Medications mostly associated with priapism events: assessment of the 2015-2020 Food and Drug Administration (FDA) pharmacovigilance database entries

Nicolò Schifano[1,2], Paolo Capogrosso[3], Luca Boeri[2,4], Giuseppe Fallara[1,2], Omer Onur Cakir[6,7], Fabio Castiglione[6,7], Hussain Alnajjar[6,7], Asif Muneer[6,7], Federico Deho'[3], Fabrizio Schifano[5], Francesco Montorsi[1,2], Andrea Salonia[1,2]

[1]Università Vita-Salute San Raffaele, Milan, Italy

[2]Division of Experimental Oncology/Unit of Urology; URI; IRCCS Ospedale San Raffaele, Milan, Italy

[3]ASST Sette Laghi – Circolo e Fondazione Macchi Hospital, Varese, Italy

[4]Department of Urology, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

[5]Psychopharmacology; Drug Misuse; and Novel Psychoactive Substances Research Unit; School of Life and Medical Sciences, University of Hertfordshire, Hatfield, Herts, UK

[6]Institute of Andrology, Department of Urology, University College London Hospitals NHS Trust

[7]Division of Surgery and Interventional Science, UCL

CORRESPONDING AUTHOR:
Andrea Salonia, MD, PhD, FECSM
University Vita-Salute San Raffaele
Division of Experimental Oncology/Unit of Urology, URI-Urological Research Institute
IRCCS Ospedale San Raffaele
Via Olgettina 60, 20132 Milan, Italy
Tel. +39 02 26436763; Email: salonia.andrea@hsr.it

ABSTRACT

A range of drugs have a direct role in triggering ischaemic priapism. We aimed at identifying: a)which medications are associated with most priapism-reports; and, b)within these medications, comparing their potential to elicit priapism through a disproportionality analysis. The FDA Adverse Event Reporting System (FAERS) database was queried to identify those drugs associated the most with priapism reports over the last 5 years. Only those drugs being associated with a minimum of 30 priapism reports were considered. The Proportional Reporting Ratios (PRRs), and their 95% confidence intervals were computed. Out of the whole 2015-2020 database, 1233 priapism reports were identified, 933 of which (75.7%) were associated with 11 medications with a minimum of 30 priapism-reports each. Trazodone, olanzapine and tadalafil showed levels of disproportionate reporting, with a PRR of 9.04 (CI95%:7.73-10.58), 1.55 (CI95%:1.27-1.89), and 1.42 (CI95%:1.10-1.43), respectively. Most (57.5%) of the reports associated with the phosphodiesterase type 5 inhibitors (PDE5Is) were related with concomitant priapism-eliciting drugs taken at the same time and/or inappropriate intake/excessive dosage. Patients taking trazodone and/or antipsychotics need to be aware of the priapism-risk; awareness among prescribers would help in reducing priapism-related detrimental sequelae; PDE5I-intake is not responsible for priapism by itself, when appropriate medical supervision is provided.

Keywords: Priapism; Pharmacovigilances; Adverse Drug Reaction Reporting Systems; Psychotropic Drugs; Trazodone; Antipsychotic Agents

INTRODUCTION

Priapism is a pathological condition defined as an erection lasting longer than 4 hours that persists beyond, or is unrelated, to sexual interest or stimulation [1,2]. Whilst non-ischaemic priapism is rare and is usually secondary to perineal trauma [3], ischemic priapism is indeed the more common subtype, resulting from decreased venous outflow with venous stasis in the corpora cavernosa of the penis [1]. It remains a serious urological emergency which, if left untreated, could lead to hypoxia-related destruction of the sinusoidal endothelium and corporal fibrosis, with eventual permanent erectile dysfunction [1]. Timely management of this emergency is paramount, as extensive cavernosal-tissue necrosis is a highly likely event occurring after 48 hours of priapism [4]. Treatment of ischaemic priapism cases depends on the episode-duration, ranging from corporal aspiration/irrigation, intra-cavernosal injection of sympathomimetics, proximal vs. distal shunting procedures, and/or prompt insertion of a malleable penile prosthesis when extensive and irreversible hypoxic damage has occurred [2,4]. The incidence of this condition is believed to be 1.5 cases per 100,000 person-years [5], although one could expect levels of under-reporting, due to patients' embarrassment or after spontaneous resolution without intervention. A predisposition to transient and self-limiting recurrent episodes of priapism (e.g. "stuttering priapism") shares its aetiology with ischaemic priapism and frequently progresses to a complete form [1]. Although idiopathic episodes of priapism are common, pharmacologically-induced priapism is now considered the predominant etiology [6]. In fact, priapism has been related to a number of commonly prescribed medications, as well as illegal drugs [1]. The growing use of a range of prescription medications such as antidepressants, antipsychotics and intra-cavernosal injections, and the increase in the abusing levels of recreational drugs such as cocaine, alcohol, cannabinoids and amphetamines [7,8], is expected to lead to an increase of pharmacologically-induced priapism cases. Pharmacologically-induced priapism is invariably associated with ischaemic features [1], thus it may determine the above mentioned permanent detrimental outcomes for the penile

function. Hence, it is desirable that the clinicians involved in the prescription of these index medications are well aware of their potential to cause ischaemic priapism, although it is more likely to occur among individuals with certain susceptibility features [1,2].

Although a cause-effect association in eliciting ischaemic priapism events is already well-established for some specific drugs, the range of medications deemed to be potentially responsible for priapism is indeed wide and little is known regarding the drugs which are associated with more reports of this adverse drug reaction (ADR). Indeed, most of the available scientific evidence relating to drug-induced priapism issues comes from both case reports and limited numbers of case series. To this respect, real-world data from the post-marketing phase might be useful to gather valuable figures. The pharmacovigilance purpose is to detect, collect and monitor spontaneously reported ADRs, with measures of disproportionality being considered the validated statistical tools of choice to detect a signal of disproportionate reporting (SDR) from the range of pharmacovigilance databases [9]. Disproportionality measures, however, should be used to test only biologically plausible associations [9].

Consistent with this, we aimed here at: a) identifying the range of medications possibly associated with priapism events; and, b) assessing their signals of association with priapism based on a disproportionality analysis. The voluntary reports of suspected ADRs in the United States (U.S.) were analyzed, through the FDA (Food and Drug Administration) Adverse Event Reporting System (FAERS) pharmacovigilance database.

METHODS

The FDA is responsible for supervising the medicinal products in the U.S.; and the FAERS database collects those ADRs being submitted to the FDA [10]. ADRs are reported spontaneously to the FAERS by either healthcare professionals or by the patients themselves after the appearance of signs and symptoms which are being attributed to an index drug [11].

FAERS data were here made accessible through the online, ad hoc, querying tool. ADRs were recorded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) [12]. The ADR-related individual cases were identified using the Preferred Term (PT) 'priapism'.

For the purpose of the present study, the number of individual cases, rather than the number of ADRs, was considered. The number of individual cases was unequivocally identified counting the number of entries using a univocal code (case ID). However, each individual case could have been possibly associated with other ADRs which were signalled at the time of the report, along with 'priapism'. Furthermore, different reporters could have independently reported the same individual case to the FAERS [12]. The FAERS database was queried to identify all the drugs which were associated with the PT 'priapism'. A wide range of drugs were associated with at least one 'priapism' report, with only one or few reports being associated with the vast majority of these molecules. Hence, only those 11 drugs which were associated with more than 30 reports of 'priapism' were here considered (see Table 1).

Data analysis focused on a range of parameters, including: socio-demographic characteristics (i.e., age and sex); reporter's qualification (i.e., healthcare professional; consumer); ADR outcome (i.e., serious, non-serious, disabled, hospitalized, required intervention, recovered, resolved); range of other ADRs associated with the individual report; drug dosages; product commercial names; possible concomitant drug(s); and number of cases received each year. When an English literature reference was provided in the database along with the ADR-report, this was searched through the MEDLINE/Pubmed database to gather additional data regarding the report itself. Because of FDA protection of individuals' privacy,

sensible data relating to patients were here not accessible, since fully anonymized from the database itself.

To more properly evaluate the strength of the association between the drugs mostly associated with 'priapism' and their actual capability of causing this ADR, the proportional reporting ratio (PRR) approach was here adopted [13]. The PRR is the ratio between the frequency with which a specific adverse event is reported for the drug of interest, relative to all adverse events reported for that same drug, and the frequency with which the same adverse event is reported for the drug(s) in the comparison group relative to all adverse events for drugs in the comparison group [9]. The PRR is computed as follows: $PRR = \frac{A}{A+B} / \frac{C}{C+D}$, where: A is the number of individual cases associated with the index drug involving 'priapism'; B is the number of individual cases related to the index drug involving any other adverse events; C is the number of individual cases involving 'priapism' for all the remaining 10 drugs; and D is the number of individual cases involving any other ADR associated with the remaining 10 drugs [14]. A PRR greater than 1 suggests that 'priapism' is more commonly reported for individuals taking the drug of interest relative to the comparison drug(s). The PRRs have been computed for all the 11 drugs with more than 30 'priapism' reports each, along with the PRR confidence intervals [14].

Statistical analyses were carried out using the SPSS software (IBM, Armonk, NY, USA).

RESULTS

The FAERS dataset was analysed in December 2020. Overall, the whole number of the FAERS individual cases involving a 'priapism' ADR report in the time-frame here considered (i.e., January 2015-December 2020) was 1233; these figures were associated with 270 drugs having been reported at least once to be associated with the 'priapism'ADRs. Out of 1233 reports, 933 (75.7%) were associated with the 11 drugs having more than 30 reports of 'priapism' each, which included: trazodone, quetiapine, risperidone, olanzapine, aripiprazole, tadalafil, sertraline, sildenafil, methylphenidate, alprostadil and clozapine (Table 1). Out of these 11 molecules, the drug which was here most typically associated with 'priapism' ADRs was trazodone, identified in 197/1233 individual cases (16.0%).

The age of priapism occurrence was specified for most of the 11 drug-related reports (i.e., 536/773; 69.3%); the median (interquartile range - IQR) age at occurrence resulted to be 36 years of age (25-50 years). Most (190, 35.5%; and 207, 38.6%) cases were here associated with an age of occurrence between 21 and 40 years and between 40 and 60 years, respectively. Conversely, 108 (20.2%) cases were associated with an age at occurrence < 21 years of age, whilst only the remaining 31 (5.8%) individual cases were associated with an age at occurrence older than 60 years. Overall, female priapism had here been identified in only 6 individual reports. When the reporter category was specified (763/773, 98.7%), most reports (i.e., 571/773, 73.9%) were submitted by a healthcare professional, whilst the remaining 192 reports were submitted by the drug consumer. Out of the total, 669 (86.6%) cases were judged as being 'serious', whilst only 104 individual cases were reported as being 'non-serious'. Where further details regarding the outcome were disclosed, 264 patients were 'hospitalised', 48 cases 'required surgical intervention', and 27 cases were associated with a 'disabled' outcome.

The resulting PRRs which were calculated for all the medications with more than 30 reports each, along with their 95% confidence intervals, are reported in Table 1. Within this group of high-risk

medications, trazodone, olanzapine and tadalafil showed significant levels of actual disproportionate reporting, with a PRR of 9.04 (CI95%: 7.73-10.58), 1.55 (CI95%: 1.27-1.89), and 1.42 (CI95%: 1.10-1.43), respectively. Quetiapine, risperidone and aripiprazole priapism reports were here well represented as well (Table 1).

In order to provide further details to better interpret the sildenafil and tadalafil findings, an additional sub-analysis of the 113 phosphodiesterase type 5 inhibitors (PDE5Is)-related individual reports was here performed. In 28 (24.8%) cases, PDE5Is were taken in association with other medications which are already well-known for being related with priapism (i.e., trazodone, intra-cavernosal injections of prostaglandins, various antipsychotics, cocaine, alcohol [1]). Conversely, in 3 (2.7%) cases PDE5Is were ingested with medications for which a pharmacokinetic interaction with PDE5Is is already known (i.e., itraconazole, tacrolimus). Furthermore, of 113, 32 (28.3%) individual reports were instead associated with PDE5Is' idiosyncratic intake modalities (e.g., accidental exposure to product by a child, intentional overdose, suicide attempt, intentional misuse, accidental overdose, incorrect/extra dose administered, drug abuse, off-label use, product used for unknown indication/without prescription, medication error), and PDE5Is were prescribed for issues related to pulmonary hypertension in 2 (1.8%) cases. Hence, only less than half of the PDE5I-related individual reports (namely, 48/113, 42.5%) were instead associated with: no concomitant drugs taken at the same time/concomitant drugs not disclosed; or, absence of statements which were considered suggestive of inappropriate intake/excessive dosage ingested or unusual indications.

DISCUSSION

To the best of our knowledge, this is the first and largest scale study aimed at systematically analysing a pharmacovigilance database, such as the FAERS one, to investigate pharmacologically-induced priapism. This database, together with the European Medicines Agency (EMA) and the World Health Organization's Drug Monitoring Program [15], is considered a world-wide reference standard [16]. Although a large number (i.e., 1233 individual reports) of 'priapism' reports were identified in the FAERS database in the relatively short 2015-2020 timeframe, current findings most likely represent a gross under-estimate of the real prevalence of this issue. In fact, one could argue that patients' embarrassment and/or spontaneous resolution without intervention may have prevented, to a large extent, spontaneous reporting [17].

The analysis here performed concluded for significant levels of disproportionate reporting for trazodone, olanzapine and tadalafil vs. the remaining drugs associated with more than 30 'priapism' reports each, with PRR values of 9.04 (CI95%: 7.73-10.58), 1.55 (CI95%: 1.27-1.89), and 1.42 (CI95%: 1.10-1.43), respectively. Overall, these results should be interpreted as significant signals of disproportionate reporting (SDRs) [18]. Whilst the lower bound of the 95% confidence interval greater or equal to one is typically considered to define a SDR, a PRR $\geq$3 is instead most commonly considered as representing a strong SDR [18]. In order to appropriately interpret these findings, it must be kept in mind that this disproportionality analysis compared among them a list of medications which are already known for being associated with levels of potential to elicit priapism episodes. Based on these premises, it appears that, among the high-risk list of drugs here analysed, trazodone generated indeed the strongest SDR, whilst olanzapine and tadalafil seemed somewhat more prone to cause priapism vs. the other drugs of the database (except for trazodone). The propensity of trazodone to elicit priapism is already well documented in the literature [19–21]. Although a number of medications identified in this list may be prescribed by sexual medicine specialists, most of these drugs are typically

prescribed by psychiatrists and primary care doctors. It is of outmost importance that physicians prescribing trazodone are aware and prepared to face this possible detrimental side effect [20], as this medication is still prescribed to more than 27 million Americans [17]. To this respect, some 229 male patients younger than 50 years taking trazodone were surveyed regarding their pre-treatment counselling: only less than 20% of the patients were informed about the possible risk of prolonged erections and priapism [20]. The concomitant use/abuse of other legal and/or illegal drugs known to cause priapism may increase the risk of trazodone-induced priapism, due to a synergistic effect [6].

Drug-induced priapism is associated with the low-flow mechanism, which is secondary to an inadequate corporal venous outflow [1]. Some antipsychotics and the antidepressant trazodone may cause priapism due to their high-affinity antagonism for the a1- and a2-adrenergic receptors [6]. The overall result of this a-adrenergic blockage is a shift of the penile vascular equilibrium into the direction of prolonged erection/intracavernosal stasis. In the flaccid state, the penile arterioles are tonically contracted due to the a-adrenergic activity [6]. The inhibition of the a1-receptors of the penis produces enhanced penile blood inflow through arterial dilatation, which results in blood entrapment in the cavernosal sinusoids [6]. The engorgement of the sinusoids results in the compression of the sub-tunical emissary venular plexuses between the tunica albuginea and the peripheral sinusoids, which eventually results in a reduction of the venous outflow [22]. Moreover, the blockage of the presynaptic a-2 adrenergic receptors may prevent the release of norepinephrine [23], inhibiting the detumescence. Of clinical importance, manifest priapism affects only a fraction of those patients using a-adrenergic-antagonist medications, thus suggesting the possible role of a background of enhanced individual susceptibility to the adrenergic blockade in those who experience this event [24]. One could argue that single-nucleotide polymorphisms (SNPs) of the cytochrome P450 drug oxidases may affect drug metabolization rates in these patients [24]. Further different mechanisms may explain the development of pharmacologically-induced priapism. The influence of some medications (e.g., the atypical antipsychotics) on serotonin receptors (e.g., either with a stimulatory action or with an inhibitory effect,

241 depending on the specific serotonin receptor) in the central nervous system (CNS) accounts for another
242 possible mechanism for drug-induced priapism [25]. Although those antipsychotics which show more
243 pharmacodynamic affinity for a-adrenergic receptors are expected to be more prone to elicit priapism
244 events, all antipsychotic medications (i.e., both typical and atypical, even those with lower affinity for
245 a-adrenergic receptors) have been associated with priapism [26]. For instance, aripiprazole presents
246 with the lowest affinity to a-1 adrenergic receptors among all the atypical antipsychotics and yet there
247 have been clinical reports of aripiprazole-induced priapism [26]. Antipsychotic-induced priapism is
248 usually associated with: increasing dosage, restarting the treatment after an abstinence interval,
249 switching to a different class of antipsychotic and pharmacodynamic interactions [27]. This may
250 suggest that the addition of a second a-adrenergic antagonizing drug (e.g., the combination of two
251 antipsychotics and/or the combination of trazodone with an antipsychotic) may facilitate the occurrence
252 of priapism.
253 Only few case reports/series [28–36] of priapism have been described in the literature in patients taking
254 PDE5Is. It is unlikely that prescribed PDE5Is alone can cause ischaemic priapism events [37], with
255 most anecdotal published reports relating instead to specific conditions which may represent additional
256 risk factors for ischaemic priapism. For some of these literature reports [36], the PDE5I-consumption
257 was associated with concomitant prescribing/misusing drugs well-known for causing priapism. PDE5Is
258 are mainly metabolized by the cytochrome P450 3A4 hepatic isoenzyme [38]. Pharmacokinetic
259 interactions in patients taking concomitantly PDE5Is with other drugs which are known to increase the
260 PDE5I steady-state concentrations, including cytochrome P450 3A4 inhibitors (e.g., itraconazole [32],
261 cannabis [38]), were considered responsible for priapism events in some of these cases. Remaining
262 PDE5I-related prolonged erections/manifest priapism events have been reported in: children following
263 an accidental ingestion [30]; in a patient of with a sickle cells' trait [33]; and, in subjects taking
264 large/massive dosages of PDE5Is for self-poisoning purposes [34]. Overall, current FAERS-related
265 findings are fully consistent with the existing anecdotal literature, with only a minority of the

266 ‘priapism’ individual reports being here not associated with the risk factors above mentioned.
267 Conversely, it is possible that additional details regarding these reports (e.g., concomitant drugs taken
268 by the patient, intentional overdose, pre-existent haematologic conditions) were not disclosed for a
269 number of PDE5I-related priapism reports. Notwithstanding the overall satisfactory safety levels of
270 these medications [37], with current data one would not be able to rule out a possible increased risk of
271 priapism when the erectogenic PDE5I molecules are used inappropriately. Indeed, although a poorly
272 investigated topic, a range of surveys [39,40] have described the increasing levels of self-
273 prescribing/intentional abuse of these medications. In a survey [39], up to 21.5% of young reported to
274 have ingested PDE5Is, and most frequently in association with alcohol and/or other drugs, without a
275 prescription. These idiosyncratic combinations may facilitate, as discussed, the occurrence of priapism
276 events, with cannabinoids having been reported to alter the PDE5Is’ steady-state concentrations [38].
277 Further substances of abuse, including ethanol, cocaine, and amphetamine mixtures have been
278 associated with priapism [1].

279 *Limitations*

280 Whilst the analysis of spontaneous reporting systems should be considered as a starting point for
281 identifying drug safety issues, this may present with a range of limitations. Indeed, the
282 pharmacovigilance approach may not conclusively prove causality between a specific drug and a given
283 ADR [12]. In fact, the ADR may be a symptom of another illness; it could be associated with another
284 medical product taken by the patient at the same time; or, caused by their interaction.
285 Disproportionality studies do not allow quantification of the clinical risk; only from the amalgamation
286 with clinical data it is possible to draw a more definite conclusion about the harm potential of any index
287 drug. Incidence of drug-induced priapism cannot be determined based on these data, since drug-
288 induced priapism events are overall likely going under-reported, due to patient embarrassment;
289 subclinical priapism events/prolonged erections (e.g., erections lasting less than 4 hours); and failure to
290 report the ADR itself [17]. Levels of voluntary reporting are in fact depending from several factors,

including the individual's perception about the possible risks associated with the medication; the index molecule clinicians' awareness of safety concerns; its market availability levels; and extent of use [12]. One could then argue that the cases here identified, together with those anecdotally reported in the previous literature, may well represent only the most atypical cases of drug-induced priapism. Furthermore, duplicate 'priapism' individual case reports (e.g., due to: a consumer and healthcare professional reporting the same event; multiple healthcare professionals treating the same patient reporting the same event; and, an event being reported by both the consumer/healthcare professional and the sponsor) could have created here misleading signals of disproportionate reporting.

Notwithstanding the potential weaknesses associated with the analysis of pharmacovigilance databases, current findings have significant clinical implications. The drugs identified in this analysis are widely prescribed worldwide; hence, even if the number of patients with drug-induced priapism may be small, the issue should be considered of clinical relevance. Patients taking trazodone or antipsychotics need to be aware of the risk of ischaemic priapism in order to facilitate an early management of the condition. Those patients with other risk factors for priapism, and especially those taking concurrent high-risk drugs, should be counseled even more thoroughly, as they may be more susceptible to this serious reaction. Appropriate awareness among prescribing clinicians would also help in reducing the long-term consequences associated with priapism. Although this analysis identified a range of reports being associated with PDE5Is, the correct, under medical supervision, use of these medications is very unlikely associated with a clinically significant risk of developing a priapism event. Ease of access to these medications through non-authorized providers, including rogue websites where no regulatory controls take place, should be however strongly discouraged. Finally, prompt reporting of drug-induced priapism events should further be promoted.

Acknowledgements: None

Conflict of Interest: None Declared

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

360 **REFERENCES**

[1] Salonia A, Eardley I, Giuliano F, Hatzichristou D, Moncada I, Vardi Y, et al. European association of urology guidelines on priapism. Eur Urol 2014;65:480–9. https://doi.org/10.1016/j.eururo.2013.11.008.

[2] Salonia A, Bettocchi C, Carvalho J, Corona G, Jones TH, Kadioglu A, et al. EAU Guidelines on Sexual and Reproductive Health 2021.

[3] Arrichiello A, Angileri SA, Buccimazza G, Di Bartolomeo F, Di Meglio L, Liguori A, et al. Interventional radiology management of high flow priapism: review of the literature. Acta Biomed 2020;91:e2020010. https://doi.org/10.23750/abm.v91i10-S.10233.

[4] Zacharakis E, Garaffa G, Raheem AA, Christopher AN, Muneer A, Ralph DJ. Penile prosthesis insertion in patients with refractory ischaemic priapism: Early vs delayed implantation. BJU Int 2014;114:576–81. https://doi.org/10.1111/bju.12686.

[5] Eland IA, Van der Lei J, Stricker BHC, Sturkenboom MJCM. Incidence of priapism in the general population. Urology 2001;57:970–2. https://doi.org/10.1016/S0090-4295(01)00941-4.

[6] Hwang T, Shah T, Sadeghi-Nejad H. A Review of Antipsychotics and Priapism. Sex Med Rev 2021;9:464–71. https://doi.org/10.1016/j.sxmr.2020.10.003.

[7] Rubin R. Use of Illicit Drugs Continues to Rise. JAMA - J Am Med Assoc 2019:322(16):1543. https://jamanetwork.com/journals/jama/article-abstract/2753347 (accessed August 18, 2021).

[8] Zhao H, Berdahl C, Bresee C, Moradzadeh A, Houman J, Kim H, et al. Priapism from Recreational Intracavernosal Injections in a High-Risk Metropolitan Community. J Sex Med 2019;16:1650–4. https://doi.org/10.1016/j.jsxm.2019.07.024.

[9] Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol 2011. https://doi.org/10.1111/j.1365-2125.2011.04037.x.

[10] Kumar A. The Newly Available FAERS Public Dashboard: Implications for Health Care Professionals. Hosp Pharm 2019;54:75–7. https://doi.org/10.1177/0018578718795271.

[11] EMA. Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 4). Heads Med Agencies 2017.

[12] Nicolo' Schifano, Stefania Chiappini, Fabio Castiglione, Andrea Salonia FS. Is medicinal ketamine associated with urinary dysfunction issues? Assessment of both the European Medicines Agency (EMA) and the UK Yellow Card Scheme pharmacovigilance database-related reports. LUTS Low Urin Tract Symptoms 2020.

[13] Chiappini S, Schifano F. A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database. CNS Drugs 2016;30:647–54. https://doi.org/10.1007/s40263-016-0359-y.

[14] European Medicines Agency. Guideline on the use of statistical signal detection methods in the EudraVigilance data analysis system 2008.

[15] WHO. The WHO Programme for International Drug Monitoring 2015.

[16] Felicetti P, Trotta F, Bonetto C, Santuccio C, Brauchli Pernus Y, Burgner D, et al. Spontaneous reports of vasculitis as an adverse event following immunization: A descriptive analysis across three international databases. Vaccine 2016. https://doi.org/10.1016/j.vaccine.2015.09.027.

[17] Scherzer ND, Reddy AG, Le T V., Chernobylsky D, Hellstrom WJG. Unintended Consequences: A Review of Pharmacologically-Induced Priapism. Sex Med Rev 2019;7:283–92. https://doi.org/10.1016/j.sxmr.2018.09.002.

[18] Grundmark B, Holmberg L, Garmo H, Zethelius B. Reducing the noise in signal detection of adverse drug reactions by standardizing the background: A pilot study on analyses of proportional reporting ratios-by-therapeutic area. Eur J Clin Pharmacol 2014. https://doi.org/10.1007/s00228-014-1658-1.

[19] Dutta R, Matz EL, Overholt TL, Anderson WB, Deebel NA, Cowper M, et al. Patient Education

Is Associated With Reduced Delay to Presentation for Management of Ischemic Priapism: A Retrospective Review of 123 Men. J Sex Med 2021;18:385–90. https://doi.org/10.1016/j.jsxm.2020.11.017.

[20] Shah T, Deolanker J, Luu T, Sadeghi-Nejad H. Pretreatment screening and counseling on prolonged erections for patients prescribed trazodone. Investig Clin Urol 2021;62:85–9. https://doi.org/10.4111/icu.20200195.

[21] Matz A, Ambinder D, Spencer E, Phillips J, Wong NC. Review of Priapism Litigation in the United States. Urology 2021. https://doi.org/10.1016/j.urology.2021.05.001.

[22] Panchatsharam PK, Durland J ZP. Physiology, Erection. Physiol Erection [Updated 2021 May 9] 2021:In: StatPearls [Internet]. Treasure Island (FL): S. https://www.ncbi.nlm.nih.gov/books/NBK513278/ (accessed August 18, 2021).

[23] Traish A, Kim NN, Moreland RB, Goldstein I. Role of alpha adrenergic receptors in erectile function. Int J Impot Res 2000;12:S48–63. https://doi.org/10.1038/sj.ijir.3900506.

[24] Greiner T, Schneider M, Regente J, Toto S, Bleich S, Grohmann R, et al. Priapism induced by various psychotropics: A case series. World J Biol Psychiatry 2019;20:505–12. https://doi.org/10.1080/15622975.2018.1520396.

[25] Dent LA, Pharm D, Brown WC, Pharm D, Murney JD. Citalopram-Induced Priapism n.d.:0–3.

[26] Trivedi SK, Mangot AG, Sinha S. Aripiprazole-induced priapism n.d.

[27] Koirala S, Penagaluri P, Smith C, Lippmann S. Priapism and risperidone. South Med J 2009;102:1266–8. https://doi.org/10.1097/SMJ.0b013e3181c04775.

[28] Goldmeier D. Prolonged erections produced by dihydrocodeine and sildenafil. Bmj 2002;312:44. https://doi.org/10.1136/bmj.312.7022.44.

[29] Aoyagi T, Hayakawa K, Miyaji K, Ishikawa H, Hata M. Sildenafil induced priapism. Bull Tokyo Dent Coll 1999;40:215–7. https://doi.org/10.2209/tdcpublication.40.215.

[30] Cantrell FL. Sildenafil citrate ingestion in a pediatric patient. Pediatr Emerg Care 2004;20:314–

5. https://doi.org/10.1097/01.pec.0000125660.50937.b5.

[31] Kumar R, Cantrell FL, Galatti L, Fioravanti A, Salvo F, Polimeni G, et al. Penile fracture after priapism due to sildenafil ingestion: Out of frying pan into the fire. J Anal Toxicol 2015;39:314–5. https://doi.org/10.1182/blood.v95.5.1878.

[32] Galatti L, Fioravanti A, Salvo F, Polimeni G, Giustini SE. Interaction between tadalafil and itraconazole [4]. Ann Pharmacother 2005;39:200. https://doi.org/10.1345/aph.1E383.

[33] Kassim AA, Fabry ME, Nagel RL. Acute priapism associated with the use of sildenafil in a patient with sickle cell trait [3]. Blood 2000;95:1878–9. https://doi.org/10.1182/blood.v95.5.1878.

[34] Matheeussen V, Maudens KE, Anseeuw K, Neels H. A non-fatal self-poisoning attempt with sildenafil. J Anal Toxicol 2015;39:572–6. https://doi.org/10.1093/jat/bkv071.

[35] Sharma D, Kumar M, Pandey S, Agarwal S. Penile fracture after priapism due to sildenafil ingestion: Out of frying pan into the fire. BMJ Case Rep 2018;2018:1–2. https://doi.org/10.1136/bcr-2018-226562.

[36] Khan QS, Tucker P, Lokhande A. Priapism: What cause: mental illness, psychotropic medications or poly-substance abuse? J Okla State Med Assoc 2016;109:515–7.

[37] Rezaee ME, Gross MS. Are We Overstating the Risk of Priapism With Oral Phosphodiesterase Type 5 Inhibitors? J Sex Med 2020;17:1579–82. https://doi.org/10.1016/j.jsxm.2020.05.019.

[38] McLeod AL, McKenna CJ, Northridge DB. Myocardial infarction following the combined recreational use of Viagra and cannabis. Clin Cardiol 2002;25:133–4. https://doi.org/10.1002/clc.4960250310.

[39] Bechara A, Casabé A, De Bonis W, Helien A, Bertolino MV. Recreational Use of Phosphodiesterase Type 5 Inhibitors by Healthy Young Men. J Sex Med 2010;7:3736–42. https://doi.org/https://doi.org/10.1111/j.1743-6109.2010.01965.x.

[40] Gebreyohannes EA, Bhagavathula AS, Gebresillassie BM, Tefera YG, Belachew SA, Erku DA.

Recreational Use of Phosphodiesterase 5 Inhibitors and Its Associated Factors among Undergraduate Male Students in an Ethiopian University: A Cross-Sectional Study. World J Mens Health 2016;34:186–93. https://doi.org/10.5534/wjmh.2016.34.3.186.

Table 1: The 11 molecules most typically associated with individual reports of 'priapism' in the FAERS pharmacovigilance database

Drug	*Number of individual cases associated with priapism in the database (n)*	*Percentage of the individual cases of priapism when compared to all the compounds in the database (%)*	*PRR (CI95%)*
Trazodone	**197**	**15.98%**	**9.04 (7.73-10.58)**
Quetiapine	153	12.48%	0.69 (0.63-0.75)
Risperidone	130	10.54%	0.82 (0.69-0.98)
Olanzapine	**106**	**8.60%**	**1.55 (1.27-1.89)**
Aripiprazole	80	6.49%	0.73 (0.58-1.26)
Tadalafil	**74**	**6.00%**	**1.42 (1,10-1.83)**
Sertraline	58	4.70%	0.62 (0.48-0.80)
Sildenafil	39	3.16%	0.74 (0.54-1.01)
Methylphenidate	33	2.68%	1.11 (0.78-1.58)
Alprostadil	32	2.60%	0.90 (0.63-1.28)
Clozapine	31	2.51%	0.26 (0,18-0.37)

Keys: FAERS= FDA (Food and Drug Administration) Adverse Event Reporting System, PRR= Proportional Reporting Ratio, CI95%= 95% Confidence Interval