Are finasteride-related penile curvature/Peyronie's disease Adverse Event Reports worthy of further clinical investigation? Disproportionality analysis based on both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) pharmacovigilance databases

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ABSTRACT

A limited number of studies have described patients on finasteride showing findings which were consistent with Peyronie's disease (PD). We aimed to detect a pharmacovigilance signal of possible association between finasteride and PD-related clinical features. The Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database was queried to identify the 10 drugs which were associated the most with the adverse drug reactions (ADRs) recorded as 'penile curvature' and/or 'Peyronie's disease'. A similar analysis, including the same drugs, was carried out for the EMA (European Medicines Agency) EudraVigilance (EV) database. Descriptive data have been analyzed, and Proportional Reporting Ratios (PRRs) have been computed against the other 9 drugs of the database. Overall, 860 reports of 'penile curvature' and/or 'Peyronie's disease', were identified in the FAERS database, 214 of which (24.9%) were associated with finasteride. Most reports (56.9%) were submitted by healthcare professionals. Where a treatment-indication was stated, the vast majority of reports (176/210;83.8%) were associated with androgenetic alopecia. The outcome of most ADRs was 'serious' (82.2%), with 96 ADRs resulting in levels of permanent disability. For 97/214 individual cases, penile curvature/PD reports were not part of a syndromic cluster suggestive of post-finasteride syndrome (PFS). The PRR resulted 6.6 (C.I.95%: 5.6-7.8) and 11.8 (C.I.95%: 9.08-15.33) respectively in the FAERS and in the EV databases. Notwithstanding the related limitations and biasing factors of pharmacovigilance studies based on spontaneous reporting, the PRR values here identified should be interpreted as strong signals of disproportionality. These findings, per se, are however not useful to confirm any causal association. Clinical studies are needed to investigate on the possible role for finasteride in causing PD-related clinical features, an hypothesis which remains highly speculative due to the very questionable quality of present data.

INTRODUCTION

Peyronie's disease (PD) is a condition associated with fibrosis and plaque development in the penile tunica albuginea [1]. PD-related clinical features include penile curvature, pain, shortening of the penis, and erectile dysfunction (ED), according to the phase of the disease [1]. This condition typically affects males at midlife (e.g., between 45 and 60 years) [1], often resulting in significant clinical issues, since preventing sexual intercourse and/or reducing sexual satisfaction [2]. Men with PD usually suffer from significant psychological distress [2]. The aetiology of PD has yet to be clarified, although it is likely that repeated tunical micro-traumatisms are behind the initiation of PD-associated inflammation and fibrin deposition [3]. Most men are exposed to levels of micro-traumatism during sexual intercourse, only a minority will however develop PD [4]; hence, PD is thought to occur in genetically susceptible/vulnerable individuals. PD has been associated with some risk factors, including diabetes mellitus, high blood pressure, dyslipidaemia, autoimmunity, ED, history of lower urinary tract endoscopic investigation/surgery, tobacco smoking, and alcohol misuse [1,5].

Among the other risk factors, testosterone deficiency (TD) has been associated with PD, even if the findings are largely heterogeneous and discordant [4,6,7]. Overall, it is established that androgens have a role in guiding the foetal-male-genitalia development [8]; furthermore, a number of pre-clinical [9,10] and clinical [4] studies have suggested that testosterone influences the penile structure during adult life as well.

5a-reductases are a family of isozymes expressed in androgen-target organs, including the penis; their biological role is fundamental as they catalyze the transformation of the circulating androgens into more potent agonists of the androgen receptors (ARs), such as dihydrotestosterone (DHT) [11].

Finasteride and dutasteride are synthetic 5a-reductase inhibitors (5ARIs) which have been approved for treating both benign prostatic hyperplasia (BPH) and androgenetic alopecia (AGA) [12]. The possible sexual-related adverse effects of 5ARIs were not recognized for long. Indeed, safety reporting has been

inadequate in clinical trials with the assessment of these particular side-effects not having been accurately captured or reported [12]. To date, a body of emerging evidence suggests that these medications may elicit undesirable sexual and psychological adverse effects; this has led to growing concerns about the safety of 5ARIs [12]. The use of beta-blockers anti-hypertensive compounds has also been linked with PD as well in a few small and dated case series [3], but there is no other evidence in the literature to date showing levels of a robust association between PD and any other drugs.

Whilst not uniformly recognized by the scientific community, post-finasteride syndrome (PFS) is a constellation of adverse side effects that can develop during and/or after discontinuing finasteride treatment [12]. Patients who are affected by PFS may present with a range of symptoms, including also penile shortening and penile curvature [11], which are indeed distinctive features of PD. Only a limited number of published case reports/series have described patients having been treated with finasteride showing findings which were consistent with penile plaque and fibrosis development of the tunica albuginea of the penis [11,13]. Several pharmacoepidemiologic methods may be used to identify the range of specific adverse drug reactions (ADRs) of interest, with case-control prospective studies being widely used for this purpose [14]. However, they require intense efforts; are expensive; and time consuming. Thus, real-world data, from the post marketing period, might be useful in revealing potential and until then undetected risks for the use of a pharmaceutical in regular clinical care. Pharmacovigilance is based on detection, collection and monitoring of spontaneously reported ADRs; the analysis of pharmacovigilance databases is being considered as an important source of information for setting up future prospective studies, which can eventually be capable of confirming/confuting the possible drug-ADR causal association [14]. Measures of disproportionality are considered the validated statistical tools of choice to detect a signal of disproportionate reporting (SDR) from the range of pharmacovigilance databases [14]. Disproportionality measures, however, should be used to test only biologically plausible associations [14].

We aimed here at: a) detecting and assessing a possible pharmacovigilance signal of disproportional reporting between 5ARIs and PD-related clinical features; and, b) identifying the range of further medications possibly associated with PD-related clinical features. The voluntary reports of suspected ADRs in the European Economic Area (EEA) and in the United States (U.S.) were analyzed, through both the FDA (Food and Drug Administration) Adverse Event Reporting System (FAERS) and the European Medicines Agency (EMA) EudraVigilance (EV) pharmacovigilance databases.

MATERIAL AND METHODS

The EMA is responsible for the safety monitoring of medicines operating through EV, a system managing and analyzing information on suspected ADRs to medicines which have been authorized in the EEA [15]. In the U.S., the FDA is responsible for supervising the medicinal products; the FAERS is the database storing those ADRs being submitted to the FDA [16].

In both cases, ADRs were spontaneously reported by healthcare professionals or the patients themselves that observed signs and symptoms which could have been caused by an index drug. [17].

Both the EV and the FAERS databases were here analyzed. EV and FAERS-related data were accessible through the respective online querying tools. ADRs were recorded according to the Medical Dictionary for Regulatory Activities (MedDRA), which is a clinically validated international medical terminology used by regulatory authorities [18]. The ADR-related individual cases were identified considering the following Preferred Terms (PTs): 'penile curvature' and/or 'Peyronie's disease'.

In the analysis performed, the number of individual cases (e.g., instead of the number of ADRs) for both databases was here considered. Each case/individual patient in the databases is identified through a code (case ID). The number of cases/individual patients was unequivocally identified counting the number of values in the EV local number column of the ADRs' database. Each of the individual cases could however have been associated with several ADRs, other than 'penile curvature' and/or 'Peyronie's disease', which were signalled at the time of the report. Furthermore, different reporters/senders could have independently signalled the same individual case to the EV or FAERS [18]. The FAERS database was queried to identify all the drugs which were associated with the above-mentioned PTs. Within FAERS, a vast range of molecules were found to be associated with at least one report of 'penile curvature' and/or 'Peyronie's disease'. Most typically, however, only one or few reports were here identified to be associated with the vast majority of these molecules. Hence, only those 10 drugs which resulted to be the most frequently associated with 'penile curvature' and/or

136 ‘Peyronie’s disease’ were here considered (see Table 1). A similar search, focusing on the same 10
137 drugs, was carried out in the EV database.
138 Data analysis focused on a range of parameters, including: socio-demographic characteristics (i.e., age
139 and sex); reporter’s qualification (i.e., healthcare professional; consumer); ADR outcome (i.e., serious,
140 non-serious, disabled, hospitalized, required intervention, recovered, resolved); range of other ADRs
141 associated with the individual report; drug dosages; product commercial names; possible concomitant
142 drug(s); and number of cases received each year. Because of FDA and EMA protection of privacy and
143 integrity of individuals, data relating to patients affected were fully and completely anonymized from
144 the database itself.
145 To more properly compare finasteride vs. the 9 remaining drugs most frequently associated with
146 ‘penile curvature’ and/or ‘Peyronie’s disease’, the proportional reporting ratio (PRR) approach was
147 here considered [19]. The PRR is defined as the ratio between the frequency with which a specific
148 adverse event is reported for the drug of interest, relative to all adverse events reported for that same
149 drug, and the frequency with which the same adverse event is reported for the drug(s) in the
150 comparison group relative to all adverse events for drugs in the comparison group [14]. The PRR is
151 computed as follows: $PRR = \frac{A}{A+B} / \frac{C}{C+D}$, where: A is the number of individual cases with finasteride
152 involving ‘penile curvature’ and/or ‘Peyronie’s disease’ here selected; B is the number of individual
153 cases related to finasteride involving any other adverse events; C is the number of individual cases
154 involving ‘penile curvature’ and/or ‘Peyronie’s disease’ for all remaining 9 drugs; and D is the number
155 of individual cases involving any other adverse events associated with the remaining 9 drugs [20].
156 A PRR greater than 1 suggests that the adverse event is more commonly reported for individuals taking
157 the drug of interest relative to the comparison drug(s). To date, no ‘gold standard’ universally accepted
158 threshold establishes the value of PRR to be considered suggestive of a Signal of Disproportional
159 Reporting (SDR); however, a value ≥3 has been widely reported to be strongly indicative of an actual

SDR [21]. The finasteride-related PRRs have been computed for both the EV and FAERS datasets. The PRR confidence intervals were here calculated as well, indicating the lower and upper bounds of the 95% confidence interval [20].

Moreover, in order to identify how many reports of 'penile curvature' and/or 'Peyronie's disease' occurred in a cluster that was suggestive of PFS, the range of ADRs which were associated with the individual reports was here analyzed. For this purpose, a range of PTs were considered consistent with symptoms of the PFS cluster [11]. Individual cases associated with two or more of these PTs, identified from different areas (e.g., physical, psychological and sexual) were here considered occurring in a cluster suggestive for PFS. The remaining individual cases were considered as having occurred in isolation from the remaining features of the PFS cluster.

The Medical Expenditure Panel Survey [22] (MEPS) is a set of large-scale surveys of families and individuals, which provides the most complete source of data on the use of health care across the U.S. Each annual MEPS sample size is of about 15,000 households. Complete data regarding the prescribed medications for each year has been weighted to produce national estimates of the total number of prescriptions for the drugs included in the analysis in the U.S. from 2005 to 2018.

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

RESULTS

Both the EV and FAERS datasets were analysed in November 2020. Overall, the whole number of the FAERS individual cases involving 'penile curvature' and/or 'Peyronie's disease' in the 1992-2020 time-frame was 860; these figures were associated with 252 drugs having been reported at least once to be associated with the 'penile curvature' and/or 'Peyronie's disease'ADRs. Out of these 860 reports, 563 (65.5%) were associated with the 10 drugs that were here taken into consideration, which included: finasteride, dutasteride, sildenafil, tadalafil, vardenafil, alprostadil, collagenase-Clostridium Hystolyticum, ramipril, mirtazapine and golimumab (see Table 1). Similarly, 222 reports of 'penile curvature' and/or 'Peyronie's disease' ADRs were associated with the same 10 medicinal products in the EV database. Out of the 10 molecules having been here considered, the drug which was most typically associated with 'penile curvature' and/or 'Peyronie's disease' ADRs was finasteride, identified in 214/860 individual cases (24.9%) from the FAERS database.

Finasteride-related ADRs in the FAERS database

In the time frame 1992 to September 2020, some 18,166 ADRs were here found to be associated with finasteride in the FAERS database. Out of these 18,166 ADRs, 214 (1.2%) were related to 'penile curvature' and/or 'Peyronie's disease' reports. The number of individual cases of 'penile curvature' and/or 'Peyronie's disease' by received year is reported in Figure 1. In order to provide additional data which would be useful to interpret the present figures, the national number of finasteride prescriptions in the U.S. has been estimated based on the MEPS database (see Figure 1).

Although for most reports (e.g., 117/214; 54.7%) the age of occurrence was not specified, for the remaining 97 cases median age at reporting 'penile curvature' and/or 'Peyronie's disease'ADRs was 44 years old. When the reporter type was specified (197/214, 92.0%), most reports (e.g., 112/197, 56.9%) were submitted by a healthcare professional, whilst the remaining 85 reports were submitted by the consumer. Out of the total, 176 cases were judged as being 'serious' (82.2%), whilst only 38 individual

cases were reported as being ‘non-serious’. Furthermore, 96 cases were associated with a ‘disabled’ outcome, 34 patients were ‘hospitalised’ and 5 cases ‘required surgical intervention’.

For most of the individual cases (210/214; 98.1%) it was possible to identify the reason(s) for finasteride prescription, based on: a) the data retrieved from the specific field of the database; b) the product commercial name; c) the dosage prescribed; or, d) a combination of the above. For 176/210 (83.8%) individual cases, the reason for prescription was AGA, whilst only 34/210 cases were associated with a BPH diagnosis.

The other associated ADRs for the individual reports here identified were also analysed. For 97/214 (45.3%) individual cases, ‘penile curvature’ and/or ‘Peyronie’s disease’ reports were not part of a syndromic cluster that was considered suggestive for PFS (see Methods section). For the remaining 117 individual cases, the ‘penile curvature’ and/or ‘Peyronie’s disease’ ADRs were reported in the context of a cluster of symptoms which were considered distinctive of PFS. When finasteride-related data was matched against all the remaining 9 molecules here considered (Table 2), the PRR resulted to be 6.6 (C.I. 95%: 5.6-7.8).

Finasteride-related ADRs in the EV database

Overall, 6000 ADRs’ individual cases were associated with finasteride in the EV database. Out of these, 108 (1.8%) were ‘penile curvature’ and/or ‘Peyronie’s disease’ cases. Although for most reports (e.g., 82/108, 75.9%) the age of occurrence was not specified, the ‘penile curvature’ and/or ‘Peyronie’s disease’ ADRs typically occurred in the 18-64 years range, with only two ADRs having occurred in patients older than 65. Most of these reports (e.g., 97/108; 89.8%) were submitted by healthcare professionals, and the final ADR outcome was specified only for 49/108 (45.4%) of all ADR reports. When detailed, only 7/49 (e.g., 14.3%) patients were reported as having recovered or still recovering, whilst the remaining ADRs (e.g., 85.7%) were not yet resolved at the time of reporting. When finasteride-related data was matched against all the remaining 9 molecules here considered (Table 3), the PRR resulted to be 11.8 (C.I. 95%: 9.08-15.33).

DISCUSSION

To the best of our knowledge, this is the first and largest scale study aimed at identifying finasteride-related penile curvature/PD issues as reported to pharmacovigilance databases such as the FAERS and the EMA's EV ones. These databases, together with the World Health Organization's Drug Monitoring Program [23], are considered world-wide reference standards [24]. Current findings may suggest the existence of a potential finasteride-related contribution in causing PD, although serious concerns regarding the possible influence of biasing factors should be considered. Only very few previous studies, albeit focusing on either single case reports or small case series, had aimed at ascertaining if there is a possible association between a specific drug and PD [3]. Furthermore, this was the first pharmacovigilance paper proposing/testing a specific pharmacologically-plausible hypothesis of the possible detrimental influence of 5ARIs in initiating the PD-related pathogenesis. Although a large number (e.g., some 214 and 108, respectively from FAERS and EMA) of 'penile curvature' and/or 'Peyronie's disease' ADRs being associated with finasteride was here identified, current findings may represent a gross under-estimate of the real prevalence of this issue. In fact, ADRs reports were here submitted spontaneously, and one could argue that misperception regarding 5ARIs' safety may have prevented healthcare professionals or patients from reporting.

The analyses of disproportionate reporting concluded here for finasteride-vs.-other drugs PRR values of 11.8 and 6.6, as respectively resulting from the EV and the FAERS databases. Overall, these results should be interpreted as strong signals of disproportionate reporting [21]. Furthermore, clear consistency levels were here identified between the FAERS and EV databases analysis. The higher signal here identified from the EV vs. the FAERS database may reflect a different perception of the possible side effects of finasteride; a different market availability of the molecule; and a different extent of its use in the EEA vs. the U.S., respectively.

The lower number of finasteride-related ‘penile curvature’ and/or ‘Peyronie’s disease’ reports before 2011 vs. more recent years (see Fig. 1) may partially be explained with the increasing levels of finasteride prescriptions over the years, although the “stimulated reporting effect [25]” may concur to this finding.

Finasteride, at 1 mg daily dosage, represented a major breakthrough in the AGA treatment [26]. Early-onset male AGA is a common condition that can affect up to 30% of the population by the age of 30 years [27]. These patients often seek medical advice at a young age for hair-restoration approaches and receive a prescription for finasteride 1 mg [28]. Conversely, its 5 mg daily dosage is approved for treating BPH, which is more prevalent after 50 years of age [12]. In a previous review of the FAERS data, median age at reporting for PFS-cluster symptoms was 35 and 61 years for the 1 mg and the 5 mg finasteride dosages ($p<0.001$), respectively [29]. Similarly, most (83.1%) of the individual reports of finasteride-associated ‘penile curvature’ and/or ‘Peyronie’s disease’ in the FAERS were related to the low dosage finasteride, which is typically prescribed to the younger AGA patients [30]. The higher number of reports being associated with the 1 mg dosage may be explained with: more overall prescriptions of finasteride 1 mg vs 5 mg; less likelihood to report among the older patients taking finasteride 5 mg, due to the age-related sexual dysfunction and/or decrease of sexual activity which may mask PD; and higher likelihood to report among the youngers, as PD is expected to be relatively less frequent in this category of patients.

Penile curvature may present indeed with different levels of severity, with the degree of curvature being one of the factors that impacts the most on sexual disability which, in turn, was reported to be the strongest predictor of the need for surgical management [31]. Data from the FAERS database seemed to suggest that the vast majority of the individual cases were serious (82%), and almost half (96/214) resulted in levels of disability. Furthermore, 5 cases ‘required surgical intervention’ and 34 patients

were ‘hospitalized. Indeed, although further details were here not made available, one could argue that part of these hospitalizations could be related to surgical management.

Penile curvature has been previously associated with 5ARIs in a very limited number of small case series [11,32] and in a previous analysis of the FAERS database [29], with this association having been identified only in the context of the debated PFS. Although debated as a distinct nosologic entity, patients suffering from this syndrome show a range of symptoms including: ED, loss of libido, gynecomastia, depressive symptoms, muscle atrophy, cognitive impairment, penile shortening and penile curvature [29]. However, it was previously suggested that some subjects may actually show only some clinical features of PFS, and there is no high-quality evidence that symptoms systematically occur in a specific PFS-related cluster [33]. Our findings in the FAERS database are consistent with this, since we found that a relevant portion (e.g., 45.3%) of individual cases were not associated with remaining PFS-related clinical features of the typical PFS syndromic cluster.

Sexual dysfunction issues seem to be quite commonly associated with 5ARIs. Wessells et al. [34] have tried to estimate the incidence of sexual dysfunction in a randomized, double-blind, study with a 4-year follow-up of a total of 3,040 patients treated with finasteride 5 mg/day for BPH versus placebo. They found that 15% of the patients in the case group reported sexual adverse effects vs 7% in the placebo group ($p<0.001$). Irwig et al. [32] identified 54 males with finasteride-associated sexual side effects. Interestingly enough, a very significant proportion of them (e.g., 19%) presented with clinical features that were consistent with PD. Ganzer et al. [11] identified a number of patients experiencing persistent side effects associated with finasteride 1mg; they were surveyed with the help of a comprehensive survey/questionnaire addressing all the possible PFS-related symptoms. Among 131 responders, 103 (79%) reported levels of penile shrinkage (e.g., an issue possibly consistent with PD), but a proper diagnosis of PD was established in some 26 patients (20%), a figure which, despite the study limitations, should be considered as clinically significant.

One could argue that finasteride-related impaired local androgenic metabolism (e.g., insufficient active androgenic metabolites being produced locally due to 5a-reductases inhibition) may be responsible for the possible association finasteride-penile curvature. According to a few pre-clinical studies [9,10], low androgen levels may directly impact on collagen metabolism, inducing tunical plaques' formation. Shen et al. [9] identified significant levels of irregular arranging of collagen fibers in both castrated and finasteride-treated mice in comparison with controls. Interestingly, in castrated and finasteride-treated mice serum levels of DHT were similar, whilst testosterone levels were expectedly normal in those treated with finasteride; this may suggest that DHT levels may have a prominent influence on penile-tunica ultrastructure. However, the impact of testosterone deficiency in plaque development in the real-life clinical setting has yet to be established conclusively [6,7]. A recent literature review aimed at investigating the clinical association between PD and testosterone deficiency; the majority of the identified studies, albeit characterized by both small sample-size and methodological flaws, showed levels of association between PD and TD [4]. Conversely, a more recent cross-sectional study showed that serum testosterone levels and curvature severity were not correlated in 149 patients with chronic-phase PD [7]. It is of interest that both TD and PD typically affect middle-aged males, despite most penile micro-traumas are supposed to more likely impact the young, more sexually active, subjects [4]. Conversely, TD and PD may be associated in middle-aged men due to the less rigid erections, which are hypothesized to predispose these men to penile microtraumatic events [4]. Hence, one could argue that finasteride may have not directly caused here PD due to its possible potential of disrupting the tunical collagen-deposition. Its association with PD may be instead secondary to finasteride-related ED, which in turn predisposes to penile microtraumatic events. In fact, 5a-dihydrotestosterone (5a-DHT) plays a key role in expression and activation of nitric oxide synthase (NOS) which is a key factor for erectile function [12]. Reduced levels of 5a-DHT have also been linked with penile smooth muscle cells' death and connective tissue deposition with corporal fibrosis, hence contributing to ED as well [12].

Only a minority of those prescribed with finasteride 1 mg present with sexual-related symptoms and this may well be related to some type of genetic predisposition. A number of specific polymorphism patterns of the androgen receptor's gene have been reported to be related to altered response levels to androgens [35]. It was previously hypothesized that PFS patients could carry these polymorphisms, which may become clinically evident only after the inhibition of the 5a-reductases and the consequent drop of DHT [36]. Dutasteride was also related with a relevant number of 'penile curvature' and/or 'Peyronie's disease ADR reports, although less reports were recorded vs. finasteride. The most likely explanation of this finding is related with the different prescription levels for these medications, or a lower likelihood to report for the patients taking dutasteride for BPH treatment, who are typically older, less sexually active and possibly suffering from concomitant ED.

Apart from finasteride and dutasteride, a range of molecules (Table 1) were here mostly associated with 'penile curvature' and/or 'Peyronie's disease. Whilst not being the focus of this paper, a disproportionality analysis was here performed for some of these molecules. Overall, the most represented were here the phosphodiesterase Type 5 Inhibitors (PDE5Is) (e.g., sildenafil, tadalafil, vardenafil). PDE5Is can be associated with penile curvature/PD due to their potential to rehabilitate to sexual activity even older males with weaker erections, a condition that may be associated with higher chances of penile micro-traumatic events [4]. The same argument may be valid for intracavernous alprostadil, although this association is more likely to involve a direct detrimental effect of drug injections in the tunica albuginea [37]. Further molecules here associated with 'penile curvature' and/or 'Peyronie's disease' included the collagenase Clostridium Hystolyticum, ramipril, mirtazapine and golimumab. Collagenase Clostridium Hystoliticum is a treatment for PD which is delivered locally, via direct injection into the tunical plaque. Worsening of the curvature after this treatment has been anecdotally reported [38].

346 Even though the study of spontaneous reporting systems should be considered as a starting point for
347 identifying an index drug's safety issues, the analysis of voluntarily reported ADRs presents with a
348 range of limitations. First, a number of factors may affect reporting, such as media attention, possible
349 litigation (e.g. class action lawsuits), the nature of the adverse event, the drug-indication, the extent and
350 quality of manufacturer's surveillance system and the reporting regulations. Second, the "stimulated
351 reporting [25]" effect, which may happen after warnings and/or label changes that are issued by the
352 FDA, may have influenced a relative increase of the reports from 2011 to 2015. In fact, there have been
353 two label changes to finasteride regarding sexual dysfunction issues, the first in March 2011 which was
354 even further updated in April 2012. Third, the 'penile curvature' and/or 'Peyronie's disease' ADR
355 reports were self-reported and not verified objectively here; may have been pre-existing; and might
356 have been based instead on possibly altered patient's perceptions regarding these conditions. Moreover,
357 the number of any given compound-related ADRs may not reflect the extent of the molecule's potential
358 of actually causing PD. In fact, levels of reporting, which is voluntary in nature, are depending on the
359 individual's perception about the possible risk associated with the medication; the index molecule
360 clinicians' awareness of safety concerns; its market availability levels; and extent of use. As a
361 consequence, the number of suspected reactions in a pharmacovigilance database should never be used
362 to determine the likelihood of a side effect occurring. Suspected ADRs do not conclusively prove
363 causality between a specific drug and a given ADR; the ADR may be a symptom of another illness, it
364 could be associated with another medical product taken by the patient at the same time or caused by
365 their interaction. Also, we acknowledge that the criteria that were here identified for defining an
366 individual case as being related/unrelated with a cluster suggestive of PFS were not based on a
367 standardized and scientifically-recognized diagnostic definition, which is still lacking to date. We
368 acknowledge also that a number of PTs (i.e., depressive symptoms, anxiety, libido-alterations) that
369 were here considered consistent with PFS might also represent a direct psychological distress

associated with penile curvature/PD itself. The estimations of the overall number of prescriptions in U.S. using the MEPS data may have introduced inaccuracy. Finally, it is important to emphasize that disproportionality studies do not allow quantification of the clinical risk. None of clinical trials, spontaneous notifications, case-control studies, or cohort studies, taken alone should be considered as conclusive evidence for evaluating drug safety issues. Only from the convergence of several lines of evidence it is possible to draw a more definite conclusion about the harm-potential of any index drug. Present figures will need to be interpreted with extreme caution, given the limitations which are proper of any pharmacovigilance approach, an approach which could well be associated with biases in reporting over the years. Indeed, the most important and basic pharmacovigilance principle is that the existence of a report does not establish causation, therefore pharmacovigilance data by themselves are not an indicator that the drug is causing the reported adverse events. A clinical trial is necessary to confirm a possible cause-effect relationship. Hence, the hypothesis here discussed remains entirely speculative, and will need to be substantiated by prospective clinical studies.

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Figure Legends:

Figure 1: (A) Number of individual cases of ‘penile curvature’ and/or ‘Peyronie’s disease’ being associated with finasteride in the FAERS database by received year. (B) Number of total estimated prescriptions of finasteride in the U.S., based on the MEPS data.