Frailty and treatments for benign prostatic hyperplasia

STEVE CHAPLIN

Many older men are likely to have lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). Having LUTS can increase the risk of frailty, and the drugs used to treat the symptoms can exacerbate the problem. This article examines these risks and how they can be reduced.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls</td>
<td>Collapse, legs gave way, &quot;found lying on floor&quot;</td>
</tr>
<tr>
<td>Immobility</td>
<td>Sudden change in mobility, &quot;gone off legs&quot;, &quot;stuck in toilet&quot;</td>
</tr>
<tr>
<td>Delirium</td>
<td>Acute confusion, &quot;muddledness&quot;, sudden worsening of confusion in someone with previous dementia or known memory loss</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Change in continence – new onset or worsening of urinary or faecal incontinence</td>
</tr>
<tr>
<td>Susceptibility to side-effects of medication</td>
<td>Confusion with codeine, hypotension with antidepressants</td>
</tr>
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</table>

Table 1. Frailty syndromes

Frailty is “a state of increased vulnerability to poor resolution of homeostasis following a stress, which increases the risk of adverse outcomes including falls, delirium and disability.” Depending on how this is measured, the prevalence of frailty among men over 64 years old has been estimated at 4–19 per cent, with rates doubling after age 80–85 years.

Fit for Frailty, published by the British Geriatrics Society, the Royal College of General Practitioners and Age UK, set out best practice for caring for older people living with frailty. Frailty is not necessarily associated with older age, disability or ill health but it should be suspected when a person presents with a frailty syndrome (see Table 1). Of these, the adverse effects of medication are a particular concern.

Polypharmacy is recognised as a risk factor for frailty. It is more prevalent with increasing age: one in six people in their 70s and almost one in four of those aged over 80 years may be prescribed 10 or more medicines. The risk of adverse effects leading to hospital admission and drug interactions increases with the number of medicines prescribed.

Benign prostatic hyperplasia and frailty

Benign prostatic hyperplasia (BPH), as indicated by lower urinary tract symptoms (LUTS) not likely to have an alternative cause, is increasingly common with age and, in one 2005 UK study, was reported by more than 30 per cent of men aged over 80 years (see Figure 1).

Having LUTS increases the risk of frailty. Compared with men with mild symptoms, having moderate symptoms increased the risk of a fall by 11 per cent and of two falls by 21 per cent; the increased risks for severe symptoms were 33 and 63 per cent respectively. The symptoms most strongly predicting falls were urinary urgency, difficulty initiating urination and nocturia, which is at least partially consistent with the hypothesis that the increased risk may be linked with hasty visits to the toilet at night.

Drug treatment for BPH

Medication review with older people is recommended to reduce the treatment burden and the risk of adverse events. Treatment for BPH improves
bothersome symptoms and may therefore reduce some of the risks posed by frailty but it may also be associated with troublesome adverse effects, drug interactions and longer term complications. Balancing benefit and risk in people with frailty means making a careful choice of pharmacological class and agents within a class.

The options for drug treatment for bothersome voiding symptoms associated with BPH are an alpha-blocker (alfuzosin, doxazosin, tamsulosin, terazosin) and/or a 5-alpha reductase inhibitor (5-ARI; dutasteride, finasteride) (see Table 2). An anticholinergic agent may additionally be considered for men who have storage symptoms after treatment with an alpha-blocker. The risk posed by anticholinergic drugs in older frail people is well recognised but the potential problems of the more widely used alpha-blockers and 5-ARIs have received less attention. In the 2005 UK study, about 20 per cent of men with LUTS were using medication, of which alpha-blockers accounted for about three-quarters and 5-ARIs for one-quarter.

**Alpha-blockers**
The alpha-blockers are preferred for men who have moderate to severe symptoms but have smaller prostate volumes. These agents are vasodilators but their selectivity for receptor subtypes differs and this influences their impact on blood pressure. Patients prescribed alfuzosin or terazosin should be warned of the risk of profound first-dose hypotension; tamsulosin is generally considered to have least effect on blood pressure. All alpha-blockers pose a risk to people with frailty. They lower blood pressure and are associated with hypotension, dizziness and syncope, and an increased risk of falls, fractures and admission to hospital. The risk appears to be greatest during the first eight weeks of treatment and then diminishes, but it persists during maintenance use and recurs when restarting treatment.

A consensus panel concluded that tamsulosin offered questionable benefits in the treatment of older people with LUTS and that other alpha-blockers should be avoided, largely because of lack of evidence of efficacy in this age group and safety concerns. In a meta-analysis of 124 clinical trials involving a total of 58,500 men, terazosin was associated with a significantly greater risk of adverse effects and treatment discontinuation due to adverse effects than tamsulosin or alfuzosin, which were not significantly different from one another.

Treatment with alpha-blockers should be reviewed after four to six weeks and then every 6–12 months. Clinically, the most important drug interaction with alpha-blockers is the risk of additive hypotension. This can occur with most classes of drugs prescribed for cardiovascular disorders and some centrally-acting drugs such as tricyclic antidepressants (SSRIs are an alternative). Phosphodiesterase type 5 (PDE5) inhibitors, eg sildenafil, which are vasodilators, may increase the risk of hypotension and should be used at the lowest possible dose; combinations with doxazosin and terazosin are not recommended.

**5-alpha reductase inhibitors**
The 5-ARIs finasteride and dutasteride are preferred to the alpha-blockers in men with large prostate volume; they relieve symptoms more slowly (taking up to six months) but may reduce BPH progression. They are well tolerated, have few contraindications and a low risk of drug interactions but they are associated with sexual dysfunction (see Table 3).

The 5-ARIs are not associated with an increased risk of fracture overall, or

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Moderate to severe LUTS</td>
<td>Alpha-blocker</td>
</tr>
<tr>
<td>LUTS plus prostate &gt;30g or PSA &gt;1.4ng/ml, and who are at high risk of progression</td>
<td>5-alpha reductase inhibitor</td>
</tr>
<tr>
<td>Bothersome moderate to severe LUTS and prostate &gt;30g or PSA &gt;1.4ng/ml</td>
<td>Alpha-blocker plus 5-alpha reductase inhibitor</td>
</tr>
<tr>
<td>Storage symptoms after treatment with an alpha-blocker</td>
<td>Consider adding an anticholinergic agent</td>
</tr>
</tbody>
</table>

**Table 2.** Treatments recommended by NICE for bothersome lower urinary tract symptoms (LUTS)
Dutasteride as monotherapy or combination therapy in the CombAT study

Figure 2

Table 3

Table 3. Adverse effects associated with the 5-alpha reductase inhibitor dutasteride and the alpha-blocker tamsulosin, alone and in combination over four years in the CombAT study.

<table>
<thead>
<tr>
<th>Drug-related adverse events occurring in ≥1 subject</th>
<th>Combination (n=1610) %</th>
<th>Dutasteride (n=1623) %</th>
<th>Tamsulosin (n=1611) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile dysfunction</td>
<td>9</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Retrograde ejaculation</td>
<td>4</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Ejaculation failure</td>
<td>3</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Semen volume decreased</td>
<td>2</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>Gynaecomastia</td>
<td>2</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nipple pain</td>
<td>1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 2. Mean changes from baseline in International Prostate Symptom Score (IPSS; total score, and storage and voiding subscores) after four years’ treatment with tamsulosin or dutasteride as monotherapy or combination therapy in the CombAT study.

Summary

Many older men with frailty are likely to have LUTS associated with BPH among other co-morbidities. Both LUTS and its treatment can increase the risk of severe events. Alpha-blockers may increase the risk of falls and fracture but offer greater symptom relief than the 5-ARIs, which in turn are better tolerated and may delay progression. A careful balance between benefit and risk is required when considering how best to reduce polypharmacy.

References

10. NICE. Managing medicines in care homes. SC1, March 2014. www.nice.org.uk/guidance/sc1
12. NICE. Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes. NG5. March 2015. www.nice.org.uk/guidance/ng5


Declaration of interests
None to declare.

Steve Chaplin is a medical writer specialising in therapeutics

Forthcoming events

The forthcoming events section highlights some of the many courses, meetings and conferences of interest to prescribers planned over the coming months.

Nurse Prescribing
Date: 30th January 2017
Venue: De Vere West One, 9-10 Portland Pl, London
Telephone: 01932 429933
Email: www.healthcareconferencesuk.co.uk/contact
Website: www.healthcareconferencesuk.co.uk

This important national conference provides an essential update for current and aspiring nonmedical prescribers on prescribing for pain.

Advanced Medicine
Date: 13-16 February 2017
Venue: Royal College of Physicians, London
Telephone: 020 3075 2389
Email: conferences@rcplondon.ac.uk
Website: www.rcplondon.ac.uk

The Advanced Medicine programme will explore areas of medicine experiencing the most change and innovation, delivered by eminent speakers in their field.

Mental Health in Primary Care
Date: 22 February 2017
Venue: Rowley Mile Centre, CB8 0TF
Telephone: 01223 884324
Email: eanglia@rcgp.org.uk
Website: www.rcgp.org.uk

This one-day course aims to teach successful techniques that allow staff in primary care to undertake mental health consultations. The course will raise your confidence in assessing risk and suicidality and will suggest treatment and support patients with various mental health problems.