

Case Report

Drug-Induced Erectile Dysfunction: Two Interesting Cases

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Abstract

Erectile dysfunction (ED) is the inability to achieve or maintain an erection that is required for satisfactory sexual performance, and affects a considerable proportion of men around the globe at least occasionally. Although roles for nonendocrine and endocrine pathways have been proposed, presence of comorbidities, psychogenic factors may contribute to its development. Large number of published reports link many commonly prescribed drugs with sexual dysfunction. Many common drugs such as anti-hypertensive, anti-psychotic, and anti-histaminic are linked with iatrogenic ED. On the other hand, psychogenic ED may be wrongly perceived to be of iatrogenic origin. While dealing a subject with ED it is important for the clinicians to take a detailed medical, surgical, sexual and drug/substance abuse history. In this article, we have described two such cases which would reflect the importance of determining the cause of ED before initiating treatment.

Keywords: Diabetes, erectile dysfunction, pharmacovigilance

INTRODUCTION

Erectile dysfunction (ED) is defined as unsatisfactory sexual performances due to consistent or recurrent inability to attain and/or maintain penile erection.^[1] More than 150 million men are estimated to be affected by ED worldwide.^[2] Sexuality remains a uniquely complex aspect of human life and experiences. The normal sexual function requires intactness in anatomical, physiological, and psychological capacities. When an individual presents with complaints pertaining to ED, it is important to emphasize eliciting medication history besides considering psychological, endocrine, cardiovascular, and metabolic health for understanding its etiology. Drug-induced ED, a common reversible disease entity, remains an important differential diagnosis, and must be always considered during work up of all individuals presenting with a history of ED. Early diagnosis and rational de-prescribing can reverse the pathology.

THE CASES

Case 1

A 40-year-old diabetic (informed consent obtained)(poorly controlled), hypertensive, and smoker was admitted to a tertiary care hospital for coronary artery bypass graft operation on April 22, 2021. He also presented with symptoms of ED. He had a maternal history of premature cardiovascular death.

He was on sitagliptin-metformin fixed-dose combination and telmisartan. He was also suffering from dyslipidemia for which he was taking atorvastatin for the past 1 year. But for the last 6 months, he stopped consuming atorvastatin as internet search suggested him that statin can cause ED. On examination, his International Index of Erectile Function (IIEF-5) score was found to be 10. Postcoronary artery bypass grafting (CABG) he was prescribed aspirin 75 mg, clopidogrel 75 mg, atorvastatin 40 mg, perindopril 8 mg and insulin therapy to achieve target HbA1c. Almost 3 months after CABG, with improved glycemic control and cessation of smoking the patient reported at outpatient department (OPD) on August 02, 2021, with improved erectile function, and his IIEF-5 score was assessed to be 23. No precise therapy for his ED was given throughout this whole period.

Case 2

A 29-year-old male patient, after taking informed consent was referred from dermatology OPD to clinical pharmacology

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OPD for medication reconciliation and possible iatrogenic ED on August 06, 2021. He was suffering from chronic urticaria and migraine. For urticaria, he was Prescribed clemastine 10 mg once daily for the last 3 months by the dermatologist and cyproheptadine 4mg twice daily which he got as over the counter drug for the last 1 month for his anorexia. He was also on amitriptyline 25 mg once daily and pantoprazole-domperidone fixed-dose combination for the last 6 months. On presentation and assessment, his IIEF-5 score was 9, suggestive of moderate ED. On clinical pharmacology consultation, cyproheptadine, clemastine, amitriptyline, and fixed-dose combination of pantoprazole-domperidone were de-prescribed. The patient was prescribed with bilastine 20 mg once daily for urticaria and flunarizine 10 mg once daily for migraine prophylaxis. Antacid syrups were asked to be taken on SOS basis. The patient revisited after 1½ months on September 17, 2021 with no further symptoms. IIEF-5 score was improved as it was found to be 22. Like the first case, apart from de-prescribing some of the drugs which we thought to be unnecessary and probably causing the ED, we did not prescribe any particular drug for his ED. The patient was young adult and not having any comorbidity and responded to our consultation very well.

Pharmacovigilance workup done to assess the causality which turned out to be “probable” for the second case using WHO-UMC Causality Assessment Scale and Naranjo’s algorithm (Score 7). Severity assessment using Hartwig-Seigel’s Scale conferred it to be a “moderate” one with Level 3. As for the first case, no such causality was established between the suspected drug and the onset of ED.

DISCUSSION

A few important biochemical mediators play an extremely important role in erectile function. The balance between contracting and relaxing biochemical factors governs the controls in the penile vessels and the smooth muscle of the corpora cavernosa. The degree of tone of the penile vasculature and the smooth muscle is mediated via respective biochemical mediators. Relaxant mediators such as acetyl choline, dopamine, adenosine triphosphate, adenosine, CGRP, prostanoids (PGE_1), vasoactive intestinal polypeptide, adrenomedullin, and endocannabinoids help in tumescence and erection and contracting biochemicals such as noradrenalin, angiotensin II, endothelin, serotonin, prostanoids ($\text{PGF}_{2\alpha}$, TxA_2), and TNF alpha cause detumescence and flaccidity. The functional state of the penis is determined by the balances in these mediators. Drugs influencing these mediators can lead to ED.^[3]

The autonomic nervous system function is extremely important for erection. Parasympathetic nervous system activity helps in sustaining and maintaining an erection through M_3 type cholinergic receptor and sympathetic nervous system stimulates to produce ejaculation and de-tumescence through α_1 type adrenergic receptor. Autonomic dysfunction

can cause ED. Drugs like beta-blockers (nonselective), α -blockers, anticholinergic drugs affecting adrenergic and cholinergic system could be responsible for ED.

In our first case, we found that the availability and consumption of false health information had caused atrocity in patient’s life. The subject wrongly perceived that the use of lipid-lowering drugs (statin) was the root cause of his ED. He had stopped taking this important medicine after going through some wrongly depicted health information over the internet. Sexual health is often neglected area in clinical practice and is one of the least discussed topics. In this case, if the patient had asked his doctor regarding the association of statin and ED, it could prevent this adverse cardiovascular event. It was probably the presence of diabetes-related autonomic neuropathy and hypertension that could be the factors leading up to the development of sexual dysfunction in this subject who was a smoker which itself is a risk factor for ED. No evidence is suggesting that statins can cause ED. If we go through the results of 2 meta-analyses of double-blind randomized controlled trials, one on studies that evaluated statins for management of ED and the other was on including any study with ED as an outcome measure, found no evidence that statins can cause ED. These two meta-analyses had suggested that a significant improvement compared with placebo in erectile function.^[4] Dissemination of the right information is extremely important and we need to be very careful in this regard. De-challenging wrong drugs can precipitate unwanted adverse outcome. In the second case, we found that patient was taking clemastine and amitriptyline which have high anticholinergic burden (anticholinergic burden score is 3 for each). If any prescription contains drugs which have a summative score of 3 or more that need to be reconciled to reduce anticholinergic burden. The use of domperidone in this patient can block the dopaminergic activity along with increase in prolactin value. Indiscriminate intake of domperidone can cause sexual problem in men^[5]. Rational de-challenging of amitriptyline, domperidone and clemastine was beneficial for this patient and his erectile function was improved after prescription reconciliation at clinical pharmacology OPD.

The etiology of ED is psycho-vasculo-neuro-hormono-iatrogenic. Most of the causes of ED are modifiable causes. Iatrogenic causes mainly are drug-induced ED. A few drugs which can cause ED are anti-hypertensives such as diuretics (thiazide, spironolactone); sympatholytics (methyldopa, clonidine) and beta-blocker (propranolol). Beta₁ selective blockers are not commonly affecting erectile function. Nebivolol, a nitric oxide donating beta₁ selective blocker is ameliorating ED and can be continued. Other drugs which cause erectile functional abnormalities are antidepressants such as SSRIs, Venlafaxine, and TCA; antipsychotics; H_2 blockers (cimetidine) ranitidine, famotidine); anti-epileptics (valproate and carbamazepine); mood stabilizer – lithium; 5-alpha reductase inhibitors (finasteride and dutasteride) and methadone.^[6] The other drugs are anti-epileptics, antihistaminics, and lipid-lowering drugs like

fenofibrate. When we suspect any drug-induced disorder, we have to establish causality. Four important area need to be evaluated for detection of causality and these are temporal relationship (event occurs after initiation of drug), pharmacological plausibility (pharmacodynamics suggest the possibility of reaction and presence of prior evidence), de-challenge (after withdrawing drug symptoms disappear), and re-challenge (after reintroduction of drug symptoms reappear). Two important scoring systems for causality assessment are Naranjo scale and WHO-UMC scale. In some cases, psychogenic causes are majorly responsible for ED in otherwise healthy young adults.^[7] It has been observed that several psychological factors influence ED through independent mechanisms and should be considered separately from medical causes.^[8] Hence, there is a possibility of false-positive response to de-challenge and re-challenge. To establish causality we can use double-blind placebo-controlled drug challenge. This may omit the false-positive response to re-challenge and reduce the chance of de-prescribing a non culprit drug.

CONCLUSION

Drug is an important etiology to cause disturbance of erectile function. Early identification and de-prescribing of the culprit drug can reverse the condition and save unnecessary costly work up for the patient. We need to be judicious and establish causality before omitting such medicine. Otherwise, de-prescribing of the nonculprit drug can be detrimental for the patient. We also have to disseminate right information to the patient for prevention of unnecessary poor adherence-related atrocities due to wrong facts present in the internet. Today all the causes of ED can be managed and hence ED is a correctable if we find the underlying cause at the earliest.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his/her consent for images and other clinical information to be reported in the journal. The patient understands that his/her name and initials will not be published and due efforts will be made to conceal his/her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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