Serenoa repens induced erectile dysfunction: Underdiagnosis and phytovigilance

Received: 20 October 2021 | Accepted: 21 October 2021

DOI: 10.1111/bcp.15129

LETTER TO THE EDITOR

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Dear Editor,

We read with interest the commentary published in the *British Journal of Clinical Pharmacology* (BJCP) on the need of paying attention to toxicity associated with herbal medicines[1]; as a group involved since may years in the activities of pharmacovigilance and phytovigilance,[2] we consider very important to report the onset of every adverse event (AE) related to the use of medicinal plants. Herein, we described a case of erectile dysfunction (ED) occurrence in a user of a prescribed galenic preparation containing *Serenoa repens* (SR). SR, commonly called Saw palmetto, is a dwarf tree growing in subtropical and southeastern United States. The active constituents are extracted from the dried ripe fruit and are currently used for the treatment of benign prostatic hyperplasia (BPH) symptoms.[3] It has a most recent and less investigated therapeutic application for androgenetic alopecia (AGA).[4] A Cochrane review concluded that the long-term administration (more than 6 months) of SR extract is not superior to placebo in reducing lower urinary tract symptoms (LUTS) consistent with BPH.[3] Nevertheless, another systematic review showed that SR extract is effective for relieving BPH symptomatology compared with placebo.[5] However, in clinical practice, the onset of AEs, including ejaculatory and ED and loss of libido, is reported.[6] In the present reported case, ED occurrence raised in a male user of a prescribed galenic preparation containing SR with blood total testosterone lowered to 9.71 nmol/L (Table 1). After 2 months of therapy, the patient noticed an improvement in symptomatology with only one awakening per night. In February 2017, herbal treatment was stopped after the discovery of ED onset. Andrological visits confirmed osteopenia/osteoporosis and primary hypogonadism. Five-month treatment with testosterone gel and 11-month treatment with testosterone injections reverted testosterone to normal blood level (17 nmol/L). Actually, the patient referred ED resolution.

The association between SR consumption and the onset of AEs related to sexual dysfunctions is occasionally reported in literature. SR products (both dietary supplements and medicinal products) are generally well tolerated and could be associated with mild or severe AEs.[7] Moreover, several case reports suggest putative idiosyncratic toxicity with the onset of hepatitis and pancreatitis as well as hot flashes and menarche anticipation.[7]

A systematic review has examined data from randomized clinical trials (RCTs) evaluating the use of SR in BPH.[6] Results showed a comparable AEs (e.g., decreased libido, impotence, ejaculation disorders, and gynecomastia) incidence rate between SR and placebo treatment as well as between SR and finasteride, tamsulosin, or alfuzosin. Moreover, a not significant total testosterone lowering after treatment with SR compared to placebo was reported.[7]

Of notice, to date the AEs related to the antiandrogen effect of SR are increasingly being reported in the Internet (i.e., social networks, forums and blogs), which plays an important role in the spreading of pseudo-scientific information.[8] The most web-reported symptoms related to the intake of self-prescribed dietary supplement containing SR are represented by depression, anhedonia, decreased libido, erectile dysfunction, morphological changes in seminal fluid, increased sebum production, loss of muscle mass, and reduced blood clotting. Moreover, as previously stated, a recent therapeutic application of SR is AGA and its use is associated with the onset of genital system disorders, especially in young subjects.[4] In this context, *e*-phytovigilance should play a relevant role in the monitoring of SR-related web-reported AEs.[8]

In vitro and in vivo studies on SR highlighted its complex mechanism of action, which could be responsible for ED onset.[7] The main plant metabolite, beta-sitosterol, is an inhibitor of the enzyme 5-alpha-reductase (5-AR) which transforms testosterone into its active derivative, dihydrotestosterone.[4,7] This mechanism is similar to that carried out by 5-alpha-reductase inhibitors (5-ARIs) such as finasteride and dutasteride.[9] SR fatty acids are potentially able to decrease the smooth muscle contraction of the prostate and bladder neck, promoting urinary flow and bladder emptying[10] with a spasmolytic effect similar to that of alpha-1-blocking agents.[11] Thus, 5-ARIs and alpha-1-blockers represent the standard therapy for BPH and BPH-associated LUTS,[5] but they could negatively affect erectile function, libido, and ejaculation.[8] Interestingly, post-finasteride syndrome (PFS), consisting in severe neuroendocrine disorders (i.e., ED, gynecomastia, and mental disorders), can often persist after drug discontinuation.[9] The similarity of SR and finasteride mechanisms of action suggests that ED observed in our patient may be a reasonably consequence of SR use. Moreover, primary and secondary hypogonadism, also confirmed in our patient, play a relevant role in the pathophysiology of ED.[12] Notably, it is important to remark the higher dosage (from 400 to 800 mg/die) and longer term use (about a year) prescribed to our patient compared to the treatments reported in clinical trials (320 mg/die, from 8 days to 12 months).[5,6]

This case report highlights a potential association between SR intake and ED onset, a neuroendocrine AE that could be explained by SR pharmacodynamics. Considering that the causal relationship between SR treatment and erectile dysfunction is still rarely

TABLE 1 Case description

Patient	February 2016	April 2016	September 2016	February 2017	July 2017
Age (years)	49				
Smoking	No				
Alcohol drinking	No				
Pathology	LUTS[a] BPH	Improvement[b]			
Comorbidities	None				
Herbal therapy	1 capsule (cps): 200 mg of *Serenoa repens* (W. Bartram)[c] 300 mg of *Urtica dioica* L.[d]				
Prescribed therapy	Two cps/die (SR 400 mg/die)		Four cps/die (SR 800 mg/die)	Stop	
Concomitant treatments	None				
AEs		(ED onset[e])		Reported ED onset[e]	
Dechallange				Yes	
Rechallenge					No
Clinical exams					
TRUS	Peripheral glandular parenchyma finely inhomogeneous; subtly hyperechoic area (15 × 9 mm in the right anterior region); prostate dimensions = 41 × 27 × 44 mm; prostate volume = 26 ml			Prostate dimensions = 44 × 24 × 43 mm; prostate volume = 24 ml; not vascularized hyperechoic area (about 13 × 9 mm); bilobed adenoma (about 30 × 22 × 26 mm), initial intra-adenomatous cystic degeneration	
Blood test				FSH: 15.2 U/L (1.7–11 U/L) testosterone level: 12.3 nmol/L (10.4–34.6 nmol/L)	Testosterone level: 9.7 nmol/L (10.4–34.6 nmol/L)
Bone densitometry				Osteopenia/osteoporosis in both lumbar and femur sites; lumbar bone mineral density (BMD): 0.882 g/cm^2; L1–L4 *T*-score Tot: −2.5 standard deviation (SD); L1–L4 *Z*-score: −1.8SD; left femur BMD Tot: 0.735 g/cm^2; *T*-score Tot: −2.2SD; *Z*-score Tot: −2.0SD	
Naranjo probability score					Probable

[a]Nicturia with 3–4 awakenings per night from 6 months.
[b]Only one awakenings per night.
[c]Small fruit extract (30% fatty acids).
[d]Leaf extract.
[e]The patient reported the ED onset (appeared in April 2016) only at January 2017.

investigated and that SR extracts are also sold with no medical prescription and potential AEs are often undetected, it is mandatory to improve SR safety profile. This issue is of particular relevance considering its recent use for AGA, especially among young subjects. Further clinical studies and appropriate *e*-phytovigilance investigations are needed.

ACKNOWLEDGEMENTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONTRIBUTORS

FF was the principal investigator. FF and FS had clinical responsibility for patients. EG, VM, NL, GC, AV, and FF performed data interpretation. EG, VM, and FS wrote the manuscript. NL, GC, and AV revised the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Eugenia Gallo[1]
Valentina Maggini[1]
Niccolò Lombardi[2,3]
Giada Crescioli[2,3]
Francesco Sivelli[1]
Alfredo Vannacci[2,3]
Fabio Firenzuoli[1]

[1]*CERFIT, Research and Innovation Center in Phytotherapy and Integrated Medicine, Careggi University Hospital, Florence, Italy*
[2]*Department of Neurosciences, Psychology, Drug Research and Child Health, Section of Pharmacology and Toxicology, University of Florence, Florence, Italy*
[3]*Tuscan Regional Centre of Pharmacovigilance, Tuscany Region, Florence, Italy*

Correspondence
Dr. Valentina Maggini, MS, PhD, CERFIT, Research and Innovation Center in Phytotherapy and Integrated Medicine, Via delle Oblate, 4-50141 Florence, Italy.
Email: valentina.maggini@unifi.it

ORCID

Valentina Maggini https://orcid.org/0000-0002-4227-7214

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