

Learning expectations at the end of the lecture

- -what is bph
- -how do you make a diagnosis
- Investigations for BPH
- Treatment for bph
- Followup for bph

introduction

- BPH=Most common diseases of aging men,
- associated with bothersome lower urinary tract symptoms (LUTS) that affect quality of life
- Interfers with normal daily activities and sleep patterns

introduction

- The prevalence of histopathologic BPH is age dependent
- Usually after 40 years of age
- At 60 years prevalence is greater than 50% and by age 85 is as high as 90%
- the prevalence of bothersome symptoms also increases with age

introduction

- Half of all men who have a histologic diagnosis of BPH have moderate to severe LUTS.
- the risks of developing complications and morbidities from untreated BPH are unclear
- there is still uncertainty regarding the likelihood that a patient with a specific symptom complex will develop complete urinary retention within a particular time frame.

introduction

- BPH-associated mortality is rare in the United States, and serious complications are uncommon
- LUTS are bothersome to many patients, and the amount of bother may differ greatly among individuals with the same degree of symptom frequency and severity

introduction

- Patient's perception of the severity of the condition, as well as the degree to which it interferes with his lifestyle is the primary consideration in choosing therapy

Benign prostatic hyperplasia

- disease process characterized by stromal and epithelial cell hyperplasia beginning in the periurethral zone of the prostate

Benign prostatic hyperplasia

- LUTS associated with BPH is caused by the extrinsic compression of the prostatic urethra leading to impaired voiding
- There are other causes of LUTS besides an enlarged prostate

BPH diff diagnosis

- Bladder cancer
- Prostate cancer
- Prostatitis
- Bladder stones
- Interstitial cystitis
- Radiation cystitis

other causes of LUTS

- Urinary tract infection
- Diabetes mellitus
- Parkinson's disease
- Primary bladder neck hypertrophy
- Congestive heart failure
- Lumbosacral disc disease Multiple sclerosis
Nocturnal polyuria

chief complaint for BPH

Bothersome LUTS

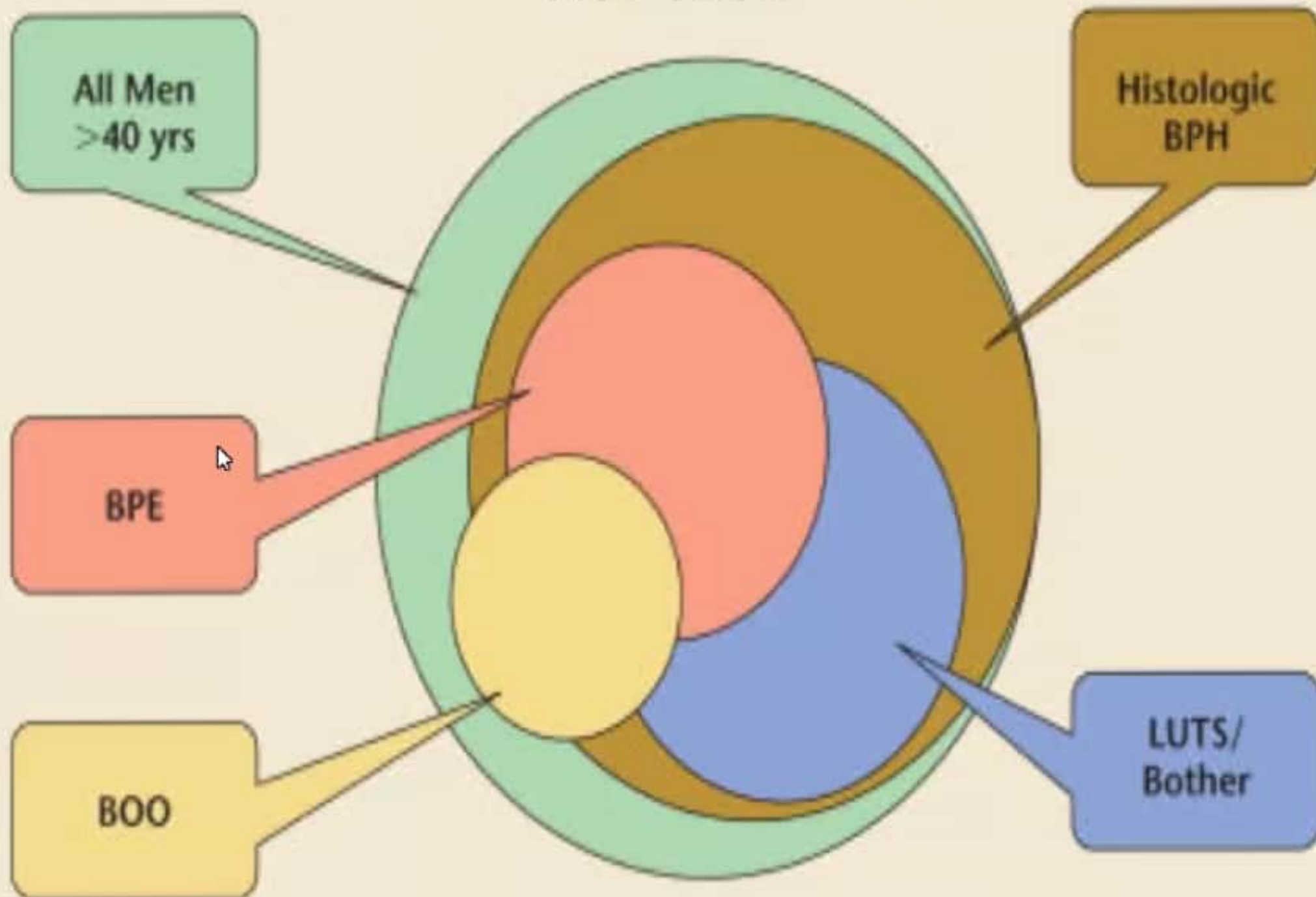
1. frequency,
2. Urgency,
3. Nocturia,
4. Decreased and intermittent force of stream
5. sensation of incomplete bladder emptying

BPH

The relationship between BPH and LUTS is complex, not all men with histological evidence of BPH will develop LUTS

- LUTS are neither specific to nor exclusive to BPH
- May be caused by other conditions in the lower urinary tract

The Problem



Diagnostic evaluation of benign prostatic hyperplasia

- **Serum prostate-specific antigen (PSA)**
- **Urine cytology in men with predominantly irritative symptoms**
- **Ipss**
- **A medical history should be taken to identify other causes of voiding dysfunction or comorbidities that may complicate treatment**

Diagnostic evaluation of benign prostatic hyperplasia

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DIAGNOSIS

- A physical examination, including both a digital rectal examination(DRE) and a focused neurologic examination, should be performed
- locally advanced prostate cancer, which also can produce LUTS, should be excluded by DRE.

DIAGNOSIS

- **Urinary flow-rate recording (uroflowmetry), specifically Qmax**
- **may predict the response to surgery and, to a lesser degree, the natural history of the disease**
- **symptom response to many therapies, specifically alpha blockers, is not dependent upon baselineflow rate..**

diagnosis

- The gold standard for diagnosis of BPH is a prostate biopsy
- Given the invasiveness of this procedure, BPH is typically diagnosed clinically with the onset of lower urinary tract symptoms, increased prostate size and decreased urinary flow rates in the absence of other obvious causes.

Flow rate

- **Men with normal flow rates but significant urinary symptoms are more likely to have nonprostatic causes for those symptoms**
- **require more extensive investigation**

ultrasound

- **Large PVR volumes (e.g., 350 mL) may indicate bladder dysfunction and predict a slightly less favorable response to treatment.**
- **large PVRs may herald progression of disease**

diagnosis

- **Patients with mild symptoms of BPH (AUA Symptom Score <7) and patients with moderate or severe symptoms (AUA Symptom Score > 8) who are not bothered by their symptoms should be managed using a strategy of watchful waiting.**

Management of Bothersome Moderate to Severe Symptoms

- watchful waiting
- medical,
- minimally invasive, or surgical therapies

Alpha-adrenergic blockers

- Alfuzosin
- Doxazosin
- Tamsulosin
- Terazosin

5 Alpha-reductase inhibitors

- Dutasteride*
- Finasteride

Combination therapy

- alpha blocker and 5 alphareductase inhibitors

Surgical Therapies

- Transurethral resection of the prostate
- Transurethral electrovaporization
- Transurethral incision of the prostate
- Transurethral holmium laser resection/enucleation
- Transurethral laser vaporization
- Transurethral laser coagulation (e.g., visual laser ablation)
- Open prostatectomy

Indications for surgery

- refractory urinary retention
- recurrent urinary retention
- recurrent haematuria refractory to medical treatment with 5-alpha reductase inhibitors
- renal insufficiency
- bladder stones.
- Increased post-void residual volume may also be used as an indication for surgery

Surgery should be considered for those men:

- moderately/severely bothered by LUTS, yet who do not improve after non-surgical treatment.
- • with bothersome LUTS, who not want medical treatment but who request active intervention.
- Surgical prostatectomy (open, TURP, TUIP, TUVF) results in significant subjective and objective improvements superior to medical or minimally invasive treatment.

TURP



Alpha blockers

- The smooth muscles of the bladder neck and prostate are under the influence of the adrenergic nervous system taking effect through α -adrenergic receptors,[1](#).

Alpha blockers

- the most important ones being the α_{1A} -adrenergic receptors, which constitute $\approx 80\%$ of the total α -receptors in the lower urinary tract

Alpha blockers

- mid-1970s evidence symptomatic relief of LUTS could be obtained by pharmacological blockade of α -adrenergic receptors

Alpha blockers

- late 1990s, α_1 -blockers became the most frequently selected form of medical therapy for LUTS.
- α -blockers are effective in most patients with LUTS and associated BPH and have a rapid onset of action

Alpha blockers

The most frequently prescribed α -blockers are

- the prazosin analogs: doxazosin, terazosin, and alfuzosin,
- structurally unrelated compound tamsulosin

Alpha blockers

- A meta-analysis indicated that these agents are similar in their effectiveness for relieving symptoms and increasing peak urinary flow rate, although differences exist in side-effect profiles [\[](#)

Alpha blockers

- The efficacy of α -blockers is well maintained over time, and there is no evidence of tolerance or tachyphylaxis to α_1 -blockade after 6–12 months' of use

Alpha blockers

- Not all patients respond adequately to α_1 -blockade,
- Response rates depend on the criteria used to define response and the eligibility criteria of the study sample

MANAGEMENT WITH 5 α -REDUCTASE INHIBITORS

- The effect of DHT can be blocked by 5 α -reductase inhibition,
- This controls the static component and obstructive symptoms of LUTS

MANAGEMENT WITH 5 α -REDUCTASE INHIBITORS

- Trials have shown that 5 α -reductase inhibitors (5ARIs) reduce circulating DHT levels by $\approx$ 70% (finasteride) and up to >90% (dutasteride)
- As a result, prostatic size is reduced by $\approx$ 20–30% over time and the serum PSA value is decreased by an average of 50%

MANAGEMENT WITH 5 α -REDUCTASE INHIBITORS

- Over 3–6 months these physiological changes are accompanied by an improvement in the AUA symptom index and the peak urinary flow rate

Gormley GJ, Stoner E, Bruskewitz RC et al. The effect of finasteride in men with benign prostatic hyperplasia. The Finasteride Study Group. N Engl J Med 1992; 327: 1185–91

Roehrborn CG, Andriole G, Boyle P et al. Effect of the dual 5 α -reductase inhibitor dutasteride on endocrine parameters and prostate volume. Eur Urol Suppl 2002; 1: 107

Roehrborn CG, Marks LS, Fenter T et al. Efficacy and safety of dutasteride in the four-year treatment of men with benign prostatic hyperplasia. Urology 2004; 63: 709–15

Gormley GJ, Stoner E, Bruskewitz RC et al. The effect of finasteride in men with benign prostatic hyperplasia. 1992. J Urol 2002; 167: 1102

Lepor H. Pathophysiology of lower urinary tract symptoms in the aging male population. Rev Urol 2005; 7 (Suppl. 7): S3–11

MANAGEMENT WITH 5 α -REDUCTASE INHIBITORS

- The proposed mechanism of action for the efficacy of 5ARIs in men with BPH is the reduction of prostate volume
- In contrast to the rapid action of α -blockers, the 5ARIs often require up to 6 months to be effective

Combat study

- CombAT (Combination Therapy with Avodart and tamsulosin) study, examined the first two years of data comparing dutasteride, tamsulosin and combination therapy

COMBAT STUDY

- showed for the first time that in a population of men with prostate volumes over 30 cc and PSA > 1.5 ng/ml (the optimal population for 5-ARI therapy), 5-ARI therapy with dutasteride resulted in significantly more symptom decrease than the alpha-blocker tamsulosin.

COMBINED THERAPY WITH α -BLOCKERS AND 5ARIS

- Combination of an α -blocker (doxazosin) and a 5ARI (finasteride) was investigated in the Prospective European Doxazosin and Combination Therapy (PREDICT) trial
- 1-year study of >1000 men with LUTS and BPH randomized to placebo vs doxazosin vs finasteride vs combined therapy

COMBINED THERAPY WITH α -BLOCKERS AND 5ARIS

- Doxazosin was effective in improving urinary symptoms and urinary flow rate in men with BPH,
- More effective than finasteride alone or placebo
- The addition of finasteride did not provide further benefit to that achieved with doxazosin alone

COMBINED THERAPY WITH α -BLOCKERS AND 5ARIS

- Similar results were obtained in the Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group study
- had a very similar design with the exception that doxazosin was replaced by terazosin
- Both of these pivotal early combined therapy trials patients were treated and followed for only 12 months.

COMBINED THERAPY WITH α -BLOCKERS AND 5ARIS

- The Medical Therapy of Prostatic Symptoms (MTOPS) trial was a 5-year study in 3047 men aged ≥ 50 years
- intended to assess the effect of this combined therapy on the risk of overall clinical progression of BPH relative to placebo

COMBINED THERAPY WITH α -BLOCKERS AND 5ARIS

- Risk of clinical progression of BPH was significantly reduced by the α -blocker doxazosin (39% risk reduction, $P < 0.001$) and by the 5ARI finasteride (34% risk reduction, $P = 0.02$).

COMBINED THERAPY WITH α -BLOCKERS AND 5ARIS

- Combined therapy with the α -blocker and the 5ARI led to a significant reduction in risk relative to placebo (66% risk reduction, $P < 0.001$), which was also significantly greater than that associated with that for either drug alone (both $P < 0.001$)

COMBINED THERAPY WITH α -BLOCKERS AND 5ARIS

- The cumulative 4-year incidence of overall clinical progression was 17%, 10%, and 10% in the placebo, α -blocker, and 5ARI groups, respectively
- This compared with 5% in the combined-therapy arm ($P < 0.001$ vs placebo or either agent alone)

Treatment algorithm

- Men with mild symptoms in general do not require treatment and are recommended for watchful waiting or conservative management
- An exception might be men with mild symptoms who have very large glands or high PSA values, as they are at increased risk for progression to more symptomatic disease states

Treatment algorithm

- Prophylactic therapy with 5ARIs might be indicated, although the potential benefit must be compared with the cost and potential risks involved.
- The treatment for men with moderate symptoms but little or no bother follows that of men with mild symptoms.
-

Treatment algorithm

Men with moderate-to-severe symptoms and bother fall into two distinct categories

1. those with smaller glands (<30 g) and lower serum PSA values (<1.5 ng/mL)
2. those with larger glands and higher serum PSA values

Treatment algorithm

- in those with small glands and low PSA α -blocker therapy offers fast symptom relief and these patients in general are at low risk for further prostate growth, progression and need for surgery

Treatment algorithm

- Those with big glands and high PSA are best treated with combined medical therapy using both an α -blocker and a 5ARI.

Treatment algorithm

- The duration of combined therapy is as of yet unresolved, but evidence from the Symptom Management After Reducing Therapy (SMART-1) trial suggests that in some men the α -blocker therapy might be suspended after 6–9 months of combined therapy with little loss of treatment effectiveness

Barkin J, Guimaraes M, Jacobi G, Pushkar D, Taylor S, van Vierssen Trip OB. α -blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5 α -reductase inhibitor dutasteride. Eur Urol 2003;

44: 461–

Treatment algorithm

The presence of bothersome symptoms indicates the need to treat

The prostate size/serum PSA value indicates how to treat these patients

Other drugs

- The role of medical therapy for lower urinary tract symptoms in men is undergoing transformation
- What was originally a 2-horse race, ie alpha-blockers and 5 α -reductase inhibitors, has now become challenged by other agents such as anticholinergics, phosphodiesterase-5 inhibitors and β 3-agonists

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MANAGEMENT WITH MUSCARINIC RECEPTOR ANTAGONISTS

- Overactivity of the detrusor muscle can result in urinary urgency, frequency, nocturia and even urge incontinence.

Stewart WF, Van Rooyen JB, Cundiff GW et al. Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003; 20: 327–36

Irwin DE, Milsom I, Hunskaar S et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC Study. *Eur Urol* 2006; 50: 1306

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MANAGEMENT WITH MUSCARINIC RECEPTOR ANTAGONISTS

- Overactive bladder (OAB) symptoms are nearly identical to storage LUTS and affect an estimated 16% of men in the USA and 11.8% in Canada, Germany, Italy, Sweden, and the UK
- the prevalence in the population is similar to that in women

MANAGEMENT WITH MUSCARINIC RECEPTOR ANTAGONISTS

- The endocrine effects of the 5ARIs, resulting ultimately in volume reduction of the prostate, are unlikely to alleviate detrusor overactivity and related OAB symptoms
- The parasympathetic nervous system regulates detrusor muscle contractility via muscarinic cholinergic pathways

MANAGEMENT WITH MUSCARINIC RECEPTOR ANTAGONISTS

- Muscarinic receptor antagonists, which inhibit the binding of acetylcholine to the muscarinic receptors, and suppress involuntary detrusor contraction, are therefore used as first-line therapy for OAB symptoms

MANAGEMENT WITH MUSCARINIC RECEPTOR ANTAGONISTS

- Oxybutynin, which was originally developed in the 1960s as a treatment for gastrointestinal hypermobility, was also found to inhibit involuntary bladder contractions.

MANAGEMENT WITH MUSCARINIC RECEPTOR ANTAGONISTS

- For thirty years it was the primary treatment for OAB, but its antimuscarinic activity is nonselective for the bladder, and it causes considerable side-effects including dry mouth

MANAGEMENT WITH MUSCARINIC RECEPTOR ANTAGONISTS

- Tolterodine was the first drug developed specifically for the treatment of OAB.
- It is a competitive muscarinic antagonist with similar affinities for muscarinic receptor subtypes M_1 – M_5

MANAGEMENT WITH MUSCARINIC RECEPTOR ANTAGONISTS

- Unlike oxybutynin, which is specific for receptor subtype M_3 , tolterodine is more target-specific and possesses stronger selectivity for the bladder than the salivary glands

MANAGEMENT WITH MUSCARINIC RECEPTOR ANTAGONISTS

- The tolerability of the drug has also been enhanced, with significant reductions in dry mouth compared with the immediate-release formulation .
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COMBINED MUSCARINIC RECEPTOR ANTAGONIST AND α -BLOCKER THERAPY

- combined therapy with a muscarinic receptor antagonist and an α -blocker, specifically in men with BOO and concomitant detrusor instability or OAB is logical

COMBINED MUSCARINIC RECEPTOR ANTAGONIST AND α -BLOCKER THERAPY

- Several studies using this combination (tolterodine combined with tamsulosin or doxazosin) found a significant improvement in symptoms frequency and severity, and quality of life without significantly affecting maximum peak urinary flow rate or detrusor pressure

conclusion

- men with larger prostate glands and higher serum PSA values have a greater risk for progression and experience greater benefit from combined therapy with α -blockers and 5ARIs

conclusions

- men with both BPH and OAB benefit from a combination of α -blocker and antimuscarinic drugs,

conclusion

- The 4-yr CombAT data provide support for the long-term use of dutasteride and tamsulosin combination therapy in men with moderate-to-severe LUTS due to BPH and prostatic enlargement