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ANTIHYPERTENSIVE AGENTS: MECHANISMS OF DRUG ACTION (HM SIRAGY AND B WAEBER, SECTION EDITORS)

Antihypertensive Treatment and Sexual Dysfunction

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Abstract Sexual dysfunction is frequently encountered in hypertensive patients. Available data indicates that sexual dysfunction is more frequent in treated than in untreated patients, generating the hypothesis that antihypertensive therapy might be associated with sexual dysfunction. Several lines of evidence suggest that differences between antihypertensive drugs exist regarding their effects on sexual function. Older antihypertensive drugs (diuretics, beta blockers) exert detrimental effects on erectile function whereas newer drugs (nebivolol, angiotensin receptor blockers) have neutral or even beneficial effects. Phosphodiesterase (PDE)-5 inhibitors are effective in hypertensive patients and can be safely administered even when multidrug regimes are used. Precautions need to be taken with alpha blockers or patients with uncontrolled high-risk hypertension, while co-administration with nitrates is contraindicated.

Keywords Hypertension · Sexual dysfunction · Erectile dysfunction · Female sexual dysfunction · Antihypertensive therapy · Antihypertensive drugs · Diuretics · Beta blockers · ACE-inhibitors · Angiotensin receptor blockers · PDE-5 inhibitors · Alpha blockers · Lifestyle modification

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Introduction

Sexual dysfunction has been previously considered to be of psychologic origin; accumulating data, however, point towards a vascular origin in the majority of affected individuals. Hypertension is associated with structural and functional abnormalities of the vessels all over the body, and genital vessels could not be an exception [1•]. In addition, hypertension treatment includes various classes of antihypertensive drugs, and sexual dysfunction could in fact be the result of a drug side effect. It is therefore significant to know - from the clinical point of view - whether sexual dysfunction is the result of hypertension per se, an adverse event of antihypertensive treatment, or a combination of both [2–4].

For the proper evaluation of hypertension effects and the contribution of antihypertensive treatment on sexual dysfunction, it has to be examined whether: i) the prevalence of sexual dysfunction is higher in hypertensives than in normotensives, ii) the prevalence of sexual dysfunction is higher in treated than in untreated patients, iii) antihypertensive therapy is associated with new-onset sexual dysfunction or worsening of preexisting disease, and iv) antihypertensive drugs exert different effects on sexual function, and a change in class could improve or even restore sexual function.

Available data clearly indicate that sexual dysfunction is more frequently encountered in hypertensive patients than in normotensive individuals [2, 5–7]. Moreover, data from observational studies consistently point towards a higher prevalence of erectile dysfunction in treated than in untreated hypertensive patients, implying that hypertension treatment contributes to sexual dysfunction [2, 5–7]. It cannot be excluded, however, that treated compared to untreated patients had more severe hypertension or significantly

higher target organ damage or more comorbidities, and these factors are the actual contributors and not the antihypertensive drug therapy.

The prevalence of sexual dysfunction in hypertensive patients is considerably high, underlining the clinical significance of this aspect in patients with hypertension. In addition, prevalence of both hypertension and sexual dysfunction is expected to rise further in the future, given their age-dependent relationship combined with the prolongation of life-expectancy [8, 9]. The magnitude of the problem within the hypertensive population combined with the lack of appropriate training in the field of sexual dysfunction in both under- and post-graduate education, calls for a meticulous approach of the hypertensive individual facing sexual problems. The European Society of Hypertension recognized the problem and took significant steps for its management. Along with lectures and round tables during the annual meetings, two newsletters have been prepared [10, 11], a working group has been formed, and the position paper of this group has been recently published [12••].

The management of arterial hypertension includes lifestyle modification and antihypertensive drug treatment. Given that hypertension and sexual dysfunction usually coincide it would be significant to know the effects of lifestyle modification and antihypertensive drug therapy on sexual function. On the other hand, PDE-5 inhibitors, which represent the main weapon in sexual dysfunction treatment, possess vasorelaxing properties and might interact with antihypertensive drugs; it would be clinically important to know the safety of these drugs when given concomitantly with antihypertensive therapy. The aim of this review is to critically evaluate available data addressing the above mentioned aspects.

Lifestyle Modification and Sexual Function

The effect of lifestyle modification on sexual activity has not been adequately addressed. Previous studies point towards a beneficial effect of lifestyle modification on sexual function. Weight reduction has been associated with significant improvements of sexual function in obese individuals with erectile dysfunction [13•]; likewise, weight loss proved to be beneficial in diabetic patients with erectile dysfunction, showing significant improvement in IIEF score (from 17.3 to 18.3) compared to insignificant changes in the control group [14]. Another line of evidence comes from effects on sexual function of gastric bypass surgery in morbidly obese males. It has been shown that drastic weight reduction in these patients had significant beneficial effects in erectile function, sexual drive, sexual satisfaction, ejaculatory function, and problem assessment [15]. Similar improvements in male and female sexual function were observed by Mediterranean diet in men and women with metabolic syndrome [16, 17]. Moreover, a regular exercise program appeared to be beneficial for sexual function beyond benefits on cardiovascular risk profile [18]. Likewise, an interval exercise program was implemented for 8 weeks in hypertensive patients with severe erectile dysfunction had positive effects on sexual functioning (IIEF score: from 8.1 to 8.9) [19]. The beneficial effects of regular exercise are supported by recent experimental data showing that regular physical exercise may attenuate the development of erectile dysfunction in rats by enhancing nitric oxide bioavailability [20].

It has to be admitted, however, that although these studies were randomized and controlled, they suffer from the small number of included individuals. In addition, several other limitations can be easily recognized [21]. In particular, in the study by Lamina et al [19], all hypertensive patients were on methyldopa, a drug known to exert negative effects on erectile function; moreover, the 1 week washout period was too short for a proper evaluation of erectile function, and the dose of methyldopa during the study as well as the percentage of patients on previous methyldopa therapy are not provided, casting doubts about the validity of study findings. In the study of Wing et al [14], patients were given concomitant therapy with insulin, antidiabetic and antihypertensive drugs, and even PDE-5 inhibitors use was allowed. Even more, individuals participating in this study were followed by their treating physicians, and adjustments in medications were free. Since antihypertensive drug categories show significant diversity on sexual function effects, the above concerns have to be taken into account.

In the effort to overcome the small size of studied populations, Gupta et al conducted a systematic review and meta-analysis of randomized, controlled trials assessing the effects of either lifestyle modification or cardiovascular drug therapy [22••] on erectile function. After a thorough search of the literature, the authors identified only six studies fulfilling prespecified criteria for a total of 740 individuals, of whom 374 were in the intervention group and 366 on the control group. Lifestyle modification was associated with a statistically significant increase in IIEF score of 2.40 (95 % CI:1.19-3.61), while the increase in IEFF score with statins was 3.07 (95 % CI:1.84-4.30). Unfortunately, the authors failed to include studies with antihypertensive drugs, while included studies have not taken into account the effects of such medication [21].

Vitamin E in animals [23], oral L-citrulline supplementation in humans [24], and complementary or alternative medicine (acupuncture, ginseng, maca) [25] have been suggested to offer some benefit; however, existing data is of limited quality and does not permit for conclusions.

Therefore, it can be concluded that available evidence point towards a beneficial effect of lifestyle modification on

sexual function. Since lifestyle modification is highly recommended in hypertensive patients, it seems rational to assume that lifestyle modification should be advised in all hypertensive patients with erectile dysfunction. Although this recommendation is not based on hard data, it seems clinically wise; however, this does not negate the need for large, controlled, randomized studies in this field.

Antihypertensive Treatment and Erectile Function

The effects of antihypertensive therapy on erectile function have been evaluated in: a) animal studies, b) observational studies, c) small clinical studies, d) meta-analyses, and e) large randomized trials.

Experimental data unveil divergent effects of antihypertensive drug classes on erectile function. Structural and functional changes in penile vessels induced by hypertension can be reversed by some drugs but remain unaffected by other drugs [26, 27]. In particular, angiotensin receptor blockers and nebivolol seem to exert beneficial effects in spontaneously hypertensive rats, while such effects are not observed with calcium antagonists or atenolol, suggesting that differences between antihypertensive drug categories may exist even between drugs of the same class.

Observational studies verify the differences observed in experimental studies. Hypertensive patients taking beta blockers and diuretics exhibit significantly worse sexual function than patients administered newer drugs, such as angiotensin receptor blockers, ACE-inhibitors, and calcium antagonists [6]. A recent observational cross-sectional study of 1,007 middle aged and older high-risk hypertensive patients taking beta blockers unraveled the high prevalence of sexual dysfunction in these patients and unveiled within class differences regarding sexual effects. Erectile dysfunction was observed in 71 % of studied patients (38.1 % mild, 16.8 moderate, and 16.1 % severe erectile dysfunction). However, the most important information comes from the observed differences between various beta blockers. In particular, metoprolol and carvedilol were associated with higher rates of erectile dysfunction, atenolol and bisoprolol with intermediate rates, and nebivolol with the lowest rates of erectile dysfunction. The same was evident for the degree of severity of erectile dysfunction [28].

Small clinical studies confirm the findings of experimental and observational studies [29–31]. The number of sexual intercourse per month was significantly lower with beta blockers than with placebo, indicating detrimental effects of beta blockers on sexual function. The detrimental role of beta blockers is evident not only for older beta blockers (atenolol), but also for newer vasodilatory agents (carvedilol). On the other hand, angiotensin receptor blockers seem to improve the number of sexual intercourse per month in hypertensive patients compared to placebo, suggesting that this class of antihypertensive agents might even have a beneficial role on sexual function.

There are no specific meta-analyses examining the role of antihypertensive drugs on erectile function due to limited available data. Relevant information comes from meta-analyses which evaluate the adverse effects of diuretics and beta blockers, in other words older antihypertensive drugs. Sexual dysfunction is frequently encountered when diuretics are used in combination with other drugs, and similar problems frequently appear in patients taking beta blockers [32, 33].

Finally, large clinical trials specifically evaluating the role of antihypertensive drugs on sexual function do not exist, since sexual dysfunction was not the primary end-point in any clinical trial. Only one study, MR-NOED, was specifically designed to assess sexual dysfunction in hypertension and showed that nebivolol significantly improves the sexual function of hypertensive patients [34•]. Relevant information can be also extracted from older studies (MRC, TAIM, TOMHS, ALPINE) [35–38]; however, this information needs to be studied with caution since these trials were not specifically designed to explore the effects of antihypertensive agents on sexual function, not even as a secondary end-point, and are used non validated questionaires. Diuretics exhibited significant detrimental effects on sexual functioning compared to placebo in MRC and TAIM, while the negative effects of beta blockers fall between diuretics and placebo [36, 37]. In TOMHS a much higher incidence of sexual dysfunction was observed in patients receiving chlorthalidone for two years compared to placebo (17.1 % versus 8.1 %; $p=0.025$); however, statistical significance did not persist at 4 years of follow-up [35]. Finally, sex life satisfaction was similar with candesartan and hydrochlorothiazide in ALPINE [38].

Taken together, the above data can be summarized as follows. Significant differences appear to exist upon the effects of antihypertensive drugs on erectile function. Older drugs (diuretics, beta blockers) exert detrimental effects, while newer drugs seem to have either neutral or even beneficial (nebivolol, angiotensin receptor blockers) effects.

Antihypertensive Treatment and Female Sexual Function

Female sexual dysfunction remains considerably understudied, possibly due to lack of physicians' familiarity with sexual aspects combined with the absence of available drugs to effectively manage this condition. Existing data is limited to a small number of experimental, observational, and small clinical studies; their findings consistently point towards similar effects of antihypertensive drugs in male and female

sexual function [7, 39, 40]. It has to be admitted, however, that further research is needed before drawing any conclusion.

A recently published study provides evidence for the effects on female sexual function of felodipine combination with either irbesartan or metoprolol [41•]. The study evaluated 160 middle-aged women with mild or moderate hypertension during a 48 week follow-up period. Female sexual dysfunction was observed in 60.4 % of study participants at baseline highlighting the high prevalence of sexual dysfunction in hypertensive women. Blood pressure was effectively lowered by both combinations, without significant differences between the two groups. Total FSFI score increased significantly with the irbesartan combination both at 24 and 48 weeks ($p=0.006$ and $p=0.001$, respectively), while it remained practically unchanged with metoprolol combination (p=NS), and the differences between the two groups were statistically significant ($p=0.002$ at 24 weeks and $p=0.001$ at 48 weeks). Irbesartan combination resulted in significant improvements in several aspects of female sexual function, such as sexual desire ($p<0.001$), arousal ($p=0.002$), and orgasm ($p=0.049$).

Of note, the study provides pathophysiological information on the hormonal and oxidative stress level. Irbesartan combination was associated with an increase in estradiol and a decrease in testosterone levels, while the metoprolol combination exerted the opposite effects. In addition, irbesartan combination was associated with less oxidative stress, and the difference between the two groups was statistically significant ($p<0.05$). Therefore, irbesartan combination provides a favorable hormonal and oxidative milieu for sexual function in hypertensive women compared to metoprolol combination.

Although the study findings are important in a field of limited research, some issues need to be highlighted. The study does not provide data regarding the influence of menopause and of concomitant cardiovascular disease on the association between drug therapy and female sexual function [42]. The main issue, however, is the clinical significance of the observed difference between the two groups. The increase in FSFI score with irbesartan was less than one point, raising concerns whether this benefit is clinically meaningful. Unfortunately, the authors do not provide data whether some patients regained sexual function with the irbesartan combination.

Switching Antihypertensive Drugs and Sexual Function

The Second Princeton Consensus management recommendation includes the following statement: “a change in class of antihypertensive medication rarely results in the restoration of sexual function” [43]. This statement is based on the absence of hard data coming from randomized controlled studies. However, available data point towards significant benefits in sexual function when prior antihypertensive therapy is switched to either nebivolol or angiotensin receptor blockers [44–48]. In addition, significant improvements were observed in orgasmic function and intercourse satisfaction, along with benefits in sexual desire and frequency of sexual intercourse [48]. It is unarguable however that relevant data comes from open studies and no definite conclusions can be drawn until information from randomized studies becomes available.

The Beta Blockers Debate

Beta blockers are a drug class of wide heterogeneity in terms of selectivity to adrenergic receptors, intrinsic sympathetic activity, and vasoactive effects. Some beta blockers, such as nebivolol, carvedilol, labetalol, and celiprolol, possess vasodilatory properties. Since vasoconstriction may contribute to vasculogenic sexual dysfunction through reduced blood supply, it could be hypothesized that vasodilatory beta blockers may diverge in clinically meaningful ways from traditional beta blockers on their effects in sexual function. However, this assumption seems to be only partially correct, since observational and clinical data suggest that carvedilol shares the detrimental effects of traditional beta blockers on sexual function [28, 29], while nebivolol might be the only exception in this class of antihypertensive drugs regarding the effects on erectile function [34, 47].

The detrimental effects of beta blockers on sexual function have been recently debated [49, 50]. Two studies reported that erectile dysfunction induced by treatment with beta blockers is primarily due to knowledge of side effects and subsides with placebo [51, 52]; therefore, beta blocker-induced erectile dysfunction seems to be perceived and not real. On the other hand, there are three carefully designed, randomized crossover studies, conducted by Fogari [29–31], aiming to evaluate specifically the effect of antihypertensive treatment in erectile function. These studies provide strong evidence for a detrimental role of beta blockers on erectile function, since beta blockers were worse than placebo, which in turn was worse than renin-angiotensin system inhibitors. Although a placebo effect, at least in some patients, cannot be entirely excluded, available data indicate that a negative effect of beta blockers on sexual function cannot be negated [49].

ONTARGET/TRANSCEND Erectile Dysfunction Substudy

The recently published substudy of the ONTARGET/TRANSCEND trials has shed light on the effects of ARBs and ACE-inhibitors on erectile function in high-risk patients

[53••]. In total, erectile function was assessed in 1,549 patients and randomized to telmisartan, ramipril, their combination, or placebo. Erectile dysfunction was observed in 55 % of patients, highlighting the high prevalence of erectile dysfunction in high-risk patients. In ONTARGET, there were no significant influences in erectile function after treatment with telmisartan, ramipril, or their combination compared to baseline, and subsequently no differences between treatment groups were observed. In TRANSCEND, telmisartan or placebo had no significant effects on erectile dysfunction, and no significant differences between the two groups were observed. In addition, there were no differences in new-onset erectile dysfunction between all treatment groups. It can thus be summarized that treatment with telmisartan and/or ramipril did not ameliorate erectile dysfunction in high-risk patients with preexisting erectile dysfunction in one hand and did not prevent new-onset erectile dysfunction in these patients on the other hand.

The findings of this substudy are very important since data derive from two large randomized studies, and merit a thorough analysis. First of all, it has to be taken into account that RAS-inhibitors were used as add-on therapy in patients already on a multidrug regime. In particular, beta blockers were used by 57.7 % of patients, diuretics by 23.7 % and Ca-antagonists by 39.2 % of patients; these drugs might have influenced erectile function. We therefore believe that the right interpretation of the study findings is that RAS inhibitors do not improve erectile function in high-risk patients who are already on multidrug medication, including beta blockers and diuretics.

It would be significant to know the effects of ARBs and ACE-inhibitors on erectile function in patients without prior or in-study administration of beta-blockers and/or diuretics. However, the authors did not provide such information, possibly due to small numbers of such patients in the two studies. It is therefore clear that no conclusions can be drawn based on these studies regarding the effects of RAS inhibitors alone or in combination on erectile function in treated hypertensive patients. Another concern is the rather high percentage of patients not filling follow-up questionnaires. Indeed, IIEF score was available in only 1,043 out of 1,519 initial participants (68.7 %). A "drop-out" rate of 32.3 % is unusually high and raises concerns about the validity of study findings.

PDE-5 Inhibitors in Hypertension

PDE-5 inhibitors act by blocking the PDE-5 isoenzyme that is localized all over the systemic vasculature, including the genitalis, inhibiting the sequential breakdown of cyclic guanosine monophosphate (cGMP) [54]. Sildenafil was the first PDE-5 inhibitor approved by the FDA for the treatment of erectile dysfunction in 1998, and rapidly became a blockbuster drug [55]. Currently, newer PDE-5 inhibitors such as vardenafil and tadalafil are widely available, while other molecules are under experimental and clinical investigation. Compared to sildenafil, vardenafil is more potent, while tadalafil presents a longer period of action (with a 17-hour half-life), and minimal food interactions and visual effects [56].

PDE-5 inhibitors are very effective in treating erectile dysfunction; however, their safety was questioned in hypertensive patients, due to the ability of PDE-5 inhibitors to induce vasodilation. Systemic blood pressure reductions observed with the use of PDE-5 inhibitors raised concerns about potentially hazardous hypotension in patients receiving antihypertensive medication [57–59]. However, concerns seem to be outdated, since blood pressure reductions observed both in normotensive subjects and hypertensive patients are usually small and clinically insignificant [60–62]. Several lines of evidence indicate that PDE-5 inhibitors are not associated with significantly higher incidence of adverse events in hypertensive patients, even on a concomitant multidrug regime [63]. Therefore, PDE-5 inhibitors may be effectively and safely co-administered with antihypertensive medication, with alpha blockers and nitrates being the only exception.

Concomitant administration of PDE-5 inhibitors with alpha blockers might result in significant orthostatic hypotension. The risk for clinically meaningful hypotension is significantly attenuated when: a) the two drugs are not administered simultaneously but with a time difference of several hours, b) selective urinary alpha blockers are used that primarily inhibit $a1_A$ and $a1_D$ receptors (tamsulozin, alfuzosin), instead of non-selective alpha blockers that primarily inhibit $a1_B$ receptors and used for the treatment of hypertension (prazosin, doxazosin, terazosin), c) low doses of both drugs are used with careful titration, and d) patients are on stable therapy with one class for several months before the addition of the second class. The use of all three PDE-5 inhibitors, therefore, is not discouraged by FDA, provided that their starting doses are low in the case of patients already on alpha blockers. Likewise, patients on optimal doses of PDE-5 inhibitors may be prescribed low starting doses of alpha blockers.

Clinically hazardous symptomatic hypotension has been observed when PDE-5 inhibitors were used together with organic nitrates. Hypotension is induced by the vasodilating cGMP overactivity, attributed to the combination of increased cGMP production (by nitrates) and decreased cGMP catabolism (by PDE-5 inhibitors). Therefore, all PDE-5 inhibitors should be avoided in patients receiving either short- or long-acting nitrates. Vice versa, in case PDE-5 inhibitors were administered, nitrates should not be given in patients with acute coronary syndrome or pulmonary edema necessitating nitrate therapy, until after several hours.

Poor adherence to antihypertensive drug therapy is a critical contributor to unsatisfactory blood pressure control rates. The contribution of erectile dysfunction in poor adherence to

antihypertensive drug therapy has been highlighted in a study of hypertensive patients with erectile dysfunction. It was shown that sildenafil use for erectile dysfunction resulted in significant improvements in adherence rates (from 48 % to 66 %) [64]. Use of PDE-5 inhibitors in hypertensive men are associated with initiation rather than withdrawal, and addition rather than rejection of antihypertensive treatment [65]. It should be noted, however, that initiation of PDE-5 inhibitors in hypertensive patients should follow adequate blood pressure stabilization and is therefore contra-indicated in patients with untreated, poorly controlled, accelerated, or malignant hypertension; these patients are considered "high-risk" for cardiovascular events, and should be evaluated by a cardiologist before taking PDE-5 inhibitors [43].

Conclusions

The frequent co-existence of hypertension and sexual dysfunction and the impact of antihypertensive drugs on sexual function raise the question whether sexual dysfunction is the result of hypertension per se, an adverse event of antihypertensive treatment, or a combination of both. Several lines of evidence indicate that drugs used in the treatment of hypertension can indeed deteriorate sexual function, but this effect appears mainly with older generation drugs (beta blockers, diuretics) while newer agents (nebivolol, angiotensin receptor blockers) might even improve sexual function. Life-style modification seems to benefit sexual function and should be advised in all hypertensive patients with sexual dysfunction. PDE-5 inhibitors have offered new perspectives in the management of erectile dysfunction, they are effective and safe in hypertensive patients, but their use should follow appropriate consultation. Extensive research is required to elucidate the effects of antihypertensive drugs on sexual function, especially in female patients and the combination of antihypertensive drugs.

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- •• Of major importance

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