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REVIEW OF THE POSITIVE AND NEGATIVE EFFECTS OF CARDIOVASCULAR DRUGS ON SEXUAL FUNCTION

**A proposed table for use in
clinical practice**

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INTRODUCTION

In the US, the class ‘lipid regulators’ was the most prescribed drugs class in 2010 with 255.5 million prescriptions, beta blockers (plain and in combinations) and ACE inhibitors followed on the second and third place with 191.5 million and 168.7 million prescriptions, respectively [1]. In this era of high life expectancies, this therapy will be received during a substantial part of patients’ life [2]. The side effects induced by antihypertensive drugs, including sexual dysfunctions, are strongly associated with an impaired quality of life [3]. As many as 70% of hypertensive patients who experience side effects are non-compliant with their antihypertensive medication and have a 40%-60% higher rate of therapy discontinuation, compared to patients whose quality of life is unaffected [4]. Some classes of antihypertensive drugs have shown to cause sexual dysfunction, but others have been described to have beneficial effects on sexual health. Physicians and especially cardiologist and general practitioners should be aware of these possible effects of the medication they prescribe, because it makes them able to minimise sexual side effects and maximise quality of life and compliance with therapy. However, previous data obtained by our research group (part I) showed that cardiologists seem to lack the sufficient knowledge about the effects cardiac medication can have on sexual function [5].

With this review we aimed to provide a practical overview of the available literature regarding the effects of eight widely used classes of cardiovascular agents on sexual function. A clear overview table applicable for both male and female patients was provided for use in clinical settings.

METHODS

Data sourcing

A review of the literature was assessed using PubMed and MEDLINE, searching for articles from 1970 to 2012. The search strategy involved the (MeSH) terms 'sexual dysfunction', 'erectile dysfunction', 'sexual side effects', 'side effects', 'sexual adverse effects' and 'adverse effects' consecutively in combination with the MeSH terms: Adrenergic Beta Antagonists, Angiotensin-Converting Enzyme Inhibitors, Angiotensine Receptor Antagonists, diuretics, Calcium Channel Blockers, hydroxymethylglutaryl-CoA Reductase inhibitors, Digoxine and more general terms: 'antihypertensive agents', 'beta blocker', 'beta receptor antagonist', 'diuretic' , 'α1-adrenoceptor antagonist', 'Angiotensin Converting Enzyme inhibitor', 'Angiotensin Receptor blocker', 'calcium channel blocker', 'digoxin', 'heart glycosides', 'statins' and 'nitrates'. The last search was conducted in March 2013. The reference list was hand-searched and all relevant studies and reviews were read and reviewed.

Study selection

All clinical studies reporting about effects on male or female sexual function in relation to a cardiovascular agent were included. These included: animal studies, observational studies, small clinical studies, meta-analyses and randomized controlled trials. Studies not published as full-text articles, single case reports and opinion articles were excluded, as well as articles not written in English. Hard copies of all relevant articles were obtained and read in full. Since the purpose of this review was to provide a positive overview table listing the effects of the eight most widely used cardiac drugs classes for use in clinical practice, we used randomized controlled trials (RCT), double-blind cross-over studies and questionnaire based prospective and retrospective studies in human males and females for the overview tables (Tables 1 and 2).

RESULTS

Table 1. Overview of studies* showing effects of antihypertensive agents on sexual function in (human men and women

Effect on sexual function	Beneficial	Neutral	Negative
β-blockers	Nebivolol: Doumas et al., 2006 Brixius et al., 2007	Medical Research Council, 1981	Bauer et al., 1978
		Wassertheil-Smoller et al., 1991	Hogan et al., 1980
		Rosen et al., 1994	Suzuki et al., 1988
		Neaton et al., 1995	Fogari et al., 1998
		Grimm et al., 1997	Buchardt et al., 2000
		Perez-Stable et al., 2000	Fogari et al., 2001
		Franzen et al., 2001	Llisteri et al., 2001
			Fogari et al., 2002
			Ko et al., 2002
			Fogari et al., 2004 (♀)
			Doumas et al., 2006 (♀)
			Cordero et al., 2010
			Ma et al., 2012 (♀)
Diuretics		Croog et al.,1988	Bulpitt et al., 1973
		Prisant et al. 1999	Hogan et al., 1980
		Doumas et al., 2006 (♀)	Medical Research Council,1981
			Curb et al., 1985
			Wassertheil-Smoller et al., 1991
			Chang et al,; 1991
			Duncan et al., 1993
			Rosen et al., 1999
			Grimm et al., 1997
			Ogihara et al., 2000
			Epstein et al., 2011
α-blockers	Grimm et al., 1997	Lowe et al., 1994	
		Fawzy et al., 1995	
		Lepor et al., 1997	
		Buchardt et al., 2000	
		Llisteri et al., 2001	
		McConnell et al., 2003	
		Kirby et al., 2003	
		De Rijke et al., 2004	

Table 1. continued

Effect on sexual function	Beneficial	Neutral	Negative
ACE inhibitors	Croog et al.,1986	Croog et al.,1988	Llisteri et al., 2001
	DiBianco et al., 1991	Suzuki et al., 1988	
	Gupta et al., 1995	Fletcher et al., 1990	
	Mancini et al., 1996	Steiner et al., 1990	
	Gupta et al., 1998	Pelmer et al., 1992	
		Grimm et al., 1997	
		Fogari et al., 1998	
		Doumas et al., 2006 (♀)	
ARBs	Fogari et al., 2001	Suzuki et al., 1988	
	Llisteri et al., 2001	Rosen et al., 1994	
	Dusing et al., 2003	Fogari et al., 1998	
	Yamamoto et al., 2003	Fogari et al., 2002	
	Della Chiesa et al., 2003	Bohm et al., 2010	
	Fogari et al., 2004 (♀)	Doumas et al., 2006 (♀)	
	Ma et al., 2012 (♀)		
	Chen et al., 2012		
	Segal et al., 2012		
Calcium channel blocker		Suzuki et al., 1988	Tanner et al., 1988
		Morrisette et al., 1993	
		Omvik et al., 1993	
		Kroner et al., 1993	
		Grimm et al., 1997	
		Ogihara et al., 2000	
		Burnier et al., 2007	
		Doumas et al., 2006 (♀)	
Statins	Saltzman et al., 2004	Mastalir et al., 2011	
	Herrmann et al., 2006	Trivedi et al., 2012	
	Dogru et al., 2008		
	Gokkaya et al., 2008		
	Dadkhah et al., 2010		
Cardiac glycosides		Kley et al., 1982	Stoffer et al., 1973
		Kley et al., 1984	
		Bellman et al., 1984	

* Randomized controlled trials, double-blind crossover studies and questionnaire based prospective studies.

1. β -blockers:

Several reports have shown serious side effects on sexual function due to the use of (centrally acting) β -blockers; in particular erectile dysfunction (ED) and loss of desire have been reported [12;14;16;44]. One of the proposed mechanisms by which β -blockers may induce sexual dysfunction is inhibition of the sympathetic nervous system, which is involved in the integration of erection, emission and ejaculation, in the regulation of luteinizing-hormone secretion and in the stimulation of testosterone release [45]. Indeed, several studies showed a depression in testosterone level in patients receiving a β -blocker [18]. In contrast, in other more recent trials no significant adverse effects on sexual function were found with metoprolol [46], propranolol [47], acebutolol [18] and atenolol [8]. In the few studies concerning sexual function in female patients with antihypertensive treatment, metoprolol seems to negatively affect female sexual function index scores (FSFI) [20], especially in comparison with ARBs which seem to ameliorate FSFI scores [48;49]. After reviewing 15 trials involving 35.000 subjects, Ko et al. reported that the frequency of sexual dysfunction with β -blockers was 21.6% and 17.5% in the placebo group. In addition, β -blockers were associated with an increased risk of reported impotence in men (RR, 1.22; 95% CI, 1.05-1.41). Risk of withdrawal due to a sexual dysfunction was substantially increased (RR, 4.89; 95% CI, 2.98-8.03); however, the annual absolute increase in risk of withdrawal was only 2 per 1000 patients (95% CI, 0-5) [19]. Silvestri et al. showed that knowledge and prejudice about side effects of beta-blockers can produce anxiety, which may cause erectile function [50]. A critical review used this study to underpin their doubts about the sexual side effects of β -blockers [51]. All in all, the final word has not been said about the effect of β -blockers on sexual function, yet the majority of studies about regarding this topic point to negative effects of first- and second-generation β -blockers. The guidelines regarding management of ED published by The British Society for Sexual Medicine highly recommend routine assessment of sexual function prior to initiation of antihypertensive treatment [52]. Furthermore, if patients present with sexual dysfunction during treatment with β -blockers a switch to Nebivolol, a novel third-generation β -1 blocker with a greater degree of selectivity for β -1 adrenergic receptors, might be a solution. Nebivolol appears to have a very low risk of sexual side effects compared to other agents in its class [6;53;54]. In a study designed to compare the effects of metoprolol and Nebivolol in erectile tissue (MR-NOED), Nebivolol was even shown to significantly improve erectile function of hypertensive patients due to nitric oxide modulation [7]. In concordance with the recent review by Baumhakel et al., we can conclude that selective β -blockers might impair erectile function. However, considering the strong correlation and pathophysiological link between endothelial and erectile function, beta-blockers with beneficial effects on nitric oxide synthase and oxidative stress can improve erectile function [55].

2. Diuretics:

Diuretics are considered one of the most implicated classes regarding sexual dysfunction. Although the mechanism remains ill defined [56], striking results with respect of drug treatment in male hypertensive patients were obtained in the Medical Research Council Trial [57], a single blind study on the basis of

23,582 patients-years. In this trial the prevalence of impotence was measured by questionnaires after 2 years of treatment with propranolol, bendroflumethiazide or placebo. Impotence was mentioned in 10.1% of the placebo group, in 13.2% of the propranolol group and in 22.6% of the bendroflumethiazide group. Incidence of withdrawal from randomized treatment because of impotence (rates per 1000 patient-years) was 0.89 in the placebo group, 5.48 in the propranolol group and 19.58 in the bendroflumethiazide group. The TOMHS trail (The Treatment Of Mild Hypertension Study) a 4-year follow up, double-blind RTC in 557 men and 345 women, showed that chlortalidone at a dose of 15 mg/day may also be suspected to negatively affect sexual function in men [11]. In the Trail of Antihypertensive Interventions and Management (TAIM), erection-related problems worsened in 28% of patients receiving chlortalidone, in 11% of patients receiving atenolol and in 3% of patients receiving placebo [8].

Smaller studies pointed to hydrochlorothiazide and chlortalidone causing loss of libido and ED [58;59]. However, sex-life satisfaction was similar for treatment with hydrochlorothiazide (alone or in combination with atenolol) and the more modern treatment with candesartan alone or in combination with the calcium antagonist felodipine [60]. In one of few studies addressing sexual function in women thiazide diuretics may be associated with decrease in vaginal lubrication [61]. In addition, although an effective anti-aldosterone agent, spironolactone has a tendency to produce undesirable sexual adverse events; at standard dose, breast tenderness, gynaecomastia and erectile dysfunction can occur in men, whereas menstrual abnormalities may occur in premenopausal women [62]. These adverse effects are due to binding of spironolactone to progesterone and androgen receptors and represent a substantial reason for drug discontinuation [63]. In the treatment of hypertension, when compared with spironolactone, the selective mineral corticoid receptor antagonist eplerenone provides a reduced incidence of gynecomastia [64]. The potassium-sparing diuretics amiloride and triamterene do not seem to affect sexual function [62].

3. α -adrenergic antagonists:

Since α -adrenergic antagonists are first-line therapy for benign prostate hyperplasia (BPH) but only second line agents for the treatment of hypertension (doxazosine and terazosin), most knowledge regarding sexual adverse effects α -adrenergic antagonists comes from BPH-studies. A recent systematic review on the effect of α_1 -adrenoceptor antagonists on male sexual function was performed by van Dijk et al.[65]. They showed α -adrenergic antagonists used as treatment for hypertension does not seem to adversely effect sexual desire. The net effect of α -adrenergic antagonists on erectile function is likely to depend on the balance between pro-erectile effects in the brain and the penis and anti-erectile effects as a result of blood pressure lowering mechanisms. A 4-year RCT comparing doxazosine in the treatment of hypertension showed that α -adrenergic antagonists were not associated with ED; it may even improve pre-existing sexual dysfunction [11].

Ejaculatory dysfunction, predominantly an ejaculation and decreased ejaculate volume, is associated with tamsulosin and silodosin, which are superselective α_{1A} -adrenergic receptor antagonists. Ejaculatory dysfunction is rare with α_1 -adrenergic receptor antagonists that are not selective for the α_{1A} -adrenergic receptor subtype, namely alfuzosin, doxazosin, and terazosin [66;67]. In conclusion, the α -adrenergic antagonists prescribed as second-line antihypertensive treatment does not seem to affect erectile function or ejaculatory function.

4. Cardiac glycosides

In a community-based epidemiologic study of 1709 men, analysis of data on multiple cardiovascular medications, digoxin use had the highest association with complete ED [68]. The mechanism of action is not completely understood. Early studies linked sexual dysfunctions to hormonal alterations observed with digoxin use [69;70]. Later studies failed to confirm a relationship with digoxin use and changes in serum hormone levels [71-73]. Another theory proposed is the digoxin-associated inhibition of the corpus cavernosum smooth muscle sodium pump activity, which promotes corporeal contraction and impedes nitric oxide induced relaxation, leading to ED [68].

5. ACE inhibitors

Angiotensin-converting enzyme (ACE) inhibitors, particularly captopril, have been associated with improved sexual function [46;51,52]. It has been suggested that potential favorable sexual side effects of captopril were secondary to improved cardiac function; however, sufficient data to support this hypothesis do not exist [74]. The TOMHS trail

showed a significant decrease of sexual activity rate through 24 month in men taking enalapril, compared to placebo [11]. But, in a comparing study between the ACE inhibitor lisinopril and the β -blocker atenolol, lisinopril only caused a temporary decline in sexual activity. After 4 weeks of treatment the sexual intercourse rate was reduced but tended to recover with ongoing treatment. Atenolol on the other hand caused a chronic worsening of sexual function [17]. The fact that ACE inhibitors work through other channels than the sympathetic nervous system in lowering blood pressure might in part explain their reduced impact on sexual function. Furthermore, ACE inhibitors have been reported to reverse endothelial dysfunction by preventing the effects of angiotensin II, prolonging the half life of nitric oxide and decreasing degradation of bradykinin. This latter is a potent stimulator of nitric oxide and prostacyclin release and may therefore benefit erectile function [34]. It can be concluded that ACE inhibitors have no effect, or may even have a positive effect on sexual function, but its precise role remains to be elucidated.

6. Angiotensin II receptor antagonists (ARBs)

Multiple studies showed beneficial effects of ARBs on sexual function. In a cross-over study comparing atenolol with valsartan, valsartan increased sexual activity significantly compared with atenolol (which significantly reduced sexual activity); however, these changes were not significant compared with placebo [18]. Compared with carvedilol, long-term therapy with valsartan was significantly associated with improved sexual activity [16]. Dusing et al. reported reduction in ED with improved orgasmic function, intercourse and overall sexual satisfaction in a group of 2550 hypertensive patients treated with valsartan [75].

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, thereby possibly promoting the development of ED [76]. In hypercholesterolemic apolipoprotein E knockout mice, endothelial function of the corpus cavernosum as a surrogate for ED was improved in tandem with a reduction in aortic plaque load by ARB treatment [77]. Observational studies showed an increase in sexual activity in hypertensive subjects or patients with metabolic syndrome, treated with an ACE inhibitor or ARB compared to patients with other therapies such as β -blockers [15;76;78]. No differences were seen between use of ramipril, telmisartan or a combination of the two and there was no evidence for adverse effects of both treatments on erectile function [61]. The beneficial effects on sexual function were confirmed in a study among 2202 hypertensive patients, reporting an increase of sexual intercourse per week when treated with Valsartan. A recent double-blind randomized study among 1549 patients in which 400 participants

received ramipril, 395 telmisartan and 381 a combination of the two, no benefits of ARBs on erectile dysfunction has been proven [79]. It has to be marked however that ARBs were added on top of previous multidrug regime in high-risk patients and thus conclusions regarding the effects of ARBs monotherapy cannot be drawn [80]. In recent randomized trials, Irbesartan use after nerve-sparing prostatectomy in patients with normal preoperative erectile function was shown to improve erectile function recovery [81]. Losartan seemed to have positive effects on erectile function as well [82]. Concerning female sexual function, Valsartan has been shown to improve sexual desire and sexual fantasies, while atenolol significantly worsened these items [49]. Likewise, women treated with the combination Irbesartan-Felodipine showed significant higher FSFI scores than those treated with the Metoprolol-Felodipine combination [48].

Overall, ARBs seems to have beneficial effects on sexual function and, if possible, should be used in treatment of patients complaining of sexual side effects of other cardiovascular agents, or in men with pre-existent ED.

7. Calcium Channel Antagonists

These agents increase dilatation and lower blood pressure by reducing calcium entry into the smooth muscle of the blood vessels [83]. Due to this mechanism of action, calcium antagonists are not expected to cause sexual dysfunction [44]. Indeed, in the TOMHS trial, amlodipine did not appear to affect sexual function [11], neither did nifedipine [84], nifedipine or diltiazem in other studies [85;86]. In two early studies, gynecomastia and problems with ejaculation occurred in patients who received calcium channel blocker therapy, probably related to hyperprolactinemia [14;87]; this was never investigated in later studies. In a double blind comparative study in 451 patients of both sexes, patients were allocated either to treatment with the calcium channel blocker amlodipine or with the ACE inhibitor enalapril for 50 weeks after a 4 week placebo run-in. Sexual function was not different between the two groups [85]. Taken together, the available data suggest that calcium channel antagonists do not a detrimental effect on sexual function.

8. Statins (3-hydroxy-3-methylglaryl-coenzyme A reductase inhibitors)

Cholesterol is the biochemical precursor for testosterone. An experimental study and a RCT showed reduced testosterone in men using a statin although the average effect is modest [88;89]. Studies in small samples or with lower statin doses did not show significant changes in average testosterone levels [90]. An *In vitro* study demonstrated statin effects on human testicular testosterone synthesis [91] and in animals effects on the morphology and function of Leydig cells have been seen after statin administration [92]. In

a prospective observational study among 93 men it was suggested that ED following statin therapy is more likely in patients with severe endothelial dysfunction due to established cardiovascular risk factors including age, smoking and diabetes [93]. On the other hand, statins have been reported to improve erectile function when the cohorts had no other cardiovascular risk factors accept for untreated ED [94-96]. Furthermore, statins seem to increase the beneficial effects of sildenafil through endothelial function benefits [97-100]. These endothelial function benefits may rely on the antioxidant effects of statins [[101;102], which clearly predominate over the pro-oxidant effects [103]. On the whole, evidence shows that statins can have a beneficial effect on erectile function because the beneficial effects seem to be more powerful than the negative effects on the testosterone level [104].

Table 2. Practical overview of the effect of commonly prescribed cardiac drugs classes on sexual function

Drug	Effect
β-blockers*	-
Cardiac Glycosides	-
Diuretics†	-
α-blockers	±
ACE inhibitors	±
Calcium channel blockers	±
Angiotensin Receptor Blockers	+
Statins	+

Information from randomized controlled trials, reviews, double-blind cross-over studies and prospective questionnaire studies in men and women;

* Except for Nebivolol, this seems to have positive effects;

† Except for potassium sparing diuretics, which do not appear to cause sexual adverse effects;

- = negative effect, ± = no effect, += positive effect

DISCUSSION

Based on absence of hard data coming from randomized controlled studies, the Second Princeton Consensus Management Recommendation state that ‘a change in class of antihypertensive medication rarely results in the restoration off sexual function’ [105]. However, the available data point towards significant benefits in sexual function when switching prior antihypertensive therapy [4;75;78;106]. This review demonstrated that significant improvements in male and female sexual function can be achieved when cardiovascular drug treatment is switched to either Nebivolol or an ARB and that use of statins can improve sexual function. Also, several lines of evidence indicate that older-generation beta blockers, digoxin and diuretics can indeed deteriorate sexual function. This knowledge should become incorporated in cardiologists and general practitioners practices, because it is necessary to be able to offer patients a tailor-made medical treatment, to avoid or diminish side effects and therewith improve compliance with therapy.

For this review we used RCTs next to double blind crossover studies, observational- and questionnaire studies. The impact of the studies was not scored or indexed for; consequently, definite conclusions can not be inferred from this review. It should be kept in mind that more than two-third of the hypertensive patients require combination therapy of at least two drugs to reach their blood pressure goals. Therefore, combination therapy or therapeutic strategies will have to be compared in the future with respect to their effects on sexual function [56]. Nevertheless, hard data from large randomized controlled trials regarding the switch of cardiovascular drugs in monotherapy or multidrug regimens for the benefit of sexual function are lacking. This review can be helpful for cardiologists, urologists, general practitioners and other healthcare professionals who deal with patients complaining from sexual dysfunction during treatment with cardiovascular agents. The overview table shows clearly which effects were found in the numerous studies that were performed until now.

Poor adherence in antihypertensive drug therapy is a critical contributor to unsatisfactory blood pressure control rates and erectile dysfunction has been shown to contribute to poor adherence [4]. Management of sexual dysfunction induced by hypertension and its related medication represents a challenge in the everyday clinical practice. For patients presenting with sexual dysfunction during cardiovascular drug therapy, lifestyle modification and switching medication according to the information conveyed above should be the first line of action unless the current treatment is absolutely indicated [107]. Since ARBs are now generic, it should be considered to use them as first line therapy in men in which erectile function is important (most men); rather then relying on switching

in the case they are brave enough to mention ED. If there is no advantage for treatment of ACE-inhibitors above ARBs, we suggest ARBs should be considered as first line therapy, instead of allowing sexual dysfunction to happen and then prescribe a (self-funded) PDE-5 inhibitor, because this is not a satisfactory solution for most patients. However, in males with persisting erectile dysfunction (and despite the use of ARBs) PDE-5 inhibitors should be offered as the next step, since they exert beneficial effects through improved adherence. It was shown that hypertensive men with erectile dysfunction are more likely to initiate rather than discontinue, and add rather than reject antihypertensive medication when receiving PDE-5 inhibitors [108].

Literature about effects of antihypertensive drugs in female sexual function is limited, but findings from small observational and clinical studies point towards similar effects of antihypertensive drugs in male and female sexual function [4;20;109]. Female cardiac patients presenting with sexual dysfunction, should receive the same treatment and advice as male patients concerning lifestyle modifications. And, if not contraindicated ARBs should be considered as first line therapy in females too, as literature points to benefits of ARBs compared to beta-blockers in female sexual function. If these measures are insufficient, a referral to a sexologist or a gynaecologist can be considered.

As was seen in the evaluation of cardiologists concerning their knowledge and practice patterns in regard to sexual dysfunction [110] and the sexual side effects of cardiovascular medication [5]. Cardiologists lack sufficient knowledge and training to provide solutions and advise necessary to ameliorate patients sexual function and with that, to ensure adherence to cardiovascular treatment. In our opinion, appropriate education of cardiologists and other involved healthcare professionals is needed to overcome this problem. Furthermore, sexual effects of cardiovascular medication in both male and female dysfunction are a broad area for future research; in the meanwhile the proposed overview table can be of help in the clinical setting.

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