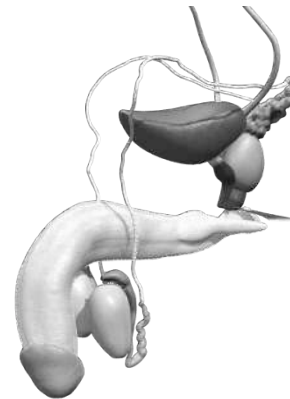


Advances in the Management of Benign Prostate Hyperplasia

Dr Anthony C.F. Ng
 Professor
 Division of Urology, Department of Surgery
 The Chinese University of Hong Kong

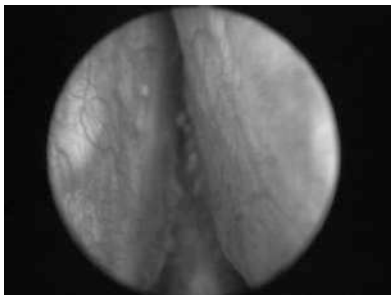
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PRIMA

Prostate



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Incidence in Hong Kong

- HK Urological Association 2006 Survey
 - 532 men over age of 40 involved in the survey
 - 70% of men have prostatic symptoms
 - Meanwhile, only 5.6% men are willing to seek for treatment
 - 29% of men considered BPH is the normal aging process and it is a minor illness

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Pathology and Pathophysiology

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BPH

- Unknown aetiology
 - Aging – important
 - Presence of testosterone
 - 26 Eunuchs →
 - No detectable prostate in 21 and
 - Small Prostate in 5
 - Testosterone – important in the development of prostate / BPH
 - Weight gain and abdominal obesity

Wu 1991
 Giovannucci et al Am J Epidem 1994

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BPH

After age of 40

- Appearance of BPH tissue
- Slowly increase in size

Symptomatic – usually above 60

- in male at age of 60 years old, 30-50% experience voiding problems



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Prevalence

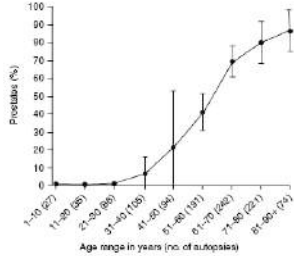
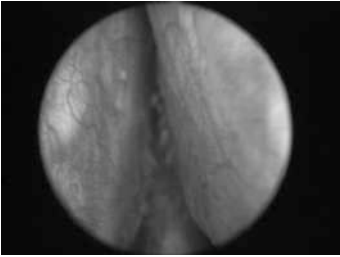


Fig. 1. Proportion of prostates with histopathological benign prostatic hypertrophy (BPH) at autopsy versus age. Mean \pm SE. Reprinted from Berry et al.²¹ with permission from Lippincott Williams & Wilkins.

Berry et al. J Urol 1984; 132: 474-9


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Prostate – the Problem



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Obstructing



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Squeeze



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Pathophysiology

- Benign Prostate Hyperplasia
 - Static component
 - Dynamic component
- Secondary changes in bladder
 - Detrusor hypersensitivity (OAB)
- Complications
 - Urinary tract infection, bladder stone formation
 - Acute or chronic retention
 - Renal failure

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Treatment

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BPH

•Treatment

- Conservatives / Watchful waiting
- Medical
 - Alpha-blocker / 5-alpha reductase inhibitors
 - PDE5 inhibitor
- Minimally invasive therapy
 - Thermotherapy – RF, HIFU, TUMT
 - Tissue ablation – PVP, HoLRP
- Surgical
 - TURP – Monopolar / Bipolar
 - Open prostatectomy
- Others
 - Long term catheter
 - Stenting

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Medical Treatment

Alpha-Adrenergic Receptor Blocker

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Theory of using α -AR blocker

- Lepor and Shapiro reported that α 1-AR are abundant in the prostate and bladder neck and sparse in the bladder body
Lepor et al J Urol 1984; 132: 1226
- The area density of prostate smooth muscle measured from prostatic biopsy was shown to have direct relationship with the improvement of peak flow rate by terazosin
Shapiro et al The Prostate 1992; 21: 297

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Current α 1-AR blocker

- Non-selective: Phenoxybenzamine
- Selective:
 - Prazosin (Minipress)
 - Terazosin (Hytrin)
 - Doxazosin (Cardura)
 - Alfuzosin (Xatral, Xatral SR, Xatral XL)
- Subtype selective (1a)
 - Tamsulosin (Harnal)
 - Silodosin (Rapaflo)

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Side effects

- The primary adverse events reported with α 1-AR blocker are
 - orthostatic hypotension
 - dizziness
 - tiredness (asthenia)
 - nasal congestion
 - ejaculatory problems
- Discontinuation rate due to AE
 - For Alfuzosin & Tamsulosin = 4 ~ 10% (similar to placebo)
 - For Doxazosin & Terazosin = + 4 ~ 10%

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Marberger et al Eur Urol 2004; 45: 411

How to overcome SE?

- Traditional approach –
 - Titration
 - Start from low dose → Satisfactory or Side effects
- New approaches
 - Uro-selectivity
 - Drug designs

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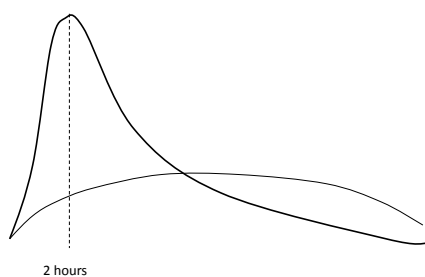
Uro-selective

- Receptors subtype selective
 - Alpha – 1 a / b / d
 - Alpha – 1 a - predominant receptor subtype at the bladder neck and prostate level
 - Subtype selective
 - Tamsulosin (Harnal)
 - Silodosin (Rapaflo)
- AE: Ejaculatory problems (retrograde / retraded)
 - Tamsulosin = 4.5 ~10% (placebo 0 -1%)

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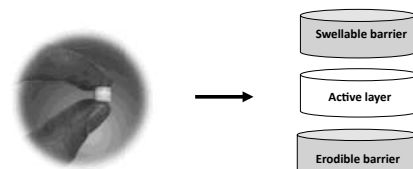
MacDonald et al Drugs 2003; 63: 1947

Traditional Formulation



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Xatral® XL (Alfuzosin) Geomatrix® * technology

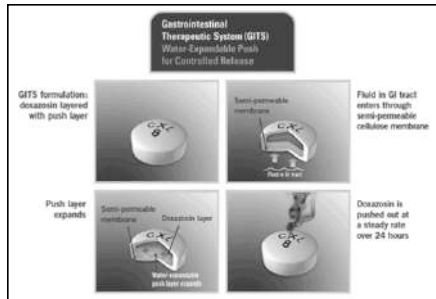


Geomatrix® technology provides consistent and predictable delivery of alfuzosin over 24 hours without plasma level fluctuations**

** GEOMATRIX® IS A REGISTERED TRADEMARK OF JAGOTEC AG, A MEMBER OF THE SKYEPHARMA GROUP OF COMPANIES

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Cardura XL® (Doxazosin)



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Slow releasing formulation

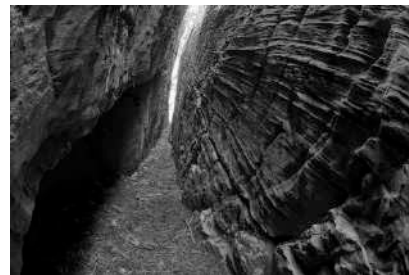
- Less haemodynamic fluctuation
- Safer for elderly patients
- Allow once a day formulation – simplified formulation
- Can allow a higher initial dosage (even maximum dose)
 - Achieve therapeutic effect faster

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5-Alpha Reductase Inhibitors

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Obstructing



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5α-reductase

- Testosterone → Dihydrotestosterone (DHT)
5-α-reductase
- DHT is essential for prostate development and growth, the development of the external genitalia and male patterns of facial and body hair growth or male-pattern baldness.

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Mechanism

- 5α-RI is the sole hormonal therapy, to date, that demonstrates both efficacy and acceptable safety for treatment of BPH
- Decrease the size of prostate
- The onset of maximal clinical effect 3-6 months
- Effects especially superior in glands > 40ml

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Boyle et al Urology 1996; 48: 398-405

Decrease in volume

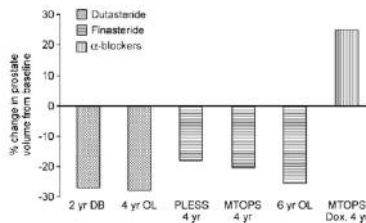


Fig. 5 – An indirect across-study comparison of long-term change in prostate volume following treatment with α -blockers, finasteride, and dutasteride [7,9-11].

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Main indications

- As second line alone
 - Not tolerate side effects or contra-indicated for α 1-AR blocker
- As combination
 - Tackle both static and dynamic components
 - Advantage of the faster onset of α 1-AR blocker + reduction in size of 5 α RI
- Prostate related haematuria

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α 1-AR blocker + 5 α RI

- Tackle both static and dynamic components
- Advantage of the faster onset of α 1-AR blocker + reduction in size of 5 α RI

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**How about my future?
 Do I eventually need surgery?**

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Natural History

- In 5 years time
 - 107 male patients with lower urinary tract symptom
 - 10 required surgery
 - 97 not required surgery; for their overall symptoms
 - 16 worsen in symptom
 - 50 static
 - 31 feel better
- Around 1/4 worsen or need surgery

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Ball AJ et al Br J Urol 1986

Can we do something to prevent progression?

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MTOPS Study



MTOPS – clinical progression

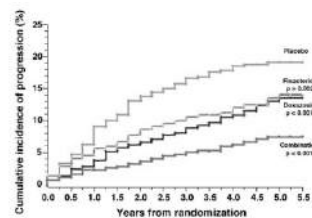


Fig. 1 – Cumulative incidence of progression of benign prostatic hyperplasia in the Medical Therapy of Prostate Symptoms (MTOPS) Study. Reproduced with permission from McConnell J et al. N Engl J Med 2003;349:2387-98.

MTOPS – Acute retention

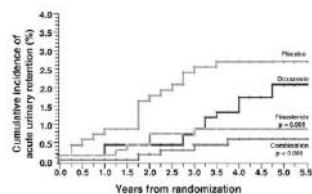


Fig. 2 – Cumulative incidence of acute urinary retention in men receiving finasteride, doxazosin, a combination of both, or placebo in the Medical Therapy of Prostate Symptoms (MTOPS) Study. Reproduced with permission from McConnell J et al. N Engl J Med 2003;349:2387-98.

MTOPS & NNT

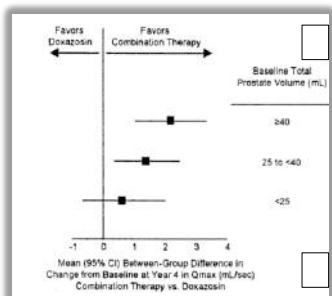
- For a single instance of overall clinical progression,
- Overall NNT were
 - combination 8.4
 - doxazosin 13.7
 - finasteride 15.0

Fitzpatrick Eur Urol 2006; 49: 581-583

MTOPS & NNT

- For a single instance of overall clinical progression,
- Overall NNT were
 - combination 8.4
 - doxazosin 13.7
 - finasteride 15.0
- In men who had larger prostates (> 40 ml on TRUS) or who had PSA > 4 ng/ml
 - for combination therapy NNT = 4.9 and 4.7, respectively,
 - for finasteride therapy NNT = 7.2 for both subgroups

Fitzpatrick Eur Urol 2006; 49: 581-583



EUROPEAN UROLOGY 57 (2010) 123–131

available at www.sciencedirect.com
journal homepage: www.europeanurology.com



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European Association of Urology

Benign Prostatic Hyperplasia

The Effects of Combination Therapy with Dutasteride and Tamsulosin on Clinical Outcomes in Men with Symptomatic Benign Prostatic Hyperplasia: 4-Year Results from the CombAT Study

Claus G. Roehrborn ^{a,*}, Paul Siami ^b, Jack Barkin ^c, Ronaldo Damiao ^d, Kim Major-Walker ^e, Indrani Nandy ^f, Betsy B. Morrill ^g, R. Paul Gagnier ^h, Francesco Montorsi ⁱ
on behalf of the CombAT Study Group

Department of Urology, University of Michigan, Ann Arbor, MI, USA

Roehrborn CG et al Eur Urol 2010; 57: 123-131

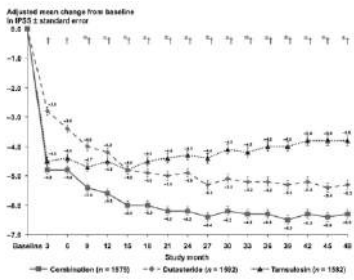
CombAT major entrance criteria

- Male aged ≥50 years
- Diagnosis of BPH by History and DRE
- IPSS ≥12 (moderate to severe symptoms)
- Prostate volume ≥30 cc by TRUS
- Serum PSA ≥1.5 and ≤10.0 ng/mL
- Two voids at screening with Q_{max} >5 and ≤15 mL/sec (moderate to severe impairment) and minimum voided volume of ≥125 mL

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Roehrborn CG et al Eur Urol 2010; 57: 123-131

Symptom changes



Adjusted mean change from baseline in IPSS standard error

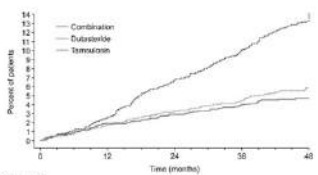
Study month

—●— Combination (n = 1870) —○— Dutasteride (n = 1982) —▲— Tamsulosin (n = 1982)

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Acute Retention of Urine / OT



	0	12	24	36	48
Combination	0	28	43	58	67
No. at risk	1870	1457	1347	1274	1274
Dutasteride	0	27	48	85	84
No. at risk	1982	1864	1765	1527	1527
Tamsulosin	0	40	102	146	151
No. at risk	1982	1864	1507	1178	1178

Fig. 3 – Kaplan-Meier estimates of time to the first episode of acute urinary retention or benign prostatic hyperplasia-related prostatic surgery.

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Roehrborn CG et al Eur Urol 2010; 57: 123-131

EAU guideline

3.2.6 Recommendations

	LE	GR
5α-reductase inhibitors should be offered to men who have moderate to severe LUTS and an enlarged prostate. 5α-reductase inhibitors can prevent disease progression with regard to acute urinary retention and need for surgery.	1b	A

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EAU guidelines 2011

Table 6. Summary of drug-Related Adverse Events after 1-year of dutasteride or finasteride [104]

	Dutasteride 0.5 mg daily N=813	Finasteride 5 mg daily N=817
Any adverse event	17%	20%
Sexual adverse event %	11%	14%
Gynecomastia		
Impotence	7%	8%
Decreased libido	5%	6%
Ejaculation disorders	1%	1%
Gynecomastia	1%	1%

Any Other drugs?

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α1-AR blocker and PDE5 inhibitor

•Tinel et al found that PDE5 mRNA was expressed in the lower urinary tract tissue of rats and that PDE5 inhibitors reduced the contraction of muscle strips.

Tinel et al. BJU Int 2006; 98: 1259-1263

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α1-AR blocker and PDE5 inhibitor

- Clinical studies suggest that PDE5 inhibitors can improve LUTS
- Combined usage of alfuzosin and sildenafil is superior to alfuzosin monotherapy in managing patients with LUTS

McVary et al. J Urol 2007; 177: 1401-1407.
Kaplan et al. Eur Urol 2007; 51: 1717-1723

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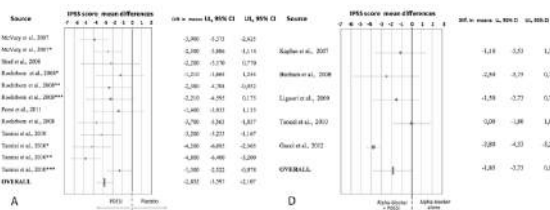
Review – Benign Prostatic Hyperplasia

A Systematic Review and Meta-analysis on the Use of Phosphodiesterase 5 Inhibitors Alone or in Combination with α-Blockers for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia

Mauro Gacci^{a,*}, Giovanni Corona^{b,c}, Matteo Salvi^d, Linda Vignozzi^e, Kevin T. McVary^f, Steven A. Kaplan^g, Claus G. Roehrborn^h, Sergio Serniⁱ, Vincenzo Mirone^g, Marco Carini^g, Mario Maggi^g

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α1-AR blocker and PDE5 inhibitor



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FDA approval

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration
Protecting and Promoting Your Health

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News & Events
FDA NEWS RELEASE
For Immediate Release: Oct 5, 2011
Media Inquiries: 1-877-310-2207, jffrey.ventura@fda.hhs.gov
Consumer Inquiries: 1-888-INFO-FDA

FDA approves Cialis to treat benign prostatic hyperplasia
The U.S. Food and Drug Administration today approved Cialis (tadalafil) to treat the signs and symptoms of benign prostatic hyperplasia (BPH), a condition in which the prostate gland becomes enlarged, and for the treatment of BPH and erectile dysfunction (ED) when the conditions occur simultaneously. Cialis was approved in 2003 for the treatment of ED.


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Surgical treatment

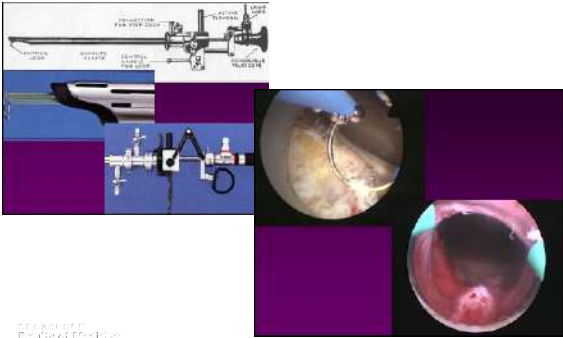

TURP – Gold Standard



Obstructing





TURP

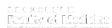
Problem of TURP

- Bleeding
- TUR syndrome – related to the use of glycine
- Difficult to learn

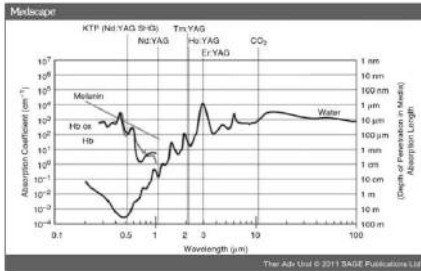


New Energy Mode


- Laser Energy
- Bipolar Energy



Laser in Urology



The AM-044 © 2011 SAGE Publications Ltd

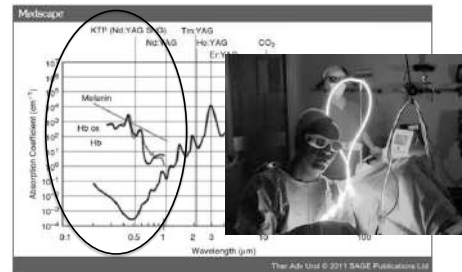


Laser and prostatectomy

- In 1990, Nd:YAG laser (side firing / non-contact)
 - Edema and prolonged sloughing of the coagulating tissue
- In 1993, Interstitial laser coagulation
 - Tissue puncture – lead to coagulation necrosis
 - Marked tissue reaction and may need prolonged catheterization

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Green Laser (KTP laser)

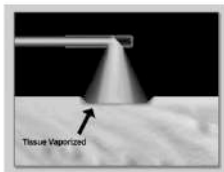


KTP = Potassium titanyl phosphate (K₂TiPO₄)

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PVP

- Green "light" (532nm) is selectively absorbed within the tissue by haemoglobin ("red") and not by water and has a short penetration depth of 0.8 mm.
- Immediate tissue vapourization



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PVP Procedure



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Photoselective vaporization with the green light laser vs transurethral resection of the prostate for treating benign prostate hyperplasia: a systematic review and meta-analysis

Jingfei Teng^{1,2}, Dongxu Zhang^{1,2}, Yao Li^{1,2}, Lei Yin¹, Kai Wang¹, Xingang Cui¹ and Danfeng Xu¹

¹Department of Urology, Changzhong Hospital, Second Military Medical University, Shanghai, and ²Department of Urology, General Hospital of Chinese People's Liberation Army, Beijing Military Region, Beijing, China

¹These authors contributed equally to this article.

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Teng J et al BJU int 2012; 111: 312 - 323

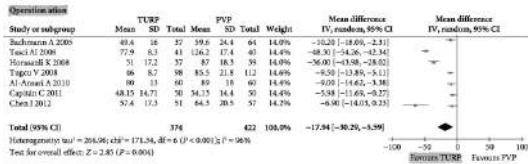
Methodology and Results

- 223 publications – 9 studies included in analysis
- TURP – 503 patients vs PVP – 535 patients
- Results:
 - NO significant difference in voiding parameters
 - Peak flow rate
 - Residual urine
 - International prostate symptom score
 - Quality of Life score

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Teng J et al BJU int 2012; 111: 312 - 323

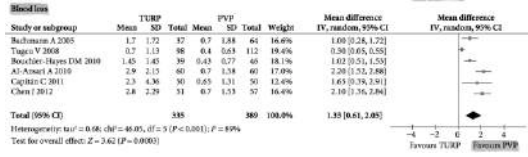
Operating Time



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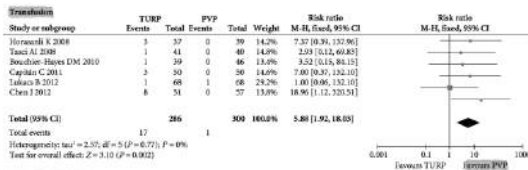
Blood loss



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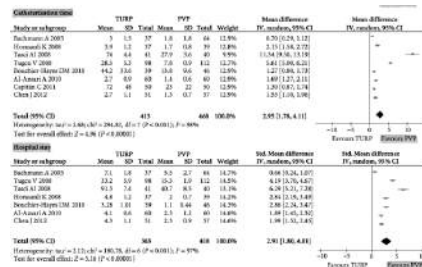
Transfusion rate



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Teng J et al BJU int 2012; 111: 312 - 323

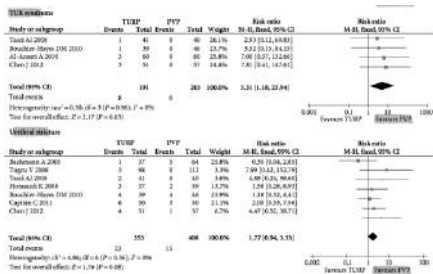
Postoperative recovery



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Complications



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Clinical advantages

- Equal efficacy
- Less complications
 - TUR syndrome
 - Bleeding – in particular suitable for patients on anticoagulation / anti-platelet agents

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Photoselective vapourization of Prostate (PVP / Green laser)

- Need to have the machine
- Need to have fibers
- May not be that convenience



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Can we have something more straight forward?

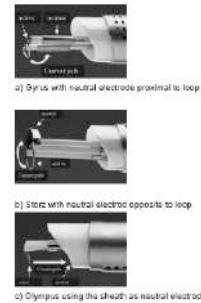
Bipolar TURP

- Can use with some of the usual diathermy machine
- More readily used in operation room
- Advantages:
 - Can use normal saline during resection, i.e. avoid the use of glycine – no TUR syndrome
 - Similar skill as standard monopolar TURP

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Bipolar TURP

Figure 3. Technical modification of (quasi)bipolar resectoscopes



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Outcome of Bipolar vs TURP

Systematic Review and Meta-analysis of Transurethral Resection of the Prostate Versus Minimally Invasive Procedures for the Treatment of Benign Prostatic Obstruction

Natasha Burke, J. Paul Whelan, Linda Goeree, Robert B. Hopkins, Kaitryn Campbell, Ron Goeree, and Jean-Eric Tarride

Emerging minimally invasive procedures for the treatment of patients with benign prostatic obstruction may have advantages over transurethral resection of the prostate (TURP). We performed a systematic literature review and meta-analysis of randomized trials published since April 2008 comparing TURP with photoselective vaporization, holmium laser ablation, and bipolar TURP. A total of 38 articles reporting results from 11 trials were included (photoselective vaporization = 3; holmium laser ablation = 1; bipolar TURP = 17). An assessment of perioperative and postoperative outcomes up to 12 months indicates benefits for these procedures. However, long-term follow-up and stronger methodological quality of the evidence is required to assess the long-term durability of the technologies. UROLOGY 75: 1015-1022, 2010. © 2010 Elsevier Inc.

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N Burke et al Urol 2010; 75: 1015-1022

Results

- Operation times, transfusion rates, retention rates after catheter removal and urethral complications did not differ significantly.
- Irrigation and catheterization duration was significantly longer with monopolar TURP ($p < 0.00001$).
- shorter catheterization period with bipolar TURP ($p < 0.001$), and a significant reduction of the number of days in hospital ($p < 0.01$)

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Plasma Vapourization

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Plasma

- One of the four fundamental states of matter (the others being solid, liquid, and gas)
- Which contains charged particles: positive ions and negative electrons or ions.

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TURIs – bipolar vapourization

CONVENTIONAL

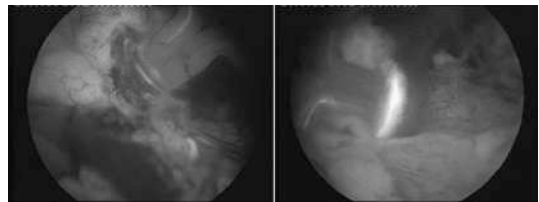
NEW



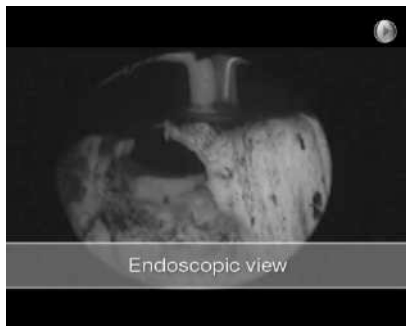
Comparison of ablation instruments (resection loop vs. TURIs plasma vaporization electrode).

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Plasma Vapourization



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Endoscopic view

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Plasma Vapourization

- Good haemostasis
- Easy to perform and learn

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Other development

- Thulium Laser – enucleation / vapourization
- Botox injection

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Conclusion

- With increase in life expectancy of male patients in our regions, there will be an continue increase in the aging population
- More and more patients will present with voiding dysfunction secondary to benign prostate enlargement
- The improvement in both medical and surgical technologies have provided many new treatment options for these patients
- We could tailor-made the treatment plan for individual patients in order to provide the best care for them

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THANK YOU

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