: 718-283-6903; Fax: 831-208-2146; E-mail: Ekaplan@maimonidesmed.org

Conflict of Interest: The authors report no conflicts of interest.

Funding: None.

STATEMENT OF AUTHORSHIP

Conceptualization, E.K.M, A.Sc.; Methodology, E.K.M, A. Sa., M.M. and J.L.; Formal Analysis, E.K.M.; Investigation, E. K.M, A.Sa., M.M., and J.L.; Writing – Original Draft, E.K.M.; Writing – Review & Editing, E.K.M., A.Sc. and J.K.

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