Talk to patients about medicine sexual side-effects: they are more common than you think

Gordijn R, Wessels W, Kriek E, et al.
Patient reporting of sexual adverse events on an online platform for medication experiences. Br J Clin Pharmacol. 2022. doi: 10.1111/bcp.15454 [Epub ahead of print].

Summary
More than 300 drugs are known to negatively affect sexual function. The researchers considered that sexual adverse events (sAE) may be more easily shared via online medication platforms, and patient-reported drug experiences might provide helpful information. This study evaluated patient reports from the online platform mijnmedicijn.nl for the frequency of sAE reporting, gender differences concerning sAE, and to assess and identify drugs with disproportional sAE reporting.

The researchers from the Netherlands searched patient reports of sAE for drug experiences. Users of mijnmedicijn.nl can share their experiences in a drug report, together with additional information such as their age, gender, drug and drug brand. Terms for sAE as used by patients were collected with a poll. The drug reports posted between 2008 and 2020 were then searched for sAE with the identified terms, and from these reports sAE frequencies and complaints were retrieved and reporting odds ratios (ROR) were calculated, stratified for gender and drug (class). sAE reporting was considered disproportional if the lower bound of the 95% confidence interval (CI) ROR was above 2.0. The results showed that for 189 drugs, sAE were identified in 2408 reports (3.9%). Women posted 1383 reports (3.5% of all female reports) and men 1025 (4.7%). Almost half of the sAE reports addressed antidepressants: 586 reports of women (ROR 4.2; 95% CI 3.8–4.7) and 510 reports of men (ROR 7.5; 95% CI 6.6–8.5). Disproportionally high numbers of sAE reports were found for 27 drugs – mostly antidepressants, hormonal contraceptives and drugs used in benign prostatic hyperplasia. Of these drugs with frequent sAE, 7 had low sAE risks in their professional drug information.

Messages for the clinic
This study demonstrates an important disparity between what we are told about the risk of sexual dysfunction with medications and what patients experience, because sexual side-effects are mentioned in only 4% of the patient-reported drug experiences at mijnmedicijn.nl, mostly for antidepressants.

Men reported notably more sexual side-effects for cardiovascular drugs than women and showed more diversity in the type of sexual side-effects reported. Illnesses such as depression, diabetes and hypertension already carry a burden of sexual dysfunction and it appears that some treatments can compound the problem. This is because the physiology of sexual function depends on the healthy function of the endocrine system, the nervous system, endothelial function and smooth muscle tone.

Common culprits for producing sAE are medications for the nervous system (105 drugs; 30%) and the cardiovascular system (89 drugs; 26%), closely followed by drugs that target the genitourinary system and sex hormones such as oral contraceptives, which were a particular problem for women.

Women reporting sAE were mostly 20–29 years old (n=506), whereas men who reported sAE were mostly 40–49 years old (n=244). Uncertainty about the association with the specific drugs was mentioned by fewer women (n=32; 2.3% of reports with sAE) than men (n=45; 4.4% of reports with sAE).

Men mentioned sAE with antidepressants relatively more often than women – venlafaxine in 22% of the reports by men (n=102) and in 10% of the reports from women (n=101). The most notable gender difference was found for cardiovascular drugs, with 152 reports with sAE posted by men and 26 reports by women. The authors point to three studies that showed higher odds ratios for men than for women of statin-associated decreased libido and SSRI-associated loss of libido and sexual dysfunction.¹ In a meta-analysis of SSRI-associated sAE, men also showed significant higher incidences of desire and orgasm dysfunction, although women reported more arousal dysfunction.² SSRIs are expected to induce some degree of genital numbness in all users,³ so it is unclear why men reported higher
percentages of SSRI-associated sexual complaints.

Not surprisingly, within drug class there was a disproportional signal attributed to the aromatase inhibitors (anastrozole) and gonadotrophin-releasing hormone (GnRH) analogues. The highest proportion of sAE was found for drugs used in BPH, with 30% of the reports including at least one sAE (ROR 9.6; 95% CI 7.7–12.0). The most commonly reported sAE type concerned a change in desire, which was mentioned in 427 reports by men (41.7%). Most of the commonly, desire-related changes were described with ‘libido’, a term used in 325 reports from men (31.7%). Besides changes in desire, men also reported changes in erectile function (n=346; 33.8%), ejaculation (n=108; 10.5%) and arousal (n=21; 2.0%). Alpha blockers cause retrograde ejaculation, 5-alpha-reductase inhibitors (5ARIs) cause lack of desire and erectile dysfunction. Combination therapy with alpha blockers and 5ARI triples the risk for ejaculatory dysfunction incidence compared with that of alpha blockers or 5ARI used individually. The phosphodiesterase-5 inhibitor tadalafil is an alternative to established drugs for lower urinary tract symptoms (LUTS), such as the aforementioned alpha blockers or 5ARIs. However, it is not just an alternative, since sexual adverse events associated with alpha blockers and 5ARIs are avoided; tadalafil is the only drug that can treat both erectile dysfunction and LUTS simultaneously.\(^4\) Other disproportionately high numbers of reports with sAE from men were lisinopril and diuretics (ROR 6.2; 95% CI 2.0–19.2).

Clearly from these data we need to warn our patients at initiation about possible sexual side-effects as many will already have underlying problems. We need to enquire about these effects at follow-up and be prepared to change the dosage or the product, or add in or replace it with a daily PDE5i to counteract the drug effect, which may be helpful in many of the offending drug classes discussed.

References
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First oral GnRH receptor antagonist for advanced hormone-sensitive prostate cancer approved in Europe

Sahu KK, Tripathi N, Agarwal N, Swami U. Relugolix in the management of prostate cancer. Expert Rev Anticancer Ther 2022. doi: 10.1080/14772560.2022.2105209 [Epub ahead of print].

Summary
Relugolix is the first oral gonadotrophin-releasing hormone (GnRH) receptor antagonist. On 29 April 2022, the European Commission approved the marketing authorisation application for Orgovyx (relugolix, 120mg) for the treatment of adult patients with advanced hormone-sensitive prostate cancer. The decision applies to all 27 European Union member states. The marketing authorisation application for Orgovyx is pending review by the UK Medicines and Healthcare Products Regulatory Agency (MHRA). The product will be available in Europe in the second half of 2022.

Based on the phase 3 HERO trial results, relugolix received Food and Drug Administration (FDA) approval for adult patients with advanced prostate cancer. The authors provide an overview of the preclinical and clinical development of relugolix and its role in the current treatment landscape of prostate cancer. They point out that relugolix leads to rapid inhibition of testicular production of testosterone and provides a rapid recovery upon its discontinuation. In the HERO trial, relugolix was associated with a superior cardiovascular safety profile compared with GnRH agonists. The authors point out that it is therefore a promising therapy for patients with pre-existing cardiovascular comorbidities, those pursuing intermittent androgen deprivation therapy (ADT), and those who desire rapid testosterone recovery during ‘off-treatment’ periods. It is important to note that in the HERO trial, very few patients received concomitant enzalutamide (n=17; 2.7%) or docetaxel (n<10; 1.3%). Relugolix is an oral drug as opposed to degarelix, which is an injection, and there may be challenges related to NHS cost, patient adherence and compliance with an oral medication in this predominantly elderly population.

Messages for the clinic
When available, finding a place for relugolix as a form of ADT in the therapeutic armamentarium for patients with prostate cancer will be a challenge. But as neoadjuvant and adjuvant treatment to support radiotherapy there is clearly a role as this approach has been shown to increase survival.

Certainly, there will be a place for a drug with enhanced cardiovascular (CV) safety compared with standard
ADT, because many patients will be elderly and have CV comorbidities and diabetes. Screening for known or underlying vascular disease and identifying those at high risk of a cardiac event is important for risk mitigation in patients with prostate cancer receiving hormone therapy.

The current GnRH antagonist, degarelix, given by a monthly subcutaneous injection, has been shown to also confer a significantly lower risk of cardiac events than GnRH agonists. Therefore, prior to treatment, patients should be stratified based on level of CV risk, and appropriate lifestyle and pharmacological interventions to mitigate CV risk should be recommended. CV risk factors and patient response to the intervention should be monitored at regular intervals. Analysis of real-world data from the UK primary care setting\(^1\) showed that the relative risk of experiencing cardiac events was significantly lower with degarelix compared with GnRH agonists (risk ratio 0.39 [95% CI 0.191, 0.799]; \(p=0.01\)).

Patients on the whole prefer tablets to injections and prefer to stay away from hospital clinics in this COVID-19 era.

In advanced hormone-sensitive metastatic prostate cancer, ADT alone is no longer the standard of care and the authors point out that the safety of relugolix has not been established in combination with many androgen-receptor-axis targeted therapies (eg abiraterone, apalutamide), cabazitaxel or lutetium Lu 177 vipivotide tetraxetan, which precludes its use in combination with these agents until further studies are performed.

References
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