

Sexual Dysfunction Related to Drugs: A Critical Review. Part IV: Cardiovascular Drugs

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Abstract

Introduction: Sexual dysfunction is a potential side effect of cardiovascular drugs: this article is a critical review of the current literature. Many studies have been published on this topic. Most of these studies are not methodologically robust, few are RCTs and most did not use a validated rating scale to evaluate sexual functioning. In addition, other methodological flaws limit greatly the conclusions of these studies. Most studies relate to male populations and only a few have been conducted on women. Also, the majority of studies on sexual dysfunction induced by cardiovascular drugs relate to antihypertensive drugs. While there is evidence to suggest that older antihypertensive drugs (diuretics, beta-blockers, centrally acting agents) have a negative impact on erectile function, newer agents seem to have either neutral (ACE inhibitors, calcium antagonists) or beneficial effects (i.e., angiotensin receptor blockers, nebivolol). Other cardiovascular drugs analyzed in this review also appear to have an inhibitory action on sexual function. For men, there is some weak evidence supporting the use of specific treatment strategies for sexual dysfunction associated with these drugs.

Introduction: Sexual Dysfunction Induced by Cardiovascular Drugs

Excluding psychotropic and antiepileptic drugs (for which there are previous published reviews [1–3]), there are many other drugs that may be responsible for sexual dysfunction.

In view of the heterogeneity of these drugs, it was considered useful to list them according to the ATC system used by the World Health Organization. ATC is an acronym for “Anatomical Therapeutic Chemical Classification System”, which can be viewed in detail on the web-site of the WHO [4].

Methods: This study was conducted in 2014 using the paper and electronic resources of the library of the “Azienda Provinciale per i Servizi Sanitari (APSS)” in Trento, Italy (<http://atoz.ebsco.com/Titles/2793>). The library has access to a wide range of databases including DYNAMED, MEDLINE Full Text, CINAHL Plus Full Text, The Cochrane Library, Micromedex healthcare series, BMJ Clinical Evidence. The full list of available journals can be viewed at <http://atoz.ebsco.com/Titles/2793> or at the APSS web site (<http://www.apss.tn.it>). In completing this review, a literature search was conducted using the key words “cardiovascular”, “adrenergic beta antagonist”, “α1-adrenoceptor antagonist”, “angiotensin converting enzyme inhibitor”, “angiotensin receptor antagonist”, “angiotensin receptor blocker”, “beta blocker”, “beta receptor antagonist”, “calcium channel blocker”, “diuretic”, “antihypertensive”, “sexual dysfunction”, “sexual side effects”, “treatment-emergent sexual dysfunction”. All resulting listed articles were reviewed.

Conclusion: The review includes studies that investigated the relationship between these drug treatments and sexual dysfunction. The purpose was to identify possible intervention strategies for sexual dysfunction related to these drugs.

In the following Tables we have indicated only the “drug class”: all drugs listed in the Tables fall within the “Anatomical Main Group” (which corresponds to the first level of the ATC classification system) called “Cardiovascular System”. Most of the studies conducted on the potential side effects of cardiovascular drugs on sexual dysfunction concern antihypertensive drugs. Most of these studies have been conducted on. Erectile dysfunction is the most frequently investigated sexual dysfunction: other sexual dysfunctions are rarely investigated (especially for women).

Although male sexual function has been studied rather extensively, female sexual dysfunction in hypertension is underexplored [5–8]: female sexual dysfunction remains substantially understudied compared to erectile dysfunction [7,9]. The main limitation of existing studies is the failure to use a standard definition for sexual dysfunction: the classification of sexual dysfunction proposed by ICD-10 or DSM-IV-TR or DSM5 (which receives the greatest international consensus) is very rarely used [10–12].

Survey methods are often inadequate: rating scales are rarely used for the detection of specific sexual dysfunctions, with the exception only of the IIEF (International Index of Erectile Function) [13] and the FSFI (Female Sexual Function Index) [14]. According to Rosen [15], however, the IIEF has many limitations: it provides little information on other domains of sexual functioning, other than erection. A second limitation of the IIEF is that it does not evaluate ejaculatory function (i.e., the volume and force of ejaculate, delayed or premature ejaculation, pain/discomfort and pleasure during ejaculation). A third limitation of the IIEF is that it does not provide information about the patient's sexual relationship or the sexual functioning of their partner. A fourth limitation of the IIEF is that it focuses exclusively on vaginal sexual intercourse, and is therefore not appropriate for use in non-heterosexual men [15]. Duncan et al. [16] have proposed the use of another questionnaire to evaluate female sexual functioning, hypertension and medication effects in premenopausal women.

Although questionnaires may not provide objective information on sexual dysfunction, the response rate to direct questioning may be less than the response rate to a questionnaire and may also be affected by the gender or ethnicity of the interviewer [17]. The failure to use specific rating scales means that the conclusions of these studies are limited and inconclusive and that further confirmatory studies are needed.

Although early reports of sexual dysfunction induced by antihypertensive drugs date as far back as 30 and even 40 years ago [18–21], few RCTs (randomized clinical trials) have been conducted.

Due to the methodological limitations of previous studies it is possible to conclude only that the sexual effects of cardiovascular drugs may be either “positive”, “negative” or “neutral”; findings that are difficult to interpret have been reported as “uncertain results”. In view of the extreme heterogeneity of study methods used in the investigation of drug-induced sexual dysfunction, it is impossible to summarize in detail the findings of these studies, which should be consulted for further information.

The findings of existing studies are contradictory. Older antihypertensive drugs (diuretics, beta-blockers, centrally acting agents) have been shown to have a negative impact on erectile function, while newer agents have been shown to have either neutral (ACE inhibitors, calcium antagonists) or beneficial effects (angiotensin receptor blockers, nebivolol) [22–35]: contrasting findings have been described by Erdmann [36] who states that erectile dysfunction is no more common with beta-blockers than with any other drug prescribed for chronic heart failure or hypertension. Similar conclusions are also reached by Ko et al. [37]. Ferrario et al. [38] report that deleterious effects of diuretics and beta-blockers on sexual function have not been consistently found, and that several controlled studies (including TOMHS and a combined analysis of 6 blind randomized prospective trials) have found little or no evidence that sexual side

effects are more common with these agents compared to other antihypertensive medications. The study by Blumentals et al. [39] appears to support the hypothesis that diuretics do not cause erectile dysfunction. Unlike other studies, Shiri et al. [40] found a higher incidence of erectile dysfunction in men using angiotensin II inhibitors compared with non-users.

Several mechanisms of action are involved in the effect of antihypertensive drugs on sexual function [41]. Oxidative stress plays a crucial role in the mechanism of erectile dysfunction, and includes endothelial dysfunction induced by decreased nitric oxide (NO) bioavailability and ROS (reactive oxygen species) overproduction [8]. Angiotensin II is synthesized in the corpus cavernosum, it is involved in detumescence of the corpus cavernosum and produces oxidative stress in the penile endothelium which in turn may lead to the development of erectile dysfunction. It is reasonable to assume that oxidative stress might also be involved in the mechanism of anti-hypertensive drug-induced sexual dysfunction in women [8]. The favorable effects of ARB (angiotensin receptor blockers) on sexual function may be related, in part, to their ability to block angiotensin II, which has recently become recognized as an important mediator of detumescence and possibly of erectile dysfunction [38]. Beta blockers (e.g., atenolol and propranolol) may potentially impact on sexual functioning through a variety of mechanisms, including a reduction in central sympathetic outflow, impairment of vasodilation of the corpora cavernosa, effects on luteinizing hormone and testosterone secretion and a tendency to produce sedation or depression, thereby causing a loss of libido [38]. Alpha blockers are believed to have the potential to interfere with corporal smooth muscle constriction [39]. Digoxin may cause erectile dysfunction by acting on corpus cavernosum smooth muscle contractility and or by influencing libido or serum testosterone, estrogen or luteinizing hormone levels [19,42]. However, other studies have shown no action of digoxin on plasma steroid levels [43,44]. There have been reports of gynecomastia caused by increased levels of prolactin during treatment with calcium channel blockers and with spironolactone [45,46]. Psychological factors (“nocebo effect”) have also been implicated as being responsible for sexual dysfunction in patients treated with antihypertensive drugs [47,48]. It therefore remains unclear whether the effects on sexual function are due to the antihypertensive drugs or due to the hypertension itself, or to both [24,25,49].

Discussion and Conclusion

▼
In keeping with Düsing [25], we found that the number of reviews and commentary articles on the effects of antihypertensive treatment on sexual function far exceeds the number of original study reports.

Table 1 Type of effect on sexual function.

negative effect	(–)
no significant effect	(+/-)
positive effect	(+)
uncertain results	(?)

We have defined the effect of drugs on sexual function as “positive” (+), “negative” (–) or “neutral” (+/-); findings difficult to interpret are referred to as “uncertain results” (?)

In addition, there is remarkably few data on sexual dysfunction and the widely prescribed combination antihypertensive treatments. In short, only a large well designed, randomized, double-blind, prospective trial can clarify questions about the specific effects of various antihypertensive drug classes on sexual function [50,51].

Although the British Society for Sexual Medicine highly recommends the routine assessment of sexual function prior to initiation of an antihypertensive treatment, this recommendation remains largely ignored by clinicians [52,53]. In fact, only a minority of CPGs (clinical practice guidelines) for the treatment of hypertension actually consider erectile dysfunction or other

Table 2 Effects of cardiovascular drugs on sexual function.

Drug class	Drug	Effect on sexual function in men	Effect on sexual function in women	Effect on sexual function in men and women
Antihypertensives, anti-adrenergic agents, centrally acting		(-) [25, 63]		
	methyldopa	(+/-) [18], (-) [64-66], (?) [67]	(?) [68]	
	clonidine	(+/-) [69], (-) [66], (?) [67]	(?) [68], (+/-) [69]	
	reserpine	(?) [67]	(?) [68]	
Antihypertensives, antiadrenergic agents, peripherally acting, guanidine derivatives				
	betanidine	(-) [18]		
	guanethidine	(-) [18, 67]	(?) [68]	
Antihypertensives, antiadrenergic agents, peripherally acting, alpha-adrenoreceptor antagonists		(-) [39]		
	doxazosin	(+/-) [70]		
	prazosin		(+/-) [69]	
Beta blocking agents, selective			(-) [6]	(+/-) [36]
	metoprolol	(-) [71], (+/-) [72]	(-) [8]	(+/-) [73]
	atenolol	(-) [74-77], (+/-) [48, 78]	(-) [79]	
	acebutolol	(+/-) [70]		
	nebivolol	(+) [71, 74, 80-83]		
	bisoprolol			(+/-) [84]
Beta blocking agents, non-selective		(-) [25, 63]		(+/-) [37]
	propranolol	(-) [64-67]		(+/-) [73]

Table 3 Effects of cardiovascular drugs on sexual function.

Drug class	Drug	Effect on sexual function in men	Effect on sexual function in women	Effect on sexual function in men and women
Beta blocking agents, alpha-1 and beta blocking agents				
	labetalol		(?) [68], (-) [85]	
	carvedilol	(-) [81, 86]		
Antihypertensives, arteriolar smooth muscle, agents acting on hydrazinophthalazine derivatives				
	hydralazine	(-) [66]		
Diuretics, low-ceiling diuretics, thiazides		(-) [25, 63, 87]	(?) [68]	
	bendroflumethiazide	(-) [63]		
	hydrochlorothiazide	(-) [66, 88-89]		(+/-) [84]
	trichlormethiazide	(-) [77]		(-) [90]
Diuretics, high-ceiling diuretics, excluding thiazides, sulfonamides.				
	furosemide	(+/-) [88]		
diuretics, low-ceiling diuretics, excluding thiazides, sulfonamides		(-) [25, 63]		
	chlortalidone	(-) [70, 74, 78, 91]		
Potassium-sparing agents, aldosterone antagonists		(-) [25, 63]		(-) [92]
	spironolactone	(-) [46, 93]		(-) [92, 94]
	eplerenone			(-) [95]
Potassium-sparing agents, other potassium-sparing agents				(-) [92]
	amiloride			(-) [92]
Cardiac glycosides, Digitalis glycosides		(+/-) [43, 44, 96]		
	digoxin	(-) [19, 42, 97, 98]		
Antiarrhythmics, class Ia				
	disopyramide	(-) [99]		

Table 4 Effects of cardiovascular drugs on sexual function.

Drug class	Drug	Effect on sexual function in men	Effect on sexual function in women	Effect on sexual function in men and women
Antiarrhythmics, class Ic	propafenon	(-) [100]		
Agents acting on the renin-angiotensin system, ACE (angiotensin-converting enzyme) inhibitors		(+) [22, 57, 76], (-) [39]		
	captopril	(+/-) [65, 77]		
	enalapril			(+/-) [70, 84, 101]
	lisinopril	(+/-) [76, 88]		
Agents acting on the renin-angiotensin system, angiotensin II antagonists (ARB: angiotensin receptor blockers)	ramipril	(+/-) [102]		
		(+) [22, 29, 38] (-) [40]		(+) [53]
	losartan	(+) [103]		
	valsartan	(+) [27, 83, 86, 104, 105], (+/-) [75]	(+) [79]	
Selective calcium channel blockers with mainly vascular effects, phenylalkylamine derivatives	irbesartan	(+) [106–108]	(+) [8]	
	telmisartan	(+/-) [102]		
		(+) [22]		
Selective calcium channel blockers with mainly vascular effects, benzothiazepine derivatives	verapamil	(-) [109], (+/-) [88]		
	diltiazem	(?) [88]		
Selective calcium channel blockers with mainly vascular effects, dihydropyridine derivatives				
	amlodipine	(+/-) [70]		(+/-) [84, 101]
	nicardipine			(+/-) [90]
	nifedipine	(-) [77], (?) [88]		
Vasodilators used in cardiac disease, organic nitrates	felodipine	(+/-) [108]	(+) [8]	
		(+/-) [40]		

sexual issues as potential adverse outcomes or as factors to consider in treatment [54]. It has been shown that sexual function is not routinely discussed with patients in cardiology practices [55]. A recent study has shown that cardiologists' knowledge about the effects of cardiovascular drugs on sexual function appears to be insufficient [56]. Increased awareness among cardiologists on sexual function, and adequate assessment and appropriate counselling of any identified sexual impairment is needed [57].

Sexual function should be assessed in all hypertensive patients, both at diagnosis and after the introduction of new drugs. The first step in its management is to identify and effectively treat any comorbid conditions. Secondly, it is prudent to adjust the antihypertensive treatment with consideration of the comorbid illness and also after taking into account the risk of sexual dysfunction for each choice of drug [58].

In men, symptomatic treatment with inhibitors of phosphodiesterase-5 has been evaluated [59, 60].

The use of alpha-blockers may lead to a significant interaction with PDE-5 inhibitors, however the use of organic nitrates, either short-acting, or long-acting in patients with ischemic heart disease, is a contraindication for the use of PDE-5 inhibitors [61, 62]. Sublingual apomorphine has also been proposed in the management of erectile dysfunction induced by antihypertensive drugs [58].

The following **Table 1–4** summarize the effect of cardiovascular drugs on sexuality.

Randomized clinical trials conducted primarily on female users are needed.

In general, further studies using specific diagnostic criteria and rating scales in order to detect and to specify the type and the extent of sexual dysfunction induced by cardiovascular drugs are needed.

The widely reported findings in the literature that some cardiovascular drugs have either neutral or beneficial effects on erectile function should be confirmed by further studies using more precise methods of investigation, in particular studies that use specific diagnostic criteria and rating scales.

Conflict of Interest



Prof. Dr. Andreas Conca has served as consultant for Lilly (Italy) and on speakers bureau of Janssen, Lilly, Otsuka, Lundbeck. Dr. Giupponi has served as a speaker for Lilly (Italy).

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