Urogynecologic Medications in Older Adults: Special Considerations

Tyler Muffly, MD, FACS

Objectives

- Briefly review aging lower urinary tract and pharmacodynamics in the older patient (especially patients ≥ 75 years)
- Discuss antimuscarinic therapy for management of overactive bladder and urgency urinary incontinence
- Synthesize evidence of long-term antimuscarinic use in elderly patients ≥ 75 years
- Discuss emerging class of β-adrenergic agonists
- Identify non-urologic medications with anticholinergic effects
Disclosure

- None

Aging Bladder

- ↓ voided volume
- ↑ Prevalence of detrusor overactivity (DO); ↓ bladder capacity associated with DO
- ↓ Bladder wall compliance with deposition of collagen and some fibrosis of wall (esp. with obstruction of bladder outlet)
- ↓ Peak and mean urinary flow
- ↑ Urinary residual volumes (variability significant)
- ↓ Sensations of bladder filling
- Mixed evidence concerning loss of detrusor contraction strength

Aging Bladder: Changes in Modulation by CNS

- Deactivation in multiple areas of brain (areas highlighted in blue) hypothesized to predisposed to DO and urgency UI
  - Medial Prefrontal Cortex
  - Pontine micturition center
  - Periaqueductal gray
  - Interactivity between modulator center tended to diminish


Aging Bladder: Functional Status and Continence

- Impaired mobility (ambulatory vs walker vs wheelchair) acts as independent risk factor for UI
- Many disorders directly and indirectly impair continence (CVA, Parkinsonism)
- Dementia, and especially Alzheimer’s dementia associated with UI

Pharmacodynamics in the Elderly

- Absorption (slows)
  - Passive mechanisms mostly via small bowel; sparse evidence about transdermal absorption; impacted by drug-drug interactions, specific ions (magnesium and calcium) and agents that ↑ gastric pH or ↓ GI motility

- Distribution (variable effects)
  - Where the drug goes and how long it takes; primary aging effects are ↓ muscle mass, ↓ total body water, ↑ body fat causing hydrophilic drugs to have ↑ body concentrations (Vd); changes often profound (1/2 life diazepam 30 hours in young adults vs 90 hours in adults > 75 years)


Pharmacodynamics and the Elderly

- Metabolism (↓ first pass metabolism)
  - Liver and first pass metabolism reasonably well studied; including role of CYP enzymes and their interactions with other drugs, foods, etc.; impact of genetic variability on this process under evaluation

- Elimination (↓ with aging kidneys)
  - Final means for exiting the body; usually via kidneys, must measure GFR rather than serum creatinine; usually use MDRD or Cockcroft equations for assessing GFR

Challenges of Pharmacotherapy in the Elderly

- Pharmacokinetics differ in elderly patients
  - ↓ micro- & macrocirculation
  - ↓ renal function
  - ↓ hepatic clearance
  - ↓ nutrition leading to ↓ serum albumin
  - ↓ body water
  - ↓ lean body mass & ↑ fat (doubles)
  - Sedentary lifestyle


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Challenges of Pharmacotherapy in the Elderly

- Number of Drugs Taken on Daily Basis Increases Risk of Drug-Drug Interaction
  - 40% of adults >65 years of age take 5-9 medications per week\(^1\)
  - 12% of adults >65 years of age take 5-9 medications per week\(^1\)
  - Rates are higher for elders in assisted living and long-term care setting\(^2\)
  - More evidence based regimens are being promulgated based on multiple medications\(^3\)

Challenges of Pharmacotherapy in the Elderly

- Common polypharmacy concerns in elderly patients with OAB
  - Diuretics or antihypertensives containing diuretics may mimic or exacerbate urgency UI
  - Acetylcholinesterase inhibitors antagonize antimuscarinics (35% of 557 patients prescribed both in one study)
  - Multiple agents with anticholinergic properties


- Elders at particular risk for adverse side effects; they occur more frequently, tend to be more severe, and exert a more negative impact

- Antimuscarinic SE risks in elders include
  - Cognitive/functional impairment: short-term memory loss, acute confusion, nightmares, fall risk
  - Dry mouth: associated with tooth decay, difficulty wearing dentures
  - Constipation: associated with an increase risk for urinary tract infection, incomplete bladder emptying, vaginal wall prolapse in women
  - Blurred vision: difficulty reading & driving, exacerbation of narrow angle glaucoma

**Crossing the Blood Brain Barrier**

- **↑ Lipophilicity** (does molecule dissolve in fat?)
  - **↑ Diffusion**

- **↑ Net charge**
  - **↓ Diffusion**

- **↓ Molecular size (bulk)**
  - **↑ Diffusion**

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**Challenges of Pharmacotherapy in the Elderly**

- Elders tend to have more co-morbidities (chronic conditions) that may be adversely influenced by administration of an antimuscarinic
  - Community dwelling elders have an average of 2.4 chronic medical conditions\(^1\)
  - Frail elders (including those >80 years of age and those in long-term care or assisted living) tend to have more\(^2\)
  - Elders taking anticholinergics with CNS side effects more likely to be diagnosed with mild dementia than non-users

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\(^1\) Schubert CC et al. JAGS 2006; 54(1): 104.
\(^3\) Ancelin ML et al. BMJ 2006; 332: 455.
Pharmacotherapy in the Frail Elder

- Principles of management
  - Pharmacotherapy more likely to fail unless combined with appropriate behavioral/management intervention
  - Dosing medications: "start low and go slow"
  - Identify all medications and all pertinent co-morbidities before prescribing medication
  - Select a medication that minimizes the risk of CNS and other adverse side effects when managing OAB

Antimuscarinics: Multiple Drugs in This Category

- Popular Antimuscarinics
  - Oxybutynin (M2 & M3)
  - Tolterodine (M2 & M3)
  - Fesoterodine (M2 & M3)
  - Trospium (M2 & M3)
  - Solifenacin (M2 & M3)
  - Darifenacin (M3)
Managing Urgency UI: Current Class of Antimuscarinic Drugs

- Tolterodine tartrate
  - Detrol IR (2 mg twice daily)
  - Detrol LA (4 mg daily)
- Fesoterodine fumarate
  - Toviaz (4.8 mg daily)
- Oxybutynin chloride
  - Ditropan IR (5-15 mg 2-3 x daily)
  - Ditropan XL (5-15 mg daily)
  - Oxytrol (TD patch; 1 patch twice weekly)
  - Gelnique (TD gel; 1 pkg daily)
- Trospium chloride
  - Sanctura IR (20 mg twice daily)
  - Sanctura XR (60 mg daily)
- Solifenacin succinate
  - Vesicare (5, 10 mg daily)
- Darifenacin HCl
  - Enablex (7.5, 15 mg daily)

Oxybutynin IR, ER

<table>
<thead>
<tr>
<th>Structure</th>
<th>Tertiary amine</th>
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<tbody>
<tr>
<td>Metabolism</td>
<td>Cytochrome P450, P3A4; active metabolite desethyloxybutynin</td>
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<tr>
<td>Selectivity</td>
<td>Nonselective</td>
</tr>
<tr>
<td>Dosing</td>
<td>5mg, 10mg, 15mg daily (ER), or 5 mg 2-3 times daily (IR) (approved ≤30mg qd)</td>
</tr>
</tbody>
</table>

Oxybutynin ER

Efficacy

Number of urgency incontinence episodes/wk

Mean change from baseline

Placebo (n=16)

Oxybutynin ER (n=34)

-7.6

-15.8*

*statistically significant difference from placebo; p value not specified


Safety/ Tolerability (10mg)

- Dry mouth: 29%
- Constipation: 7%
- Headache: 6%
- Blurred vision: 1%
- CNS adverse events:
  - Somnolence: 2%
  - Dizziness: 4%


Oxybutynin Transdermal Patch

Metabolism

Active metabolite desethyloxybutynin

Dosing

Transdermal, twice-weekly (delivery rate 3.9mg/d)


Safety & Tolerability: Oxybutynin Transdermal Patch

- Pruritus @ site – 14%
- Erythema @ site – 8.3%
- Dry mouth: 4.1% (NS compared to placebo)
- Constipation: 4.1%
- Abnormal vision: 2.5%
- Dizziness: 0.8%


TD Oxybutynin (gel)

- Oxybutynin gel, 1 gm equivocal to 10 mg orally
- Pivotal trials showed safety & efficacy in adult women with OAB and UI

**TD Oxybutynin (gel): Adverse Side Effects**

- Side Effects (from pivotal trial)
  - Dry mouth: 7%
  - Constipation: 1.3%
  - Dizziness: 1.5%


**Erythema of Skin**

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**Oxybutynin: Special Considerations in Older Patient**

- Lipophilic drug, tertiary amine (smaller molecular structure) with net ionic charge prone to cross blood brain barrier easily
- Oral formulations metabolized in liver using primarily CYP P450 and PA34 enzymes
- High prevalence of dry mouth in *oral* formulations
- Little research on pharmacodynamics of transcutaneous formulations in older old (≥75-80 years)
Tolterodine

**Structure** Tertiary amine

**Metabolism** Cytochrome P450 2D6; active metabolite 5-OH-methyl derivative

**Selectivity** Non-selective, M1, M2 and M3

**Dosing** 2mg, 4mg once daily


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**Efficacy: Double-blind RCT (12wks)**

- Mean change from baseline
- Tolterodine 2mg bid (n=514)
- Placebo (n=508)

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Mean change from baseline</th>
<th>Frequency/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine 2mg bid</td>
<td>-10.6</td>
<td>-1.2</td>
</tr>
<tr>
<td>Placebo (n=508)</td>
<td>-8.9</td>
<td>-1.7*</td>
</tr>
</tbody>
</table>

**Safety/ Tolerability (2mg bid)**

- Dry mouth: 35%
- Constipation: 7%
- Headache: 7%
- CNS adverse events:
  - Somnolence: 3%
  - Dizziness: 5%
- CV adverse events:
  - Prolongation of QT interval with 2mg bid and 4 mg bid doses

*RCT = randomized controlled trial
*statistically significant difference from placebo; p value not specified

Fesoterodine

- Pro-drug rapidly metabolized to 5HMT directly from gut via non-specific esterases
- Active metabolite is 5-hydroxymethyltolterodine (5-HMT); which also gives tolterodine pharmacologic activity
- Available in 4 and 8 mg tablets taken once daily


Fesoterodine: Adverse Side Effects

- Dry mouth 16%
- Constipation 5%
- UTI 4%
- Erythema 0%
Fesoterodine and Tolterodine: Special Considerations in Elderly Patient

- **Fesoterodine vs Tolterodine**
  - Active metabolite for tolterodine is 5 hydroxymethyl-tolterodine (5HMT); it is SPM 7605 for fesoterodine (molecular structure nearly identical for these molecules)
  - Tolterodine absorbed in bowel and metabolized in liver (CYP450 2D6 and CYP3A4); fesoterodine absorbed and converted to SPM 7605 via esterases in body; further metabolism occurs via liver (CYP450 2D6 and 3A4 pathways); SPM 7605 levels 2x higher in patients who are poor metabolizers of CYP2D6 pathway
  - Dose related response for fesoterodine directly proportional; dose related response for tolterodine unpredictable (thus the single dose option commercially available for Detrol)

Michel MC, Hegde SS. Nauyn-Schmeideberg’s Archives of Pharmacology 2006; 374: 79-85.

Fesoterodine: Superiority Head to Head Trial vs Tolterodine

- RCT compared fesoterodine 8 mg vs tolterodine
- Double blind, trial compared fesoterodine to tolterodine and placebo; powered as superiority trial based on primary outcome of fewer urge UI episodes on 3-day bladder log
- N=2417; mean ages were 57.9-59.5 yrs in 3 groups
- Fesoterodine 8 mg superior to tolterodine on primary outcome measure and most secondary measures including nocturia, urgency and severe urgency episodes, HRQOL measures

**Tolterodine & Fesoterodine: Special Considerations in Older Patients**

- Single RCT identified with mean subject age 75 years and scores ≥ 3 Vulnerable Elders Survey (indicating elders at risk for death or functional decline over 2 year period) in 562 subjects
  - Most escalated to 8 mg dose; fesoterodine performed better than placebo
  - Serious AE: 2.8% (feso) vs 2.1% Placebo (p=NS)
  - Drug discontinuation 9.3% vs 5.0% (feso vs placebo)
  - No deterioration in MMSE scores in either group
  - C/O memory impairment in 2 vs 0 (feso vs placebo); both >80 years of age
  - 1.1% experienced retention and required CIC (all > 80 yrs)


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**Trospium Chloride**

**Structure**
- Quaternary amine

**Metabolism**
- Cytochrome P450

**Excretion**
- 70% cleared renally
- 20% excreted unchanged

**Selectivity**
- Non-selective

**Dosing**
- 20mg bid (IR), 60mg daily (XR); on empty stomach, 1 hour before meal

*Physicians' Desk Reference, 61st ed. Thomson PDR: 2007*
Trospium Chloride

Efficacy: Double-blind parallel group RCT\(^{(12 \text{ wks})}\)

- Mean change from baseline

Safety/Tolerability (20mg bid)

- Dry mouth: 20.1%
- Constipation: 9.6%
- Headache: 4.2%
- CV adverse events: No prolongation of QT interval with trospium


Trospium Chloride: Special Considerations in Older Patient

- Trospium Chloride
  - Lyophobic (water soluble)
  - Large molecule (quaternary amine)
  - Positively charged

Trospium Chloride: Special Considerations in Older Patient

- Phase 1 quantitative-topographical EEG (qEEG) of 64 healthy young adult men
  - Randomized to trospium 45mg/day, tolterodine 4 mg/ day, oxybutynin 15mg/ day
  - Compared to placebo, tolterodine and trospium did not induce changes in δ (delta), α 1, α 2, β 1 or β 2 frequency bands
  - Oxybutynin affected these bands, indicating its ability to cross BBB in elevated doses in younger, healthy volunteers


Trospium Chloride: Special Considerations in Older Patient

- Lipophobic, quaternary molecule less likely to cross BBB
- Systematic review of adverse SE in antimuscarinics (69 studies, N=26,299) including trospium found similar overall adverse event profiles for darifenacin, fesoterodine, transdermal oxybutynin, solifenacin, tolterodine, and trospium but not for oxybutynin when administered orally

Solifenacin

**Structure**
- Tertiary amine

**Metabolism**
- Cytochrome P4503A4; active metabolite 4R-hydroxy solifenacin

**Half-life**
- 40.2-57.6 hrs

**Selectivity**
- M1/M3 selective vs M1

**Dosing**
- 5mg, 10mg qd

**Efficacy: Double-blind parallel group multicenter RCT**
- Placebo (n=253)
- Solifenacin 5mg (n=266)
- Solifenacin 10mg (n=264)

Mean change from baseline
- No. incontinence episodes/day
- Frequency/day

- Placebo (n=253)
  - -1.4**
  - -1.5**
  - -1.2

- Solifenacin 5mg (n=266)
  - -2.2***

- Solifenacin 10mg (n=264)
  - -2.6***

**Safety/ Tolerability (5mg)**

- Dry mouth: 10.9%
- Constipation: 5.4%
- Blurred vision: 3.8%
- CNS adverse events:
  - Dizziness: 1.9%
- CV adverse events:
  - Prolongation of QT interval with 10mg and 30mg doses

Solifenacin: Special Considerations in Older Patient

- $T\frac{1}{2}$ especially long for drugs in this class (45-68 hours)
- Impact on dosing in older old (> 80 years not well studied)
- Secondary analysis of adverse SE in 2,645 patients showed no differences in SE incidence in patients > 65 years of age\(^1\)


Darifenacin

- Structure: Tertiary amine
- Metabolism: Cytochrome P450 3A4 and 2D6
- Selectivity: High affinity for M3
- Dosing: 7.5mg, 15mg qd

Darifenacin

Efficacy: Double-blind multicenter RCT* (12 wks)

- Mean change from baseline
- RCT = randomized controlled trial

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo (n=164)</th>
<th>Darifenacin 7.5mg (n=229)</th>
<th>Darifenacin 15mg (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. incontinence episodes/wk</td>
<td>-9*</td>
<td>-1.6*</td>
<td>-1.7*</td>
</tr>
<tr>
<td>Frequency/day</td>
<td>-7.6</td>
<td>-0.8</td>
<td>-9.5</td>
</tr>
</tbody>
</table>

Safety/ Tolerability (7.5mg)

- Dry mouth: 20.2%
- Constipation: 14.8%
- CNS adverse events:
  - Dizziness: 0.9%
- CV adverse events:
  - No prolongation of QT interval with darifenacin


Darifenacin: Special Considerations in Older Patient

- M₃ selective
- Primarily M₃ selective
- Nonselective (M₂/M₃)

*Animal models

Darifenacin: Special Considerations in Older Patient

- M₃ receptors are abundant in the periphery (bladder, bowel, salivary glands) but not found in CNS; darifenacin has a greater affinity for these receptors than other drugs in the class

- Potential advantage for frail elder patient when attempting to avoid

- Systematic review and EEG study in young adult volunteers support reduced penetration of brain and comparable adverse SE profiles to others in drug class but none show superiority to others¹,²


Incidence of Constipation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent of Patients With Constipation as Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin 15 mg QD</td>
<td>21.3</td>
</tr>
<tr>
<td>Darifenacin 7.5 mg QD</td>
<td>14.8</td>
</tr>
<tr>
<td>Solifenacin 10 mg QD</td>
<td>13.4</td>
</tr>
<tr>
<td>Oxybutynin XL 5-30 mg QD</td>
<td>13</td>
</tr>
<tr>
<td>Trospium 20 mg BID</td>
<td>9.6</td>
</tr>
<tr>
<td>Tolterodine LA 4 mg QD</td>
<td>6</td>
</tr>
</tbody>
</table>

Cardozo et al. International Continence Society; October 5-9, 2003; Florence, Italy. Poster A137102.
Darifenacin & Receptor Selectivity: Clinical Evidence

- 129 patients ≥ 65 years of age randomized to darifenacin IR 5 mg tid, darifenacin ER (3.75, 7.5* or 15*mg)
  - Treatment period: 7 days
  - Cognitive function tests: simple reaction time, digit vigilance test, memory scanning test, delayed word recognition and subjective perceptions of alertness, contentment & calmness

Results
- No significant differences in simple reaction time, digit vigilance test
- Significant differences for delayed word recognition favoring placebo


Antimuscarinics and OAB: Local HRT vs Antimuscarinics

- RCT compared voiding frequency in 59 women allocated to oxybutynin IR 5 mg twice daily or ultra-low dose estradiol ring
  - Drug group mean ↓ of 3.0 voids/ day; estradiol ring ↓ voids 4.5 day (p=NS)
  - Both has statistically significant improvements in UDI and IIQ
  - No statistically significant difference between groups

β-3 agonists: New drug class for OAB

- Mirabegron (Myrbetriq) sole agent approved for use in USA as of Spring 2013\(^1\); proof of concept approved for 3 agents, solabegron, ritobegron\(^2\)
  - Granted IND by US FDA for OAB June 2012
  - Dosage: 25-50 mg once daily; swallow whole (do not crush or chew)
  - Metabolized primarily via CYP2D6 pathway
  - Some prolongation compared to placebo on QTcI interval at 4-5 hours post-dose was 3.7 msec (upper boundary of 95% CI was 5.1 msec)

1. Mirabegron Prescribing insert: [http://www.myrbetriqhcp.com/Content/pdfs/Myrbetriq_WPI.pdf](http://www.myrbetriqhcp.com/Content/pdfs/Myrbetriq_WPI.pdf)

Mirabegron: Side Effects and Adverse Side Effects\(^1\)-\(^3\)

- Hypertension: 7.5% - 11.3%\(^*\)
- ↑ pulse rate
- Dry mouth: < 3% (comparable to placebo)
- UTI: 2.7%-3.7%
- Headache: 2.0%-2.7%
- Nasopharyngitis: 2.5%-3.4%

\(^*\) Mean maximum ↑ in systolic/diastolic blood pressure 3.5 and 1.5 mmHg over placebo
\(^\wedge\) Mean gain in pulse compared to placebo (beats/ minute)
Mirabegron: Special Considerations in Older Patient

- Comparatively sparse evidence base due to newness of drug
  - Open label study of 37 patients mean age 79.9 years unable to tolerate antimuscarinics due to SE
  - Relieved thirst in 95.2% of cases and constipation in 87.5% of cases


Onobotulinum Toxin A

Onobotulinum Toxin A

- Injected into bladder under endoscopic guidance at multiple sites
- Usual dose 200-300 IU

Pivotal Trial for Botulinum Toxin A:
Adverse Side Effects (Treatment Cycle 1)

- UTI: 56% - 64%
- Urinary Retention: 20% - 32%
- Hematuria: 6% - 8%
- Dysuria: 2% - 6%
- Constipation: 1% - 6%

Botulinum Toxin A: Special Considerations in Older Patient

- Open label study of 37 older patients (mean age 81.2 years, range 75-92 years)
  - Subjects underwent intradetrusor injection of 200 IU botulinum toxin A
  - Reduces frequency of voiding and reduced pads per day (p<0.001); 3 showed no improvement after 2 injections
  - Mean duration of effect: 7.12 months
  - Lacked rigorous report of adverse SE


Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

- Eponymous list (Mark Beers MD) designed to avoid adverse SE associated with drug choice or polypharmacy
  - Designed for persons with limited expertise and direct consumer education
  - AGS now manages project; latest edition published in 2012
  - Studies of criteria have found that comparatively small number of drugs associated with majority of reported adverse SE in elderly

Resnick B, Pacala JT. JABS 2012; Guest Commentary.
Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

<table>
<thead>
<tr>
<th>Drugs and Categories of Drugs</th>
<th>Why these drugs may be inappropriate for older adults</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>These drugs cause many side effects in older adults, including confusion, drowsiness, blurred vision, difficulty urinating, dry mouth and constipation. Safer medications are available.</td>
<td>Avoid use of diphenhydramine in special situations — such as for treating severe allergic reactions — may be appropriate.</td>
</tr>
<tr>
<td>Brompheniramine</td>
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<td>Carbinoxamine</td>
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<td>Chlorpheniramine</td>
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<td>Clemastine</td>
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<td>Cypheptadine</td>
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<td>Dexbrompheniramine</td>
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<td>Dexchlorpheniramine</td>
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<td>Diphenhydramine (oral)</td>
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<td>Promethazine</td>
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<td>Triprolidine</td>
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Conclusions

- Pharmacotherapy in the elder patient presents a significant challenge, especially in persons ≥ 80 years of age
- Clinical considerations include: multiple co-morbidities, polypharmacy, increased risk of adverse side effects
- 3 antimuscarinic agents associated with clinical evidence of reduced risk for CNS penetration in the elderly patient, selection of the best agent is based on overall side effect profile, and individualized assessments of risk for drug-drug interactions or adverse effects owing to the presence of other co-morbidities