Newer Agents for the Management of Overactive Bladder

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Overactive bladder is a clinical syndrome characterized by one or more symptoms of urgency (a difficult-to-defer need to urinate), frequency (greater than eight urinations per 24 hours), nocturia, and incontinence. In persons without overactive bladder, the need to empty the bladder becomes progressively more demanding; in overactive bladder, urgency is characterized by unheralded messages of an immediate need to empty the bladder. These signals are difficult (and sometimes impossible) to delay. The inability to delay urination results in episodes of incontinence in up to 40 percent of patients with overactive bladder.

At present, the only class of drugs with widely accepted clinical effectiveness for the treatment of overactive bladder is the anticholinergics, typified by tolterodine (Detrol; Detrol LA) and oxybutynin (Ditropan; Ditropan XL). However, because these drugs create widespread blockade of cholinergic activity, they may cause anticholinergic adverse effects such as blurred vision, dry mouth, urinary retention, constipation, and central nervous system (CNS) effects such as somnolence and confusion. These effects are dose dependent but often occur at therapeutic doses. In 2004, three new anticholinergic drugs were approved by the U.S. Food and Drug Administration for the management of overactive bladder: trospium (Sanctura), solifenacin (Vesicare), and darifenacin (Enablex). These agents also have been shown to improve quality of life in women with overactive bladder and urinary incontinence. Head-to-head studies of the newer agents and immediate-release oxybutynin and tolterodine have suggested similar effectiveness across the class, although the newer agents differ in terms of tolerability. In general, the newer agents appear to be at least as effective as their predecessors, although it is unclear whether they are better tolerated. Important pharmacokinetic differences among the agents (e.g., route of elimination and time to peak plasma concentration) allow for selection of an appropriate agent based on individual factors such as cost and tolerability.
Overactive Bladder

### SORT: KEY RECOMMENDATIONS FOR PRACTICE

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpharmacologic therapy is recommended for all patients with overactive bladder.</td>
<td>A</td>
<td>17-19</td>
</tr>
<tr>
<td>All available anticholinergic agents effectively decrease the frequency of urgency and</td>
<td>A</td>
<td>26, 31</td>
</tr>
<tr>
<td>incontinence episodes; one should be offered to patients who remain symptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>despite nonpharmacologic therapy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergics should be selected on the basis of cost and tolerability.</td>
<td>C</td>
<td>19, 22, 26, 31</td>
</tr>
<tr>
<td>Extended-release formulations of oxybutynin (Ditropan) and tolterodine (Detril) are</td>
<td>A</td>
<td>23-31</td>
</tr>
<tr>
<td>better tolerated than immediate-release versions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The lowest effective dose of anticholinergics should be prescribed to avoid dose-</td>
<td>C</td>
<td>26, 31</td>
</tr>
<tr>
<td>dependent adverse effects.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 2008 or http://www.aafp.org/afpsort.xml.

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### TABLE 1

**Overview of Anticholinergic Agents for Treatment of Overactive Bladder**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Availability</th>
<th>Dose</th>
<th>Frequency</th>
<th>Cost per month (generic)*</th>
<th>Uroselective?</th>
<th>Route of elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin (Enablex)</td>
<td>ER tablet: 7.5, 15 mg</td>
<td>7.5 to 15 mg</td>
<td>Once daily without regard for meals</td>
<td>$96</td>
<td>Yes</td>
<td>Hepatic (CYP 3A4)</td>
</tr>
<tr>
<td>Oxybutynin (Ditropan; Ditropan XL)</td>
<td>IR tablet: 5 mg</td>
<td>2.5 to 5 mg</td>
<td>Two to four times daily</td>
<td>(13 to 30) 75 to 113 (24 to 36) 100 to 112 93</td>
<td>No</td>
<td>Hepatic (CYP 3A4)</td>
</tr>
<tr>
<td></td>
<td>IR syrup: 5 mg per 5 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ER tablet: 5, 10, 15 mg</td>
<td>5 to 30 mg</td>
<td>Once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transdermal patch: 36 mg</td>
<td>1 patch</td>
<td>Every three to four days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solifenacin (Vesicare)</td>
<td>Tablet: 5, 10 mg</td>
<td>5 to 10 mg</td>
<td>Once daily</td>
<td>101</td>
<td>Yes</td>
<td>Hepatic (CYP 3A4)/Renal</td>
</tr>
<tr>
<td>Tolterodine (Detril; Detrol LA)</td>
<td>IR tablet: 1, 2 mg</td>
<td>1 to 2 mg</td>
<td>Twice daily</td>
<td>112 to 115 97 to 100</td>
<td>No</td>
<td>Hepatic (CYP 2D6/3A4)</td>
</tr>
<tr>
<td></td>
<td>ER capsule: 2, 4 mg</td>
<td>2 to 4 mg</td>
<td>Once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trospium (Sanctura)</td>
<td>Tablet: 20 mg</td>
<td>20 mg</td>
<td>Twice daily at least one hour</td>
<td>89</td>
<td>No</td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>before meals or on an empty stomach</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ER = extended-release; CYP = cytochrome P450 isoenzymes; IR = immediate-release.


Information from references 1 through 9.
the interaction between acetylcholine and muscarinic receptors, causes it to contract, and the flow of urine begins. Overactive bladder occurs when the detrusor muscle contracts in the face of submaximal bladder volumes. Anticholinergic drugs suppress such contractions by interfering with the interaction between acetylcholine and muscarinic receptors.

**Nonpharmacologic Therapies**

Nonpharmacologic intervention is the foundation of treatment for overactive bladder. Pelvic floor muscle training and bladder training have been proven to be effective strategies, and in motivated patients can be more effective than medication. Traditional nonpharmacologic tools and lifestyle modification should be provided consistently as part of a balanced program for improving target symptom control. Reviews of appropriate behavioral methods and pelvic floor training are available.

**Older Anticholinergics**

Tolterodine and oxybutynin are muscarinic receptor antagonists. Oxybutynin also displays antispasmodic activity in smooth muscle. These agents are recommended for patients with overactive bladder who remain symptomatic despite nonpharmacologic therapy.

The introduction of extended-release formulations has improved tolerability without substantively impairing the effectiveness of these drugs. Completion rates in long-term studies approach 70 percent with extended-release tolterodine, but are as low as 18 percent with immediate-release oxybutynin. On average, anticholinergic therapy reduces weekly urge-incontinence episodes by 70 percent. Dry mouth is the most common adverse event, affecting 20 to 30 percent of patients administered these agents.

A Cochrane review of randomized controlled trials comparing anticholinergic drugs with placebo or no treatment in patients with overactive bladder showed that patients treated with anticholinergics were more likely to report cure or improvement in their symptoms than those receiving placebo (60 versus 45 percent; P < .05, number needed to treat = 7). Maximal cystometric capacity increased 54 mL in patients receiving anticholinergics compared with those receiving placebo. Dry mouth was reported significantly more often in the active medication group (32 versus 14 percent; P < .05, number needed to harm = 5); however, similar numbers of patients withdrew because of adverse events. Drug therapy resulted in approximately one less episode of leakage and one less void per 48 hours compared with placebo. Because the placebo-adjusted effectiveness of these agents is marginal, the clinical impact must be weighed against the risk of adverse events.

**Newer Agents**

Head-to-head studies comparing the three newer agents—trospium, solifenacin, and darifenacin—with immediate-release oxybutynin and tolterodine have suggested similar effectiveness across the class.

Although the attributes of these newer agents in theory could improve tolerability, clinical trials comparing relevant agents to validate this are lacking (Table 2).

**TROSPUIM**

Trospium, a nonselective anticholinergic agent with antispasmodic properties, is approved for the treatment of overactive bladder with symptoms of urge urinary incontinence. It is available in immediate-release and extended-release formulations.
### Table 2

**Key Clinical Trials of Newer Antimuscarinic Agents for Treatment of Overactive Bladder**

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent(s)</th>
<th>Design (no. of participants)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo-controlled studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Chapple, et al., 2005<sup>10</sup> | Darifenacin (Enablex) 7.5 to 15 mg per day versus placebo | Pooled analysis of three RCTs (1,059) | Decrease in incontinence episodes per day: –1.25 (7.5 mg), –1.5 (15 mg) versus –0.99 placebo (P < .004)
Decrease in frequency and severity of urgency, leakage, voids per day, and nocturnal awakenings |
| Cardozo, et al., 2004<sup>11</sup> | Solifenacin (Vesicare) 5 to 10 mg per day versus placebo | RCT (911)                   | Decrease in incontinence episodes per day: –1.63 (5 mg), –1.57 (10 mg) versus –1.25 placebo (P = .002)
Decreases in voids per day, urgency episodes, and nocturia; increase in bladder capacity |
| Zinner, et al., 2004<sup>12</sup> | Trospium (Sanctura) 40 mg per day versus placebo | RCT (523)                   | Decrease in incontinence episodes per day: –2.0 versus –1.3 placebo (P < .001)
Complete dryness in 21% versus 11% placebo
Decreases in frequency and severity of urgency, leakage, voids per day, and nocturnal awakenings |
| **Active-comparator studies**  |                                               |                              |                                                                                                                                                                                                         |
| Zinner, et al., 2005<sup>13</sup> | Darifenacin 15 to 30 mg per day versus oxybutynin IR (Ditropan) 5 mg per day or placebo | RCT crossover (76)         | Incontinence episodes per week: 10.9 (15 mg), 8.8 (30 mg) versus 9.5 oxybutynin, 14.6 placebo (P < .05) |
| Chapple, et al., 2004<sup>14</sup> | Solifenacin 5 to 10 mg per day versus tolterodine IR (Detrol) 2 mg per day or placebo | RCT (1,081)                  | Decrease in incontinence episodes per day: –1.42 (5 mg), –1.45 (10 mg) versus –1.14 tolterodine, –0.76 placebo
Decreases in voids per day and urgency episodes; increase in bladder capacity |
| Chapple, et al., 2005<sup>15</sup> | Solifenacin 5 to 10 mg per day versus tolterodine ER (Detrol LA) 4 mg per day | RCT (1,177)                  | Decrease in incontinence episodes per day: –1.60 (10 mg) versus –1.11 tolterodine (P < .0001)
Significant decrease in urgency episodes with solifenacin (P < .05) |
| Halaska, et al., 2003<sup>16</sup> | Trospium 40 mg per day versus oxybutynin IR 10 mg per day | RCT (358); unblinded      | Similar changes in urodynamic parameters |

**NOTE:** Differences were not statistically significant or were not tested for significance unless otherwise noted.

RCT = randomized controlled trial; IR = immediate-release; ER = extended-release.

Information from references 10 through 16.
Overactive Bladder

**Adverse effects**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo-Controlled RCT</th>
<th>Solifenacin 5 to 10 mg per day</th>
<th>Chapple, et al., 2004</th>
<th>Trospium (Sanctura) 40 mg per day</th>
<th>Chapple, et al., 2004</th>
<th>Darifenacin (Enablex) 7.5 to 15 mg per day</th>
<th>Chapple, et al., 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>20.2 to 35.3% vs 8.2% placebo (P &lt; .05)</td>
<td>7.7% (5 mg), 23.1% (10 mg), 2.3% placebo</td>
<td>36.1% oxybutynin, 4.9% placebo</td>
<td>21.8% versus 6.5% placebo (P &lt; .05)</td>
<td>9.5% versus 3.8% placebo (P &lt; .05)</td>
<td>7.7% (5 mg), 7.8% (10 mg) versus 2.6% tolterodine, 1.9% placebo</td>
<td>7.2% versus 4.0% placebo (P &lt; .05)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14.8 to 21.3% vs 6.2% placebo (P &lt; .05)</td>
<td>3.7% (5 mg), 9.1% (10 mg), 2.0% placebo</td>
<td>9.8% (15 mg), 21.3% (30 mg) versus 8.2% oxybutynin, 3.3% placebo</td>
<td>9.5% versus 3.8% placebo (P &lt; .05)</td>
<td>3.7% (5 mg), 9.1% (10 mg) versus 2.0% placebo</td>
<td>7.2% versus 4.0% placebo (P &lt; .05)</td>
<td>9.5% versus 3.8% placebo (P &lt; .05)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2.7 to 8.4% vs 2.6% placebo (P &lt; .05)</td>
<td>4.0% (5 mg), 5.9% (10 mg), 2.3% placebo</td>
<td>4.0% (5 mg), 5.9% (10 mg), 2.3% placebo</td>
<td>2.7% versus 8.4% placebo (P &lt; .05)</td>
<td>4.0% (5 mg), 5.9% (10 mg), 2.3% placebo</td>
<td>4.0% (5 mg), 5.9% (10 mg), 2.3% placebo</td>
<td>2.7% versus 8.4% placebo (P &lt; .05)</td>
</tr>
<tr>
<td>Early discontinuation</td>
<td>10.0% (5 mg), 7.1% (10 mg) versus 9.9% tolterodine, 12.0% placebo</td>
<td>3.5% versus 3.0% tolterodine</td>
<td>14.0% (5 mg), 21.3% (10 mg) versus 18.6% tolterodine, 4.9% placebo</td>
<td>10.0% (5 mg), 7.1% (10 mg) versus 9.9% tolterodine, 12.0% placebo</td>
<td>3.5% versus 3.0% tolterodine</td>
<td>10.0% (5 mg), 7.1% (10 mg) versus 9.9% tolterodine, 12.0% placebo</td>
<td>10.0% (5 mg), 7.1% (10 mg) versus 9.9% tolterodine, 12.0% placebo</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>13.1% (15 mg), 34.4% (30 mg) versus 36.1% oxybutynin, 4.9% placebo</td>
<td>3.1% versus 1.1% placebo</td>
<td>21.8% versus 6.5% placebo (P &lt; .05)</td>
<td>3.1% versus 1.1% placebo</td>
<td>3.1% versus 1.1% placebo</td>
<td>3.1% versus 1.1% placebo</td>
<td>3.1% versus 1.1% placebo</td>
</tr>
<tr>
<td>Constipation</td>
<td>9.5% versus 3.8% placebo (P &lt; .05)</td>
<td>9.5% versus 3.8% placebo (P &lt; .05)</td>
<td>9.5% versus 3.8% placebo (P &lt; .05)</td>
<td>9.5% versus 3.8% placebo (P &lt; .05)</td>
<td>9.5% versus 3.8% placebo (P &lt; .05)</td>
<td>9.5% versus 3.8% placebo (P &lt; .05)</td>
<td>9.5% versus 3.8% placebo (P &lt; .05)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3.1% versus 1.1% placebo</td>
<td>3.1% versus 1.1% placebo</td>
<td>3.1% versus 1.1% placebo</td>
<td>3.1% versus 1.1% placebo</td>
<td>3.1% versus 1.1% placebo</td>
<td>3.1% versus 1.1% placebo</td>
<td>3.1% versus 1.1% placebo</td>
</tr>
<tr>
<td>Early discontinuation (&lt; 52 weeks)</td>
<td>25.0% versus 26.7% oxybutynin</td>
<td>7.0% versus 4.0% oxybutynin</td>
<td>33.0% versus 50.0% oxybutynin</td>
<td>7.0% versus 4.0% oxybutynin</td>
<td>7.0% versus 4.0% oxybutynin</td>
<td>7.0% versus 4.0% oxybutynin</td>
<td>7.0% versus 4.0% oxybutynin</td>
</tr>
</tbody>
</table>

**NOTE:**

Chapple, et al., 2005

Solifenacin 5 to 10 mg per day

Zinner, et al., 2004

Trospium (Sanctura) 40 mg per day

Chapple, et al., 2004

Solifenacin 5 to 10 mg per day

Chapple, et al., 2005

Darifenacin (Enablex) 7.5 to 15 mg per day

Study of Trials of Antimuscarinic Agents for Overactive Bladder...
improved tolerability given the preferential location of this
receptor subtype on the detrusor wall. However, M3 recep-
tors also are present on smooth muscles in the gastrointes-
tinal tract, salivary glands, eyes, and brain. For this reason,
common adverse effects include constipation, dry mouth,
blurred vision, fatigue, and cognitive impairment.5

Results from several 12-week, double-blind, placebo-
controlled studies involving patients with approximately
20 urinary incontinence episodes per week showed that
solifenacin reduced urinary frequency by approximately
two voids per day compared with a decrease of approxi-
mately one void per day with placebo (Table 2)5,11,35

Solifenacin also significantly improved urgency, noctu-
ria, and bladder emptying. Compared with immediate-
release tolterodine, solifenacin resulted in greater decreases
in urgency and incontinence episodes but produced anti-
cholinergic side effects at a similar frequency.14,36 One
possible explanation for these findings is that trials of
solifenacin used doses up to the maximum of 10 mg,
whereas the dose of tolterodine was capped at 2 mg. Soli-
enacin improved health-related quality of life in patients
with overactive bladder and urinary incontinence.36

Another study compared 5 to 10 mg of solifenacin
daily with 4 mg of extended-release tolterodine daily.15
In this study, patients treated with solifenacin had bet-
ter symptom control but experienced more adverse
events. Again, however, the dosing strategy may explain
these findings: patients treated with solifenacin initially
were given 5 mg daily and could request an increase
in dosage after four weeks; 48 percent of patients
requested such increase and subsequently were treated
with 10 mg daily. In the tolterodine arm, 51 percent of
patients requested a dosage increase, but they already
were receiving the maximal dosage.

**DARIFENACIN**

Similar to solifenacin, darifenacin is a muscarinic recep-
tor antagonist with enhanced specificity for the M3
receptor subtype. It is approved for the management
of overactive bladder, and improves overactive bladder
symptomatology to an extent similar to that of other
agents (Table 2).10-16 One unique parameter that has
been examined with darifenacin is “warning time”: the
time from the first sensation of urgency to the time of

### TABLE 3

Factors Affecting Selection of Anticholinergic Agents for Treatment of Overactive Bladder

<table>
<thead>
<tr>
<th>Factor</th>
<th>Agent to consider</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic adverse effects</td>
<td>Darifenacin (Enablex), solifenacin (Vesicare), tolterodine ER (Detrol LA), oxybutynin ER (Ditropan XL)</td>
<td>ER products and drugs with uroselectivity may offer enhanced tolerability.</td>
<td>15, 27, 31</td>
</tr>
<tr>
<td>CNS adverse effects</td>
<td>Trospium (Sanctura)</td>
<td>Trospium may be less likely to cross the blood-brain barrier (unproven benefit).</td>
<td>31</td>
</tr>
<tr>
<td>Cost</td>
<td>Oxybutynin IR</td>
<td>ER and newer agents may be more expensive; generics are available for oxybutynin IR.</td>
<td>22</td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td>Trospium</td>
<td>Agents other than trospium are metabolized by CYP 3A4 or 2D6, which are responsible for elimination of hepatically metabolized drugs.*</td>
<td>9</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>Oxybutynin</td>
<td>Nonselectivity may offer more complete suppression of detrusor overactivity. Head-to-head studies of tolterodine and oxybutynin have suggested improved efficacy with oxybutynin.</td>
<td>27</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Oxybutynin</td>
<td>Oxybutynin is pregnancy risk category B whereas all other agents are class C.</td>
<td>2</td>
</tr>
<tr>
<td>Severe hepatic impairment</td>
<td>Trospium</td>
<td>Trospium is eliminated renally whereas all other agents undergo extensive hepatic metabolism.*</td>
<td>5, 16, 22, 35</td>
</tr>
<tr>
<td>Severe renal impairment</td>
<td>Oxybutynin, tolterodine, darifenacin, solifenacin</td>
<td>Avoid trospium because it is eliminated renally.</td>
<td>9</td>
</tr>
</tbody>
</table>

*ER = extended-release; CNS = central nervous system; IR = immediate-release; CYP = cytochrome P450 isoenzyme.

*—The overall correlation between hepatic function and drug disposition is poor.

Information from references 2, 5, 9, 15, 16, 22, 27, 31, and 35.
voluntary urination or incontinence. An increase in this duration may permit more patients to experience or maintain continence. Darifenacin increased warning time by 4.3 minutes compared with placebo (P = .003), and 47 percent of patients treated with darifenacin experienced a 30 percent or greater increase in mean warning time compared with only 20 percent of patients treated with placebo (P = .009).37

In a crossover study with immediate-release oxybutynin, the incidence of dry mouth was significantly lower with darifenacin 15 mg than with oxybutynin (13 versus 36 percent, respectively; P < .05) but not with darifenacin 30 mg (34 versus 36 percent).13 Constipation was more common in patients given darifenacin 30 mg (21 versus 8 percent with oxybutynin; P < .05) but not in those given 15 mg (10 percent). Effectiveness was similar for patients receiving either dose of darifenacin and those receiving oxybutynin. Comparisons of darifenacin with extended-release oxybutynin or tolterodine are lacking.

Selecting Pharmacologic Agents for Overactive Bladder
The availability of three newer anticholinergic drugs increases the pharmacologic armamentarium for the treatment of overactive bladder. Caution is required with each of these agents, particularly in patients with contraindications to anticholinergic therapy (e.g., untreated open-angle glaucoma, constipation, urinary retention, gastrointestinal disease). A careful evaluation of the balance between benefits and harms, with special attention paid to quality of life, is warranted when considering use of these agents. Appropriately conducted trials are needed to determine the clinical value of functional, structural, and pharmacokinetic nuances. The pharmacokinetic differences among anticholinergic agents allow for the selection of agents based on individual factors (Table 3).2,5,9,15,16,22,27,31,35 In the absence of definitive comparative data, a reasonable strategy is to select a therapy according to the individual patient and to try alternative agents if the first is not effective or cannot be tolerated.

Members of various family medicine departments develop articles for “Clinical Pharmacology.” This is one in a series coordinated by Allen F. Shaughnessy, Pharm.D., and Andrea E. Gordon, M.D., Tufts University Family Medicine Residency, Malden, Mass.

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REFERENCES