

## **REVIEW**

# **SEXUAL DYSFUNCTION IN HYPERTENSIVE PATIENTS: IMPLICATIONS FOR THERAPY**

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**Key words:** Sexual dysfunction, hypertension, treatment

### **Abstract**

Sexual dysfunction associated with hypertension or antihypertensive therapies may impact the ability of patients to stay on therapy and lead to deterioration in patients' quality of life. Therefore, it is important for practitioners to become familiar with the wide variation in sexual side effects produced by antihypertensive agents and to discuss the potential occurrence of these side effects with their patients. In many cases, a change in the patient's drug regimen may help patients overcome specific sexual side effects experienced with certain drugs. Practitioners should consider selecting an antihypertensive therapy that is highly effective in lowering blood pressure and at the same time preserves patients' quality of life. The effect of medications on sexual function remains controversial. Some blinded trials report little difference between placebo and specific medications, whereas other studies indicate that antihypertensive medications increase sexual dysfunction, which has an impact on quality of life. Recent evidence suggests that losartan, an angiotensin II antagonist, is not typically associated with development of sexual dysfunction and may actually positively impact several indices of sexual function (erectile function, sexual satisfaction, and frequency of sexual activity) as well as perceived quality of life. Thus, angiotensin II antagonists may offer a therapeutic option to prevent or correct erectile dysfunction in patients with hypertension. The favorable effects of these agents 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 erectile dysfunction.

**Mots clés :** Dysfonctions sexuelles, hypertension, thérapie

### **Résumé**

Dysfonction sexuelle associée à l'hypertension ou aux thérapies antihypertensives pourrait provoquer la capacité des patients de rester sur la thérapie et mener à la détérioration de la qualité de vie des patients. Donc, il est important que les praticiens se familiarisent avec des variations diverses des effets secondaires sexuels de médicament produit par des agents d'antihypertensif et de discuter la fréquence potentielle de ces effets secondaire avec leur patients. À bien des cas, un changement dans le régime de la drogue de patient pourrait aider les patients à vaincre les effets secondaires sexuels spécifiques expérimentés avec certaines drogues. Les praticiens devraient considérer le choix d'une thérapie antihypertensive qui est extrêmement efficace de baisser la tension artérielle et en même temps préserver la qualité de vie des patients. Les effets du médicament sur la fonction sexuelle reste controversés. Quelques tests aveugles rapportent peu différence entre placebo et médicaments spécifiques, tandis que des autres études montrent que des médicaments d'antihypertensive augment la dysfonction sexuelle, qui a une influence sur la qualité de vie. Des preuves récentes suggèrent que losatan, un angotensine II antagonist, n'est pas associé typiquement au développement de la dysfonction sexuelle et pourrait

en fait positivement avoir un impact sur des indices divers de fonctionnement sexuel (fonction érectile, satisfaction sexuelle, et la fréquence d'activité sexuelle) aussi bien que la qualité de vie perçue. Donc, angiotensine II antagoniste pourrait donner une option thérapeutique pour éviter ou corriger la dysfonction érectile chez des patients atteints de l'hypertension. Des effets favorables de ces agents sur la fonction sexuelle pourrait être semblable d'un côté, pour leur capacité de bloquer angiotensine II, qui est tout récemment acceptable comme un médiateur important de détumescence et peut-être dysfonction érectile.

## Introduction

Erectile dysfunction (ED) is the consistent inability to maintain a penile erection sufficient for adequate sexual relations. The effects of ED are profound and far-reaching, interfering with a man's self-esteem, interpersonal relationships, and overall sense of well-being.<sup>1</sup>

Despite the well known benefits of effective long-term antihypertensive drug therapy in reducing cardiovascular risk, almost three quarters of US adults with hypertension fail to achieve adequate blood pressure control.<sup>2</sup> Almost half of the hypertensive patients have poor antihypertensive drug compliance in Nigeria.<sup>3, 4, 5</sup> This statistic is, in part, attributable to the rate of discontinuation of antihypertensive medications due to the occurrence of troublesome side effects. Appearance of treatment-related side effects may actually make patients feel worse than they did before beginning antihypertensive therapy, particularly since most patients with hypertension are asymptomatic.<sup>6</sup> As many as 70% of hypertensive patients who experience side effects are noncompliant with their antihypertensive medication, and patients experiencing a negative impact on their quality of life have a 40%-60% higher rate of therapy discontinuation than patients whose quality of life is unaffected.<sup>7,8</sup> On the other hand, blood pressure control may be associated with quality of life improvement (patients feeling better). The inability of patients to stay on therapy in the long term may be one of the factors contributing to the development of hypertension-related complications.

Sexual dysfunction induced by antihypertensive medications is one of the poorly recognized side effects impacting the patient's ability to stay on therapy. Moreover, this side effect of antihypertensive medications is strongly associated with an impaired quality of life.<sup>9-11</sup> Many commonly prescribed antihypertensive medications may give rise to sexual dysfunction, which often presents in men as a decrease in libido, difficulty attaining or maintaining an erection, and ejaculation problems, and, in women, as a delay in orgasm.<sup>12,13</sup> Not all classes of antihypertensive agents share the same risk of inducing sexual problems; certain types of antihypertensive medications are generally associated with a lower risk of sexual dysfunction than others.<sup>16</sup> In fact, recent studies suggest that angiotensin II antagonists (AIIAs) may actually improve erectile function and sexual activity in male hypertensive patients.<sup>14,15</sup> The favourable effects of AIIAs on

sexual function may be related to their ability to block angiotensin II (ANG II), which has been shown to terminate spontaneous erections when administered exogenously in an experimental model of penile function.<sup>16</sup>

In view of these observations, it is important for practitioners to be aware of the sexual side effects produced by antihypertensive agents so that the selected therapy may provide an optimum balance between antihypertensive efficacy and quality of life.<sup>9, 15</sup>

## Association with antihypertensive agents and the dysmetabolic syndrome of high blood pressure

Sexual dysfunction is a frequently encountered problem in patients with hypertension and may occur either as a side effect of some types of antihypertensive medications or as a component of the dysmetabolic syndrome of high blood pressure.<sup>9,17</sup> In hypertensive males, sexual dysfunction may present in a variety of ways, including a decreased incidence of sexual activity, difficulty attaining or maintaining an erection, and problems in ejaculating.<sup>12</sup> For the most part, sexual problems have been reported to occur more frequently in patients receiving antihypertensive medication than in those with either untreated hypertension or in normotension.<sup>12,14,18-20</sup> However, as discussed below, this finding is not universal.<sup>20</sup> In the Treatment of Mild Hypertension Study (TOMHS),<sup>21</sup> a placebo-controlled trial, there was no difference in the incidence of sexual dysfunction among several antihypertensive agents when compared to placebo at 4 years. At 1 year, however, a greater incidence was noted with a diuretic than with other drugs.<sup>21</sup>

The concept of hypertension as a dysmetabolic syndrome has brought to the forefront the frequent association of high blood pressure with dyslipidaemia, insulin resistance, coagulation disorders, and peripheral vascular disease.<sup>22</sup> The anatomic and haemodynamic characteristics of the penile circulation make the process of penile tumescence inextricably linked to blood pressure, perfusion pressure, and vascular compliance. In this context, Toblli et al<sup>23</sup> reported that cavernous-tissue vascular fibrosis was present in rats with spontaneous hypertension and that the degree of vascular sclerosis in the rat penis was highly correlated with the level of arterial pressure. These intriguing observations suggest a vasculogenic mechanism of erectile

dysfunction in hypertensive subjects, since peripheral arterial disease has begun to be recognized as an early consequence or direct contributor to high blood pressure.

In keeping with the new animal studies, the recent findings of Llisteri and colleagues<sup>14</sup> demonstrate that erectile dysfunction in hypertensive patients aged 30-65 years was associated with medications that had not been usually considered to impair sexual function. Thus, hypertension-related erectile dysfunction may be a consequence of a reduction in penile perfusion pressure associated with the decrease in systemic arterial pressure induced by antihypertensive medications in the presence of an already decreased penile vascular compliance. Under this scenario, erectile dysfunction may represent a previously unrecognized early symptom of peripheral vascular disease.

### **Prevalence of sexual dysfunction in hypertensive patients**

Several reports collectively spanning more than three decades indicate that 2.4%-58% of hypertensive males experience one or more symptoms of sexual dysfunction of varying degrees of severity during antihypertensive drug therapy.<sup>12,14,18,19,21,24,25</sup> It is also true, however, that hypertensive patients also experience sexual dysfunction prior to taking medication, when compared to normotensive subjects. This finding, while quite consistent with the physiologic changes noted in hypertensive individuals, is often neglected in the overall assessment of subjects and in the formulation of a therapeutic scheme. The large variations in the prevalence of sexual problems reported in the literature most likely reflect differences in study methodology (lack of control subjects), types of antihypertensive medications taken, the presence of confounding medications, age differences of study populations, and cultural and socioeconomic factors. In the clinical practice setting, the prevalence of sexual dysfunction is likely to be even higher than that reported in clinical trials because the personal nature of this problem often leads to an unwillingness of many patients and/or physicians to openly discuss this issue.

Although most research on sexual dysfunction has focused almost exclusively on men,<sup>26</sup> women with hypertension are also at risk of developing sexual dysfunction. According to a 1994 survey, sexually active women aged 60-80 years who were receiving antihypertensive medications (atenolol, enalapril, or isradipine) experienced sexual dysfunction, manifested as a difficulty in achieving orgasm, inadequacy of vaginal lubrication, and diminished libido.<sup>13</sup> However, in the absence of a control group of hypertensive women who were not receiving antihypertensive therapy, it is difficult to accurately assess the effect of antihypertensive medication on sexual functioning.

### **Effect of sexual dysfunction on quality of life and compliance with treatment**

Sexual dysfunction associated with antihypertensive agents may impact the ability of patients to stay on therapy and lead to an impaired quality of life.<sup>9-11</sup> Sexual dysfunction is an important reason why patients discontinue antihypertensive medications, as exemplified by the findings of the Medical Research Council (MRC) trial in 17,354 hypertensive patients studied over 5.5 years.<sup>27</sup> In this study, premature withdrawal due to impotence occurred at a significantly higher rate in patients receiving either a thiazide diuretic ( $p < 0.001$ ) or B blocker ( $p < 0.001$ ) than in placebo-treated patients (12.6% and 6.3% vs. 1.3% per 1000 patient-years, respectively). However, it must be pointed out that the MRC study was of single-blind design, and thus the findings should be interpreted with caution.

Sexual dysfunction associated with antihypertensive therapies may also impact the quality of life of hypertensive patients.<sup>8, 28</sup> As early as 1982, Jachuck and colleagues<sup>29</sup> reported an association of sexual dysfunction with impairment of quality of life in hypertensive patients treated primarily with diuretics, B blockers, or methyldopa (the last, is not recommended in antihypertensive therapy because of its high association with side effects and the emergence of better options). Approximately 78% of patients who had severe quality of life impairment (according to spouses' ratings) had a reduction in or no sexual interest. In contrast, only 38% of patients with mild impairment of quality of life had reduced sexual function. It must be noted, however, that not all studies have reported a relation between antihypertensive therapy and sexual dysfunction, and in one review of six randomized trials, short-term exposure to antihypertensive drugs was associated with a prevalence of self-reported impotence that was similar to that in placebo-treated patients.<sup>25</sup> Further, in the Trial of Antihypertensive Interventions and Management (TAIM),<sup>30</sup> a multicentre, randomized, placebo-controlled trial in patients with mild hypertension, low-dose antihypertensive drug therapy (with chlorthalidone or atenolol) actually improved, rather than impaired, quality of life.

### **Types of antihypertensive therapy associated with sexual dysfunction**

Several widely prescribed antihypertensive agents, including diuretics, methyldopa, clonidine, guanethidine, and B-blockers (especially those that are nonselective), are known to cause sexual problems or exacerbate existing problems.<sup>9,31,32</sup> However, not all classes of antihypertensive agents share the same risk of inducing sexual problems, and certain classes of antihypertensive agents tend to be associated with a higher prevalence of sexual dysfunction than others.<sup>9,15</sup> Differences among the various classes of antihypertensive agents have been noted in men with

respect to erectile dysfunction, decreased libido, impaired ejaculation, gynaecomastia, and priapism. Conclusions regarding an association between antihypertensive therapy and sexual dysfunction are limited by the fact that several of the studies were poorly controlled and results were based on questionnaires. This is one of the factors responsible for the lack of recognition of sexual dysfunction as a component of the hypertensive process rather than as a consequence of antihypertensive medications.

Compared with placebo or other classes of antihypertensive agents, a higher prevalence of male sexual dysfunction has been reported in some studies of diuretics, including spironolactone, which inhibits dihydrotestosterone binding, and thiazide diuretics (e.g., chlorthalidone), as well as B blockers.<sup>12,15,21,24,33,34</sup> Beta blockers (e.g., atenolol and propranolol) may potentially impact 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.<sup>15,34</sup> However, as noted, deleterious effects of diuretics and B blockers on sexual function have not been consistently found, and several controlled studies, including TOMHS and a combined analysis of six randomized, blinded, prospective trials, have found little or no evidence for a greater risk of occurrence of adverse sexual sequelae between these agents and other antihypertensive medications.<sup>26,35,36</sup> Variations in the design of the studies, the inclusion of a placebo control arm, and the characteristic of the population under investigation are factors adding to the difficulties in recognizing the nature of the mechanisms that associate sexual dysfunction with hypertension and its medications.

Centrally acting antiadrenergic agents, such as methyldopa and clonidine, also give rise to male sexual dysfunction, possibly by decreasing sympathetic outflow as well as diminishing libido and ejaculation. Direct vasodilators, including hydralazine and minoxidil, may produce erectile dysfunction and priapism, but this appears to be uncommon.<sup>37</sup> There is little evidence to suggest that calcium channel blockers (CCBs) result in erectile dysfunction, although impotence associated with verapamil has been described,<sup>38</sup> and in one study, CCBs were second to angiotensin-converting enzyme (ACE) inhibitors in their association with erectile dysfunction.<sup>14</sup> Moreover, gynaecomastia and problems with ejaculation have been reported with CCB therapy.<sup>34,39</sup>

### ***Evolving role of angiotensin II (ANG II) as a mediator of erectile dysfunction***

While the physiology of erection is a complex, neurovascular event regulated by psychologic and hormonal factors,<sup>32</sup> corporal and vascular smooth muscle tone and contractility play a key role in modulating penile blood flow and, hence the erectile process. Erection occurs due to nitric oxide-mediated relaxation of corporal and arterial smooth muscle,

allowing increased blood flow into the sinusoidal spaces.<sup>32</sup> Nitric oxide, released from the endothelium and from noradrenergic, noncholinergic cavernous nerves during sexual stimulation, appears to be the principal mediator of erection, although vasoactive polypeptide and prostaglandins may also be involved.<sup>32,37</sup>

Recent evidence suggests that ANG II may play an important role in detumescence and possibly erectile dysfunction.<sup>16,40</sup> ANG II has been identified in human corpus cavernosum (primarily in endothelial cells lining blood vessels and smooth muscle bundles within the corpus cavernosum), where its tissue concentration is 200 times higher than plasma levels and 10 times higher than in aortic or mesenteric vessels.<sup>16</sup> Superfused cavernosal tissue from human subjects undergoing penile prosthesis implantation synthesizes (presumably via local endothelial ACE) and spontaneously secretes ANG II. Local ACE may therefore regulate smooth muscle tone in a paracrine fashion via production of ANG II, which in turn stimulates contraction of corporal and vascular smooth muscle via an ANG II receptor. This constricts blood flow through the penile arteries and reopens the venous plexus, thereby allowing penile flaccidity to return. This mechanism is consistent with a recent study indicating that the ACE DD genotype (a deletion polymorphism in the ACE gene associated with high circulating and tissue levels of ACE) may represent an important risk factor for vasculogenic erectile dysfunction.<sup>40</sup>

The potential involvement of ANG II in regulating erectile function is illustrated by the results of Kifor and colleagues,<sup>16</sup> who utilized a canine model of penile erection. Intracavernosal administration of ANG II terminated spontaneous erections in anesthetized dogs, an effect similar to that obtained with epinephrine. Administration of the Angiotensin II Antagonist (AIIA) in the same model resulted in a dose-dependent increase in cavernosal pressure and relaxation of smooth muscle, and thus the development of an erection. These intriguing studies suggest that ANG II may be an important mediator of erectile function and may offer a mechanistic explanation for the improvement in erectile function as well as satisfaction and frequency of sexual activity observed in clinical studies in male hypertensive patients with sexual dysfunction.<sup>14</sup>

### **Conclusion**

Occurrence of sexual dysfunction in patients with hypertension may not only negatively impact the ability of patients to stay on antihypertensive therapy, but can also lead to deterioration in quality of life. Therefore, it is important for practitioners to be aware of the wide variation in sexual side effects produced by antihypertensive agents and to be willing to discuss potential occurrence of these problems with patients.

Practitioners should consider choosing an antihypertensive therapy with the lowest possible potential for sexual side effects in order to attain an

optimum balance between antihypertensive efficacy and quality of life. Recent studies indicate that AIIAs may offer a therapeutic option to prevent or correct erectile dysfunction in patients with hypertension. AIIAs have been shown to positively impact several indices of sexual function and perceived quality of life, effects possibly attributable to blockade of the effects of ANG II in mediating penile detumescence.

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