

## BPH/Prostatic Diseases

**Evaluation of Male Sexual Function in Patients with Lower Urinary Tract Symptoms (LUTS) Associated with Benign Prostatic Hyperplasia (BPH) Treated with a Phytotherapeutic Agent (Permixon<sup>®</sup>), Tamsulosin or Finasteride**Alexandre R. Zlotta<sup>a,\*</sup>, Pierre Teillac<sup>b</sup>, Jean Pierre Raynaud<sup>c</sup>, Claude C. Schulman<sup>a</sup><sup>a</sup>Department of Urology, Erasme Hospital, University Clinics of Brussels, 808 route de Lennik, B-1070 Brussels, Belgium<sup>b</sup>Department of Urology, St-Louis Hospital, Paris, France<sup>c</sup>University Pierre and Marie Curie, Paris, France

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**Abstract**

**Objectives:** Sexual function is one of the aspects in the treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) that has gained increasing attention. We compared the influence on men's sexuality of Permixon, a lipido-sterolic extract of *Serenoa Repens*, with Tamsulosin and Finasteride using a specific validated questionnaire exploring patient's sexual functions.

**Methods:** A database was created comprising patients from 3 main double-blind, randomized studies - Permixon vs. Finasteride, Permixon vs. Tamsulosin and Permixon 160 mg vs. 320 mg including a total of 2511 patients. Three hundred fifty four were on Tamsulosin, 545 on Finasteride and 1612 patients on Permixon. LUTS were assessed using the I-PSS questionnaire. Peak flow rates and prostate volume were recorded. The MSF-4 questionnaire, including 4 items that explore the patient's interest in sex, quality of erection, achievement of orgasm and ejaculation, was used across the studies. This questionnaire was demonstrated as highly reproducible and both psychometrically and clinically valid across different cultures. Correlation coefficients were given to assess the linear relationship between continuous variables.

**Results:** At 3 months, there were no statistically significant differences between the three treatment groups in terms of I-PSS or Qmax evolutions (all  $p$  values > 0.05). At 6 months, as compared to pretreatment data, there was a slight increase in sexual disorders in Tamsulosin (+0.3) and Finasteride (+0.8) treated patients while it slightly improved with Permixon therapy (−0.2). Ejaculation disorders were the most frequently reported side effects after Tamsulosin or Finasteride (both +0.2 on the specific MSF-4 question 4). There was no correlation between the evolution of the MSF-4 scores and the evolution in I-PSS neither in patients treated with Permixon, Finasteride or Tamsulosin. However, there was a slight correlation between the MSF-4 score at baseline and the I-PSS at baseline ( $r^2 = 0.032$ ). Although there was a correlation between the MSF-4 and age at baseline ( $r^2 = 0.1452$ ), there was no correlation between the evolution in MSF-4 during therapy and the age of the patients.

**Conclusion:** The present study demonstrates that Permixon therapy has no negative impact on male sexual function. Both Finasteride and Tamsulosin had a slight impact on sexual function, especially on ejaculation, although these effects were rare and in line with previous reports about these two drugs.

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**Keywords:** BPH; LUTS; Permixon; Tamsulosin; Finasteride; Sexual function

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## 1. Introduction

One of the aspects in the treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) that has gained increasing attention is sexual function.

The availability of a variety of therapies including medical therapy for symptomatic BPH has prompted to carefully balance their benefits and side effects [1,2].

Often the implications of the different treatment modalities on the sexuality of men afflicted by LUTS associated with BPH have been left aside.

Patients consulting for symptomatic BPH are not only seeking to be relieved from their symptoms but wish to maintain an acceptable quality of life, including sexual function.

In a study aiming to determine which aspects of quality of life were considered as most important in therapy of BPH, above all others, sexual activities and satisfaction with sexual relationships were cited by patients as of utmost importance [3].

Different treatments for symptomatic BPH can have similar impacts on symptoms but may produce variable responses in terms of the patient's quality of life.

It has become evident that not all men with symptomatic BPH need surgery and the introduction of medical therapies for LUTS associated with BPH has profoundly modified the perception by both physicians and patients of this condition.

Alpha-blockers and 5 $\alpha$ -reductase inhibitors play an important role in the medical treatment of LUTS but the rise of phytotherapy (plant extracts) to alleviate symptoms due to BPH has been the subject of growing interest.

The most extensively studied phytotherapeutic agent approved as a medical treatment of symptomatic BPH is a lipido-sterolic extract of *Serenoa Repens*, Permixon<sup>®</sup>. A 1-year randomized comparison with Tamsulosin showed similar improvements in peak flow and symptom scores with both drugs, Permixon being shown slightly superior to tamsulosin in reducing LUTS in severe BPH patients Debruyne et al., [4,5].

Both Finasteride and Permixon were shown effective in 2/3 of patients with no statistically significant differences in symptom score or peak flow rates improvements [6]. These trials lacked however a placebo arm.

A meta-analysis of all published trials on Permixon using 11 randomized clinical trials and 2 open label trials involving a total of 2859 patients has added evidence on its efficacy over placebo [7].

With respect to sexual function and medical therapy, retrograde ejaculation is a well-documented side-effect associated with Tamsulosin. Libido and erectile dys-

function as well as low-volume ejaculates have been described with Finasteride [1].

The present study has compared the influence on men's sexuality of Permixon with Tamsulosin and Finasteride using a specific questionnaire exploring the patient's interest in sexuality, quality of erections, the achievement of orgasm and ejaculation (MSF-4 questionnaire) [8].

## 2. Material and methods

### 2.1. Patients

A database was created comprising patients from:

- The randomized comparative study between Permixon<sup>®</sup> and Tamsulosin. This 1-year randomized trial comparing Tamsulosin 0.4 mg oad to Permixon 320 mg oad for the treatment of BPH in men aged 50–85 years included 704 patients, 354 for Tamsulosin and 350 for Permixon. Inclusion criteria and assessments have been detailed elsewhere [4]. Of note, there was a 4-week placebo run-in period for all patients.
- The randomized comparative study between Permixon 160 mg and Finasteride 5 mg/day which included 1098 patients (553 for Permixon<sup>®</sup> and 545 for Finasteride) and compared both medical therapies on a 6-month follow-up period with no run-in period [6].
- The 3-month comparative study between Permixon 160 mg and 320 mg including 715 patients. This trial had a 2 weeks wash out period.

In total the database included 545 patients treated with finasteride, 354 treated with Tamsulosin and 1612 treated with Permixon (914 pts–160 mg, 698 pts–320 mg). The difference of 6 patients between those randomized and those included in the database is explained by the fact that these either did not take the medication or had no follow-up at all.

No shift between treatment groups were observed.

### 2.2. Parameters of BPH

Lower urinary tract symptoms were assessed in all patients using the I-PSS (International Prostate Symptom Score).

Peak flow rates were measured in all patients at baseline and during follow-up. In the comparative study with Tamsulosin, a validated central computerized reading of the maximum peak flow rate was applied through a standardized artifact correction and a homogeneous interpretation of the curves [9].

Prostate volume was measured by TRUS using the prolate spheroid method.

### 2.3. Evaluation of male sexual function

The MSF-4 questionnaire was used in this study.

This questionnaire comprises 4 items that explore the patient's interest in sex, quality of erection, achievement of ejaculation and orgasm.

The MSF-4 questionnaire is a concise survey, easy to complete and available in different languages.

This questionnaire was demonstrated as highly reproducible and both psychometrically and clinically valid across different cultures, allowing easy and adequate measurement of male sexual function

in the clinical evaluation of BPH therapies in 810 patients from 5 countries [9].

The validity of this questionnaire was supported by the high level of correlation between the MSF-4 and the IIEF score, a validated 15-item questionnaire on sexual function.

MSF-4 scoring comprises a global score (from 0 to 20, higher scores indicating more sexual disorders) and subscores from 0 to 5 for each of the items.

From the entire database of patients, 14 at baseline, 20 at 3 months and 25 of those followed at 6 months did not fill the MSF-4 at follow-up visits, accounting for much less than 5% of the population analyzed.

#### 2.4. Statistical analyses

Continuous data were summarized using means and standard deviations, whereas, percentages by categories were used to describe the categorical data. The usual student test were used for the between group comparisons on continuous data and the Pears coefficient was provided to quantify the linear relationship between two variables. The closest the coefficient is to 1, the higher is the correlation.

### 3. Results

#### 3.1. Evolution in IPSS at 3 months, Q<sub>max</sub> and prostate volume

Table 1 shows the evolution in IPSS, Q<sub>max</sub> and prostate volume in patients receiving Permixon, Finasteride or Tamsulosin across the different studies.

Three-month volume variations were not recorded in the Tamsulosin vs. Permixon study.

There were no statistically significant differences in IPSS and Q<sub>max</sub> evolutions between each treatment groups (all  $p > 0.05$ ).

In contrast, there was a statistically significant difference in prostate volume change between Finasteride treated patients and those treated with Permixon ( $p < 0.001$ ).

#### 3.2. Evolution in sexual function

A first sub-analysis compared Permixon 160 mg bid and 320 mg oad in terms of MSF-4 global and questions per item. No difference was found between

groups and therefore both groups were combined for the final analysis comparing them to Finasteride and Tamsulosin (data not shown).

#### 3.3. Evolution in MSF-4 global score

Table 2 shows the changes in MSF-4 global score in patients treated by Permixon (320 and 160 mg combined), Tamsulosin and Finasteride at 3 and 6 months of therapy as compared to baseline.

There was a slight increase in sexual disorders in Tamsulosin and Finasteride treated patients while sexual function remained unchanged with Permixon therapy at 3 months and slightly improved at 6 months.

#### 3.4. Sub-analyses

##### 3.4.1. MSF-4 per items

Table 3 presents the evolution in the subscore for each of the 4 items of the MSF-4 questionnaire at 3 months.

The most important differences observed were related to ejaculation. Six-month follow-up data showed the same trend (data not shown).

##### 3.4.2. Influence of the country on the MSF-4 evolution

Patients were recruited in fourteen countries. Countries were combined in 3 different groups.

*Group a* (“Latin”): France, Spain, Italy, Greece, Portugal.

*Groupe b* (“Anglo-saxon”): United Kingdom, Belgium, The Netherlands.

*Group c* (“Germanic”): Germany, Switzerland, Czech Republic, Poland, Austria, Slovakia.

The evolution in MSF-4 scoring according to these 3 different geographical sub-classifications were analyzed. The same trends were observed for each drug throughout geographical groups. However, the most significant changes in the MSF-4 score were found among “Anglo-Saxon” countries. Trends observed at 3

**Table 1**

Evolution in IPSS, Q<sub>max</sub> and prostate volume in patients receiving Permixon, Finasteride or Tamsulosin

	Permixon 160 mg (n = 914)	Permixon 320 mg (n = 698)	Finasteride (n = 545)	Tamsulosin (n = 354)	p value
IPSS change at 3 months mean (SD)	−4.4 (4.5)	−4.0 (4.4)	−5.4 (4.9)	−4.1 (4.6)	>0.05
Q <sub>max</sub> evolution from baseline at 3 months mean ml/sec (SD)	+2.67 (5.48)	+2.34 (5.09)	+2.62 (6.22)	+1.73 (5.07)	>0.05
Prostate volume decrease from baseline at 3 months mean cm <sup>3</sup> (SD)	−2.58 (12.65)	−3.59 (10.28)	−6.73 (11.10)	NA <sup>a</sup>	<0.001 <sup>b</sup>

<sup>a</sup> NA: non available.

<sup>b</sup> Comparing Permixon vs. Finasteride and Tamsulosin for IPSS and Q<sub>max</sub>, Permixon vs. Finasteride for prostate volume.

**Table 2**

Changes in MSF-4 global score at 3 and 6 months of therapy as compared to baseline values

	Permixon (n = 1.609)	Finasteride (n = 545)	Tamsulosin (n = 354)
MSF-4 total score at baseline mean (SD)	8.2 (5.1)	8.5 (5.5)	7.9 (5.1)
Change in MSF-4 total score at 3 months mean (SD)	0.0 (2.8)	+0.5 (3.5)	+0.3 (2.9)
Change in MSF-4 total score at 6 months mean (SD)	-0.2 (3.1) <sup>a</sup>	+0.8 (3.8)	+0.3 (3.4)
% of patients improved at 3 months	30.2%	28.2%	31.0%
% of patients aggravated at 3 months	27.1%	32.0%	39.9%
% of patients stable at 3 months	42.7%	39.8%	29.1%
% of patients improved at 6 months	31.8% <sup>a</sup>	27.5%	34.4%
% of patients aggravated at 6 months	29.5% <sup>a</sup>	38.6%	40.7%
% of patients stable at 6 months	38.7% <sup>a</sup>	33.9%	24.9%

<sup>a</sup> Analysis performed on 902 patients treated with Permixon.

months were also seen at 6 months follow-up (data not shown).

### 3.4.3. Correlation between MSF-4 and IPSS

There was a slight correlation between the MSF-4 score at baseline and the IPSS score at baseline, the higher the IPSS, the higher the MSF-4 (correlation coefficient  $r^2 = 0.032$ ) (Fig. 1). Subdividing patients according to their origin (group a, b or c) did not bring additional informations nor did breaking down the MSF-4 in SLQ1 to Q4 questions (data not shown).

The relation between the evolution of IPSS and MSF-4 outcomes were analyzed separately for Permixon, Tamsulosin and Proscar at day 82 and presented in Fig. 2a, b and c. There was no statistically significant correlation between the evolution in MSF-4 scores and the evolution in IPSS neither in patients treated with Permixon, Finasteride or Tamsulosin ( $p$ -values for correlation  $> 0.05$ ).

### 3.4.4. Correlation between MSF-4 and age

At baseline, there was a correlation between the MSF-4 score and age, the elder the patients the higher was the MSF-4 score (correlation coefficient  $r^2 = 0.1452$ ) (Fig. 3). However, there was no correlation between the evolution in MSF-4 score and age (data not shown).

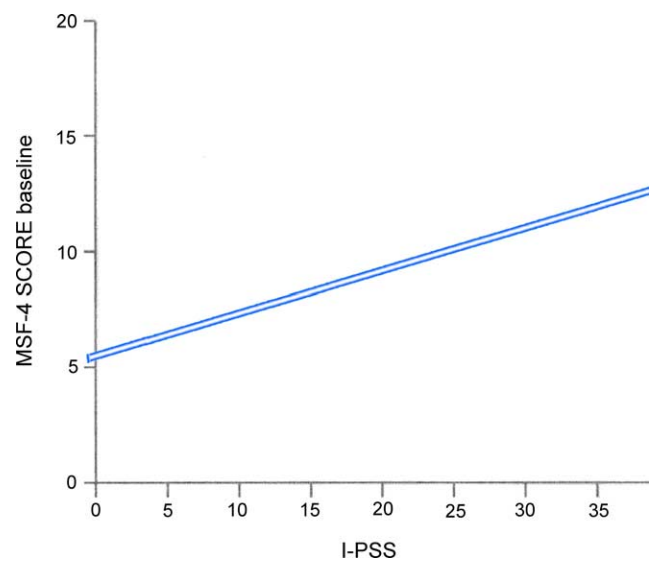


Fig. 1. Correlation between the MSF-4 questionnaire and the baseline IPSS  $r^2 = 0.032$ .

### 3.4.5. Correlation between MSF-4 and prostate volume

No correlations were found neither between MSF-4 score at baseline and baseline prostate volume, nor between the evolution in MSF-4 and prostate volume at baseline or between the evolution in MSF-4 score and the evolution in prostate volume (data not shown).

**Table 3**

Evolution in MSF-4 subscores at 3 months from baseline

Drug	ITEM			
	Interest (SLQ <sub>1</sub> )	Erection (SLQ <sub>2</sub> )	Orgasm (SLQ <sub>3</sub> )	Ejaculation (SLQ <sub>4</sub> )
Permixon (n = 1.609)	0 (0.8)	0 (0.9)	0 (1.0)	0 (1.0)
Tamsulosin (n = 354)	0.0 (0.8)	0.1 (0.9)	0.1 (1.1)	0.2 (1.3)
Finasteride (n = 545)	0.1 (1.0)	0.1 (1.0)	0.1 (1.2)	0.2 (1.2)

Data are given as mean values. Number under parentheses are standard deviations.

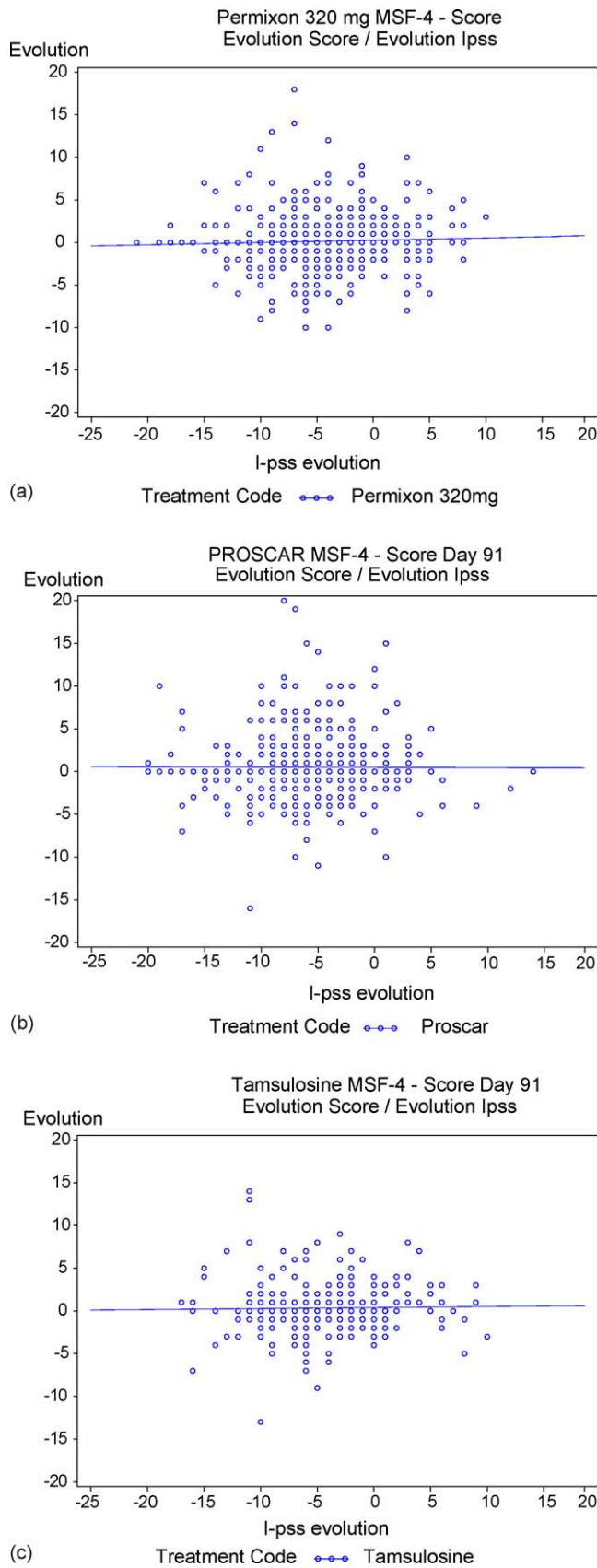


Fig. 2. Correlation between the evolution in MSF-4 questionnaire and evolution in I-PSS in patients treated by Permixon (a), Finasteride (b) and Tamsulosin (c) -Analysis performed at day 91.

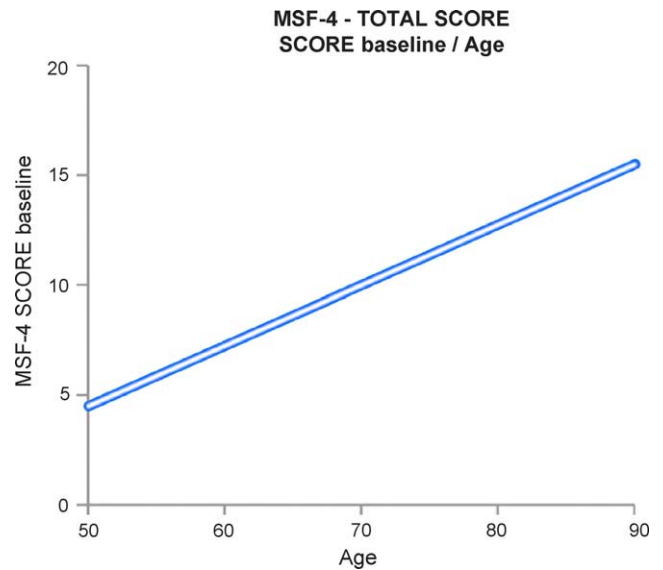


Fig. 3. Correlation between the MSF-4 questionnaire and age  $r^2 = 0.1452$ .

#### 4. Discussion

BPH and sexual dysfunction seem to appear more frequent in the elderly and whether BPH alone contributes to sexual dysfunction is a matter of controversy [1].

The causal relation of erectile dysfunction and LUTS is certainly a matter of debate. Earlier studies showed a relation between LUTS and sexual dysfunction but it is likely that LUTS and BPH do not produce direct effects on sexual dysfunction but are rather witnesses of ageing individuals [10,11].

In 1274 European men with LUTS, erectile dysfunction and reduced ejaculation were highly prevalent and were shown to be strongly related to increasing age and lower urinary tract symptom severity [12].

In the present study as well, which compared Permixon to Tamsulosin and Finasteride, correlations were observed between the MSF-4 score (measuring male sexual function) and age. The younger the patients the less likely they were to have high MSF-4 scores at baseline.

Because sexual dysfunction occurs in the same age group as men affected by symptomatic BPH, the direct or indirect side effects of treatments for BPH on sexual function may be difficult to assess.

An additional problem is the number of reproducible instruments to measure sexual function, among others the Brief Sexual Function Inventory (SFI), the International Index of Erectile Function (IIEF) or the Danish Prostatic symptom score.

Last but not least, sexual dysfunction is not a unique entity but comprises a variety of aspects, such as the erectile dysfunction, ejaculation dysfunction, decreased



libido or overall decreased sexual satisfaction, which can all be affected very differently by various treatment modalities of LUTS associated with BPH.

Of all therapies for BPH, surgical treatments as TURP and open surgery are associated with the highest incidence of sexual dysfunction, especially retrograde ejaculation in more than 50% of patients (25–99%) [13].

In a study examining patient's own evaluation of sexual dysfunction after TURP in 127 men who completed a questionnaire on sexual function, including erection, ejaculation, libido and satisfaction, of the responders, more than half stated that there was a deterioration in all of these factors, 50% blaming the surgery [14].

Since it is now well-established that both open surgery and TURP are associated with retrograde ejaculation, patients should be informed about these side effects before undergoing surgical procedures.

However the impact of therapy for BPH on sexual function may also vary from study to study.

In a longitudinal multicenter study carried out in The Netherlands on 670 consecutive patients with BPH treated with surgery,  $\alpha$ -blockers, Finasteride or followed with watchful waiting, results on sexual function were surprising.

If reduced erectile function was observed in 5–7% of men who underwent surgery, remarkably, around 10% had an improvement in function. Watchful waiting was also associated with both improvements and deterioration for the various aspects of sexual function, supporting that other mechanisms may be important too which further complicate the correct interpretation of sexual function after therapy for BPH [15].

Medical therapy is more common than surgery in developed countries nowadays and the majority of patients are treated now to improve their quality of life rather than to treat complications associated with BPH.

This is why the effects on sexual function, an important factor recognized by patients in their quality of life assessment, are increasingly studied after medical therapy for BPH.

*Serenoa repens*, a plant extract, out of which the lipido-sterolic extract (Permixon) is produced, has been studied for its clinical efficacy in randomized trials against both Tamsulosin and Finasteride [4,6].

Both trials demonstrated the absence of difference in terms of IPSS or Q max between Permixon and the  $\alpha$ -blocker or the  $5\alpha$ -reductase inhibitor.

Safety profiles between Tamsulosin and Permixon were also fairly similar, 8.2 and 7.7% of Tamsulosin- and Permixon-treated patients experiencing at least one adverse event leading to definitive treatment discontinuation [4].

However, the aspect of sexual function after Permixon as compared to Finasteride or Tamsulosin had not been studied in details yet.

We gathered a database of >2500 patients treated with these 3 drugs in several studies and who had answered the MSF-4 questionnaire.

This validated 4-item male sexual function questionnaire was chosen because of its reproducibility, its validity across in different countries, its simplicity and its high level of correlation with other questionnaires such as the IIEF.

A first preliminary analysis showed similar results on sexual function in patients treated with Permixon 160 mg bid or 320 mg oad, this is why Permixon-treated patients were analyzed as a single group.

Overall, Permixon was not associated with a deterioration in the MSF-4 global score with even a slight improvement after 6 months of therapy.

Analyzing the 4 different items of the MSF-4 questionnaire separately, neither sexual interest, erection, orgasm or ejaculatory function were modified by Permixon.

Breaking down patients according to their country of origin, differences were very minimal if any (+0.1 to -0.1) at 3 months, all groups of patients whatever their origin demonstrating slight improvements at 6 months. Patients from countries group in the Anglo-Saxon area benefited the most in terms of sexual function from Permixon therapy.

Of course, the subdivision of the 14 countries in 3 different groups (Latin countries, Anglo-Saxon and "Germanic") is certainly a matter of controversy but these results show that Permixon does not affect negatively the sexual function of treated patients, whatever their culture, and could even be associated with a minimal improvement.

Regarding treatments with Finasteride or Tamsulosin, data on sexual function after these therapies are in accordance with several other reports [1].

There were slight decreases in global sexual function over time with both Tamsulosin or Finasteride but these effects were very modest.

40.7% of patients treated with Tamsulosin, 38.6% treated with Finasteride against less than 30% treated with Permixon considered their sexual function as deteriorated after 6 months of therapy.

Logically, ejaculation disorders were the most frequently reported side effects after Tamsulosin or Finasteride.

Substratifying patients in 3 "cultural" groups, differences were noted both for Tamsulosin and Finasteride (with greater effects with Finasteride), Anglo-Saxon patients reacting more negatively about mod-

ifications in their sexual function than “Germanic” patients.

Our results about Tamsulosin or Finasteride and this type of sexual side effects profile are certainly not surprising given what is known from the literature.

Decreased libido, impotence, ejaculation disorders have been all reported in 0.8 to 9% of patients, although figures are consistently lower than 10% in the very large VA, Prowess or Pless studies [16,17,18].

Regarding Tamsulosin, the  $\alpha$ -adrenergic receptor mediated relaxation is usually not sufficient to produce retrograde ejaculation but figures of 4–6% have been usually reported [19,20].

Is it possible to predict which patients will experience sexual problems after medical therapy according to baseline parameters such as age, IPSS or prostate volume? Our study failed to find any positive predictive correlation between these different parameters and the evolution of MSF-4 score.

Similarly, Leliefied et al using logistic regression analysis to identify factors that determined changes in sexual function after treatment for BPH did not observe strong and consistent patterns that could explain changes in sexual function after treatment [15].

There are some limitations in the interpretation of the results from our large database of patients treated with Finasteride, Tamsulosin or Permixon.

It would certainly have been interesting to have follow-up data on patients with LUTS associated with BPH put on watchful waiting but these were not included in the trials comprising our database.

Although all studies were comparative, the number of patients treated with Permixon is higher because the database included a comparative trial between Permixon 160 bid and 320 mg oad. However, no differences were observed between both doses in terms of sexual function.

Furthermore, with over 1600 patients treated with Permixon and with results showing at worst that Permixon has no impact on sexual function, it is extremely

unlikely that a negative impact of Permixon on male sexual function would have been overlooked. Whether Permixon improves male sexual function is however not fully proven from the data observed in our study although some positive trends were noted.

The fact that the design and duration of the prospective comparative trials were different is not a major concern. Indeed, sexual function was evaluated at the same time (3 and 6 months) for all patients although the comparative study with Tamsulosin had 1 year of follow-up.

Similarly, although the Permal study [4] had a 4-week run-in period, baseline MSF-4 was recorded after this run-in period. Furthermore the MSF-4 evolution during the run-in was analyzed separately and was found to equal 0 thus excluding unknown biases (data not shown).

Regarding Finasteride, it is possible but speculative that since some patients may experience symptomatic improvements at a later stage than the follow-up of our database (6 months F-U), MSF-4 scores might also have been influenced if follow-up had been longer.

## 5. Conclusion

The present study analyzing the sexual function of patients with symptomatic BPH or LUTS associated with BPH treated with either Permixon phytotherapy, Tamsulosin or Finasteride, demonstrates that Permixon therapy has no negative impact on male sexual function. This was true both for the global sexual function or when sub-stratifying according to different items such as interest in sexuality, quality of erection, achievement of orgasm and ejaculation.

This is in contrast to the impact on sexual function of both Finasteride and Tamsulosin, especially on the ejaculation function, although these effects remain rare and are in line with several previous reports about these 2 drugs.

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