SciForschen
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ISSN 2470-0991

Journal of Surgery: Open Access

Editorial Volume: 2.5 Open Access

Medical Management of BPH: Is it the End for Surgical Options

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Received date: 23 Apr 2016; **Accepted date:** 06 May 2016; **Published date:** 11 May 2016.

Citation: Khanna AK, Gupta P (2016) Medical Management of BPH: Is it the End for Surgical Options. J Surg Open Access 2(5): doi http://dx.doi.org/10.16966/2470-0991.e105

The concept of medical management of symptomatic benign prostatic hyperplasia (BPH) is not new. It came in the early 80s when for the first time it was noticed that the symptoms attributed to prostatic enlargement could be managed with pharmacotherapy alone [1]. However, marginal improvement in comparison to the surgical options and increasing awareness of the side effects led to a lack of acceptance of pharmacotherapy as a standard of treatment for the next two decades. It was during this time that minimal access surgeries like transurethral resection of prostate also took precedence over open surgeries leading to much safer and faster convalescence; that further hindered the development of medical therapy as the forerunner in the management of BPH for quite some while.

In an interview, late Dr. John Fitzpatrick said that "initially, the use of drugs as a way of managing a condition that was traditionally managed surgically, if not rejected outright, viewed sceptically in many quarters by urologists." He further commented that drug therapy of symptomatic BPH nonetheless was a way of preventing surgery for many and least delaying in many others. However even after growing acceptance in the surgical fraternity when asked about the future of pharmacotherapy for BPH, he commented that "with many of the current drugs going off patent within the next 12 months, it may well be that we will hear less and less about medical therapy unless some new concept appears in the market". However even after a decade of this interview medical therapy stands strong and has found definite indications in the management of BPH [2]. A further adage to this statement comes from a very recent article published in urology by Guo et al. [3] and colleagues that explored the effects of medical therapy on TURP in china and found that over the years medical therapy has surely changed the overall requirement for surgery and implores its readers to re-evaluate whether BPH truly is a surgical disease.

A common parlance in all urology textbooks today is the fact the BPH is more of a systemic disorder than a loco-regional disease [4]. This stems from the fact that till now lower urinary tract symptoms (LUTS) were mostly attributed to symptomatic BPH, which has been proven to be an over-simplification of the disease process. If a cohort of male patients aged more than 40 years is taken from the population it is noted that around 60% of patients can harbour histologic BPH. However LUTS is noted is not found in all of them; moreover, it can be present without the evidence of histologic BPH altogether. Patients having benign prostatic enlargement (BPE) on physical or radiological examination forms even a smaller subset of the histologically proven BPH patients that may or may not have LUTS that is further mutually exclusive of having concomitant bladder outlet obstruction (BOO).

This complex interrelationship of clinical, radiological, and histopathological evidence of disease has been a subject of interest for the last decade or so, which has revealed come unique mechanisms underlying this disorder. Central to the causation of LUTS lies four different pathways. The first is the autonomic hyperactivity pathway, which suggests that the increased sympathetic tone along with chronic inflammation causes prostatic proliferation that leads to BPE and LUTS. A second pathway also is known as the pelvic atherosclerosis pathway is known to cause decreased bladder blood flow either due to atherosclerosis induced arterial insufficiency or due to high intravesical pressures leading to hypoxic changes in bladder and prostate leading to changes in the smooth muscle complex and subsequently affecting the bladder compliance. The third pathway is the nitric oxide (NO) pathway which further perpetuates the vascular insufficiency cascade. The last one, the alternate pathway is known to act by activation of rho-kinase up-regulation due to chronic inflammation either due to diabetes, smoking, dyslipidaemia or hypertension all of which can finally culminate into increased norepinephrine and endorphins and produce the syndrome complex commonly referred as symptomatic BPH.

However before we understand the medical management of the disease and its future direction we need to revisit the natural history of BPH as it the fundamental on which the medical therapy is based [5]. Though BPH is a histological diagnosis, clinically the first stage starts in the stage of compensation. The patients mostly have irritative/storage symptoms. As the severity of the disease increases, these patients start developing voiding/obstructive symptoms and gradually worsening irritative symptoms that can be recorded on the IPSS (International Prostate Symptom Score) scale, this is known as the decompensated stage. It is characterised by the weakening of detrusor and progressively increasing residual urine. These patients often land in chronic retention having an intractable frequency, intermittent voiding, excessive straining, bed wetting and overflow incontinence that severely compromises the quality of life (QoL). Sometimes these patients develop a sudden rise in outlet resistance along with sudden fall in detrusor contraction and thus landing in acute urinary retention that requires immediate intervention for bladder drainage. The last stage, however, has been termed as the stage of complications that encompasses formation of bladder diverticula, vesical calculus, recurrent haematuria and UTI that may finally culminate into B/L hydroureteronephrosis or rarely pyelonephritis.

The natural history of BPH has been examined both in population-based studies and by looking at outcomes in the placebo arms of clinical trials. However, studies have found that outcomes among patients in the placebo arms of clinical trials may not accurately reflect outcomes in the general population [6]. In clinical trials, measurements of LUTS and peak urine flow tend to show a regression to the mean; whereas, this is not seen with measurements of prostate volume and PSA. This is an important proponent of wait and watch strategy as we will be noting later in this discussion.

Before one concludes that a man's symptoms are caused by BPH, other disorders that can cause similar symptoms should be excluded by history, physical examination, and several simple tests. These disorders include Urethral stricture, Bladder neck contracture, Carcinoma of the prostate, Carcinoma of the bladder, Bladder calculi, Urinary tract infection and prostatitis and neurogenic bladder.

The American Urologic Association (AUA) recommends urinalysis and serum PSA for routine management of patients with LUTS [7]. We also obtain a serum creatinine for assessing renal function and consider maximal urinary flow rate and PVRU as optional tests. Pressure flow studies are only recommended in cases where there is reason to suspect some problem other than or in the four pillars of current management strategy are watchful waiting with self-management, medical management, minimally invasive techniques and surgical management addition to BPH.

In patients with symptoms of benign prostatic hyperplasia (BPH) who do not have any discomfort from their symptoms and no evidence of complications (such as bladder outlet obstruction, renal insufficiency, or recurrent infection), pharmacologic treatment may not be necessary [8]. These patients may be monitored and advised regarding behavioural modifications.

In one randomized trial, men given an educational intervention that included the teaching of behavioural modifications were significantly less likely to experience treatment failure (increase in IPSS or requirement for medication) compared with men followed with watchful waiting alone [9]. With the current level of evidence watchful waiting with Self-management is a Grade A recommendation for all patients with mild symptoms.

Symptomatic improvement in patients with BPH was initially noted with alpha-adrenergic blockers. Currently, the drugs that are in vogue in this group are alfuzosin, tamsulosin, and silodosin. There are specific indications that have come up for these three uroselective drugs. Alfuzosin is preferred in patients having larger residual urine and in younger age group due to the low incidence of an ejaculation which is around 1%. Tamsulosin is preferred more in patients with more irritative symptoms whereas silodosin is useful in patients with nocturia dominant features and specifically useful in old age due to its very low propensity to cause hypotension. In a study by Van Kerrebroeck et al. [10], alfuzosin was noted to bring a change in symptom score to 39.9%. In another study by Lepor et al. [11], the authors reported the efficacy of tamsulosin being dose dependent where 0.4 mg gave 41.9% and 0.8 mg gave 48.2% reduction in IPSS scores. However, these drugs failed to show any improvement in Qmax or change in post void residue. As for the pharmacokinetic profile, tamsulosin and alfuzosin takes 4 days for maximum effect and silodosin takes a maximum of 2 days, further due to the preliminary elimination of alfuzosin by the liver and silodosin by renal route, these drugs are specifically contraindication in liver and kidney failure respectively. However, the use of these drugs needs to be balanced along with its side-effects that need due consideration. The side effects due to alpha blockers are categorized as those that present within a week including hypotensive events, asthenia and dizziness and gastrointestinal upset however the latter is relatively rare. Ejaculatory dysfunction in the form of an ejaculation appears within 6 months and is most common with silodosin and is least with alfuzosin.

The next class of drugs is the 5 Alpha Reductase inhibitors (ARI) that target prostatic enlargement. Finasteride by its action on type 2 receptors and dutasteride on both type 1 and type 2 leads to a reduction in conversion of circulation testosterone to dihydrotestosterone the active form, thus reversing the process of prostatic enlargement. This effect was first studied by Narayan et al. [12] that compared finasteride 5 mg *vs* placebo and found that it decreased the prostatic volume by 16.9%, further in a study by Kirby et al. [13] noted an improvement of 38.6% in IPSS score. A comparison between tamsulosin and dutasteride by Roehrborn et al. [14] found that dutasteride consistently reduced prostatic volume by 28% in comparison to no effect or in the second study progression on tamsulosin alone[14]. In a landmark paper by Marberger [15], dubbed as the PROWESS study group they noted that finasteride significantly reduced the need for surgery and occurrence of acute urinary retention in patients with BPH [15]. However despite being highly efficacious in reducing the progression and for surgery, around 30% of patients remained non-responders, the exact reason for which is still speculative. ARI are generally considered to be safe drugs and almost all side effects are reversible on stopping these drugs. There are few concerns regarding increased incidence of aggressive prostatic cancer but these are still unaccounted for but do ask for closer surveillance of PSA levels.

With the advent of two different classes of drugs, it seemed just a matter of time till an RCT explored the possibility of combination therapy. The two large RCT's that answered this question were the MTOPS trial and the CombAT trial both suggested that combination therapy was superior to monotherapy in preventing clinical progression, reduced IPSS by 66% reduced the relative risk of acute urinary retention (ARI) by 68% and BPH-related surgery by 71% after 4 years of continuous therapy [16,17].

The current recommendations of these 2 classes of drugs and their combination find a place in all patients initially presenting with moderate to severe LUTS and ARI is specifically indicated in large prostates more than 40 ml [8].

By the end of this decade of seemingly important revelations in the medical management of a well proven surgical disease; gave the researchers that extra impetus to search for newer drugs targeting the natural history of the disease. A result of this highly targeted research was two relatively new classes of drugs the antimuscarinics and the PDE5 inhibitors.

The role of antimuscarinics was seen with a lot of skepticism due to their propensity to relax the detrusor and theoretically increasing the chances of acute retention. But once the bladder specific drugs tolterodine and solifenacin passed the initial safety trials; these drugs were noted to be highly efficacious in controlling the storage symptoms. In a study by Kaplan et al.[18], it was noted that tolterodine decreased voiding frequency by 17%, nocturia by 20% and urge incontinence by 85%, further, in a similar study by Herschorn et al. [19] fesoterodine was noted to be 100% effective in reducing urge incontinence. Following these impressive results antimuscarinics actually have come on the top in patients with compensated disease with storage symptoms only. Moreover, in patients with storage and voiding symptoms, specific parameters including the PVRU have been studied to allow the usage of these groups of drugs without the risk of AUR. In combination with alpha blockers, these drugs have been noted to decrease IPSS by 66% and nocturia by 40% that is much higher than either of the drugs alone [18].

The second group of drugs that cropped out during the same era was the PDE5 inhibitors. This group of drugs has a novel mechanism of action by affecting the cGMP levels and increasing the local NO levels leading to smooth muscle relaxation, further, their vasodilatory action on affected pelvic vasculature was also purported to have efficacious effects on the disease pathology. In a study by Roehrborn et al. [20], they noted tadalafil improved the IPSS scores by 20-30% with a dose escalation effect, with higher dosage leading to much better results. Further for the first time a novel group of drugs was available to the physicians which could simultaneously take care of LUTS and ejaculatory dysfunction (ED) that mostly co-occurred in these subgroup of patients.

With the availability of two new classes of drugs, it was a matter of time when newer combinations were sought. The combination of tadalafil and alpha blockers was found to be highly effect in patient with minimal storage symptoms and predominantly voiding symptoms whereas the combination of antimuscarinics with alpha blockers was found to be highly effective in patients with predominantly storage symptoms with minimal voiding symptoms with respect to monotherapy in any of the two groups.

With the pharmacotherapy making a definite impact on BPH and its management, the end of the decade saw a flurry of herbal medications like saw palmetto and three new classes of drugs including the beta-3 agonists, Vit D-3 agonists, and LHRH antagonists. But due to lack of RCTs only Miragebron, Beta-3 agonist could be adequately studied to warrant a separate mention.

Beta-3 adrenoceptors are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation. Mirabegron 50 mg is the first clinically available beta-3 agonist and has received approval for use in adults with OAB. Mirabegron at daily doses of 25, 50, and 100 mg demonstrated significant efficacy in treating the symptoms of OAB, including micturition frequency, urgency incontinence, and urgency and also the patient perception of treatment benefit [21]. However its combinations with existing drugs is still a matter of research and its use as a monotherapy in patients with moderate to severe LUTS is still a grade B recommendation.

But the big question that looms whether all this pharmaco-jargon will replace surgery as the gold standard. As quoted in an article by Ahyai et al. [22] "In a recent analysis of 20 contemporary RCTs with a maximum follow-up of 5 years, TURP resulted in a substantial mean Qmax improvement (+162%), a significant reduction in IPSS (-70%), QoL score (-69%), and PVR (-77%)". Moreover with newer techniques involving Bipolar TURP, laser TURP, TUNA, TUMT, Prostatic stents, Prostatic LIFT, Intraprostatic Ethanol injection, Intraprostatic Botulinum Toxin Injection, have significantly lowered the morbidity offered by surgical procedures in today's era. No medical therapy has yet been able to produce similar long lasting results as these surgical techniques do.

However, we would like to conclude by revisiting an interesting paper by Kramer et al. [23] titled "Is BPH an Immune Inflammatory disease?" in which the authors studied various inflammatory cytokines and interleukins and proposed a unique model of BPH that may be a result of immune dysfunction. They further proposed a new hypothesis suggesting a yet unknown initial insult in the form of an infection, or trauma leading to expression of foreign antigen and leading to a cellular injury that in a background of misdirected immune response could lead to activation of prostatic stem cells and culminate into BPH.

Till the time such new mechanisms are implored and a better understanding of the natural history of BPH is obtained medical therapy will remain an important pillar in the treatment of BPH albeit an adjunct to delay the need for surgery that remains the current gold standard for management of BPH.

References

1. Kahokehr A, Gilling PJ (2014) Landmarks in BPH--from aetiology to medical and surgical management. Nat Rev Urol 11: 118-122.
2. Fitzpatrick J (2006) Interview with John Fitzpatrick--combination therapy for BPH: is this the way forward? Interview by Christine McKillop. Eur urol 49: 581-583.
3. Guo R, Yu W, Zhang K, Xu B (2016) Impact of Changing Trends in Medical Therapy on Transurethral Resection of the Prostate: Two Decades of Change in China. Urology S0090-S4295.
4. Jiang M, Strand DW, Franco OE, Clark PE, Hayward SW (2011) PPARγ: a molecular link between systemic metabolic disease and benign prostate hyperplasia. Differentiation 82: 220-236.
5. Schröder FH, Blom JH (1989) Natural history of benign prostatic hyperplasia (BPH). Prostate Suppl 2: 17-22.
6. Roberts RO, Lieber MM, Jacobson DJ, Girman CJ, Jacobsen SJ (2005) Limitations of using outcomes in the placebo arm of a clinical trial of benign prostatic hyperplasia to quantify those in the community. Mayo Clin proc 80: 759-764.
7. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, et al. (2011) Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol 185: 1793-1803.
8. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, et al. (2013) EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol 64: 118-140.
9. Brown CT, Yap T, Cromwell DA, Rixon L, Steed L, et al. (2007) Self-management for men with lower urinary tract symptoms: randomised controlled trial. BMJ 334: 25.
10. Van Kerrebroeck P, Jardin A, Laval KU, van Cangh P (2000) Efficacy and safety of a new prolonged release formulation of alfuzosin 10 mg once daily versus alfuzosin 2.5 mg thrice daily and placebo in patients with symptomatic benign prostatic hyperplasia. Eur urol 37: 306-313.
11. Lepor H (1998) Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. Urology 51: 892-900.
12. Narayan P, Trachtenberg J, Lepor H, Debruyne FM, Tewari A, et al. (1996) A dose-response study of the effect of flutamide on benign prostatic hyperplasia: results of a multicenter study. Urology 47: 497-504.
13. Kirby RS, Roehrborn C, Boyle P, Bartsch G, Jardin A, et al. (2003) Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in the treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. Urology 61: 119-126.
14. Roehrborn CG, Siami P, Barkin J, Damião R, Major-Walker K, et al. (2008) The effects of dutasteride, tamsulosin, and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. J Urol 179: 616-621.
15. Marberger MJ (1998) Long-term effects of finasteride in patients with benign prostatic hyperplasia: a double-blind, placebo-controlled, multicenter study. Urology 51: 677-686.
16. McConnell JD, Roehrborn CG, Bautista OM, Andriole GL, Dixon CM, et al. (2003) The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med 349: 2387-2398.
17. Roehrborn CG, Barkin J, Siami P, Tubaro A, Wilson TH, et al. (2011) Clinical outcomes after combined therapy with dutasteride plus tamsulosin or either monotherapy in men with benign prostatic hyperplasia (BPH) by baseline characteristics: 4-year results from the randomized, double-blind Combination of Avodart and Tamsulosin (CombAT) trial. BJU Int107: 946-954.
18. Kaplan SA, Roehrborn CG, Rovner ES, Carlsson M, Bavendam T, et al. (2006) Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. JAMA 296: 2319-2328.
19. Herschorn S, Jones JS, Oelke M, MacDiarmid S, Wang JT, et al. (2010) Efficacy and tolerability of fesoterodine in men with overactive bladder: a pooled analysis of 2 phase III studies. Urology 75: 1149-1155.

20. Roehrborn CG, McVary KT, Elion-Mboussa A, Viktrup L (2008) Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding the study. J Urol 180: 1228-1234.

21. Chapple C, Khullar V, Nitti VW, Frankel J, Herschorn S, et al. (2015) Efficacy of the β3-adrenoceptor agonist mirabegron for the treatment of overactive bladder by the severity of incontinence at baseline: a post hoc analysis of pooled data from three randomised phase 3 trials. Eur Urol 67: 11-14.

22. Ahyai SA, Gilling P, Kaplan SA, Kuntz RM, Madersbacher S, et al. (2010) Meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic enlargement. Eur Urol 58: 384-397.

23. Kramer G, Mitteregger D, Marberger M (2007) Is benign prostatic hyperplasia (BPH) an immune inflammatory disease? Eur Urol 51: 1202-1216.