Cognitive Safety of Pharmacological Treatment of Urinary Incontinence: Will I make my patient worse?

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Tuesday, February 8, 2011 12 noon
Dr. Bill Black Auditorium, Glenrose Rehabilitation Hospital

Introduction

- OAB and the elderly
- How much of an issue is cognitive impairment?
- What is known about antimuscarinics and cognition?
- What is known about bladder antimuscarinics and cognition?
- Why are geriatricians reluctant to treat OAB with drugs and why should they not be?

Declaration of Conflict of Interest
(This is a mandatory requirement for all speakers at Faculty of Medicine and Dentistry University of Alberta Undergraduate, Graduate, Postgraduate or Continuing Education events)

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<table>
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<tr>
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<tbody>
<tr>
<td>I, Adrian Wagg</td>
<td>declare that in the past 3 years:</td>
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<tr>
<td>I have received manufacturer funding from the following companies*:</td>
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<tr>
<td>Astellas Pharma</td>
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<td>Pfizer Corp</td>
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<td>I have done consulting work for the following companies*:</td>
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<tr>
<td>Astellas Pharma</td>
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<td>Pfizer Corp</td>
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<td>I have done speaking engagements for the following companies*:</td>
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<td>Astellas Pharma, Pfizer, GSK</td>
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<td>I or my family hold individual shares in the following companies*:</td>
<td>None</td>
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<td>*pharmaceutical or medical/dental equipment</td>
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**OAB and the elderly**

![Graph showing prevalence of OAB and urgency incontinence by age group]

**Prevalence of storage symptoms in women in association with age**

![Graph showing prevalence of nocturia, urgency, frequency, urgency incontinence, and mixed incontinence symptoms by age group]


**Prevalence of storage symptoms in men in association with age**

![Graph showing prevalence of nocturia, urgency, frequency, urgency incontinence, and mixed incontinence symptoms by age group]


**Older people generally experience more severe incontinence than the young**

![Graph showing prevalence of nocturia, urgency, frequency, urgency incontinence, and mixed incontinence symptoms by age group]


Geriatric Grand Rounds
(http://www.ualberta.ca/~geriatri/ggr/)

Glenrose Rehabilitation Hospital
Alberta Health Services, Edmonton Zone

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Prevalence of voiding symptoms by age and sex

OAB and quality of life in older people

Geriatricians are reluctant to prescribe antimuscarinic agents

• The costs associated with OAB:
  – $63.1 million for hospitalizations
  – $1.97 billion for additional nursing home admissions

• Cognitive impairment
• Delirium
• Falls
• Beer’s criteria categorizes oxybutynin as a drug to be avoided
  • this appears to extend to all bladder drugs by association
  • What is the evidence?
Brenda

- Daytime urinary frequency: 14
- Nocturia: 3
- Urinary urgency episodes: 9 per day
- Urinary urgency incontinence: 4 per day
- No stress urinary incontinence
- No voiding symptoms
- P4+0 (NVD)
- No surgery
- Urinalysis negative
- No medications
- Bladder retraining - failed

• Alberta (and other provinces) policy is to prescribe oxybutynin to all people with UUI / OAB first
• Failure must be demonstrated before a second line agent can be given
• Alberta Blue Cross approval must be gained
  - Darifenacin
  - Solifenacin
  - Tolterodine
  - Trospium

Brenda

- Brenda’s MMSE is 26 / 30
- Should I be worried?
- Should she?

Beware...

- The use of drugs with antimuscarinic properties is associated with low cognitive performance among community-dwelling elderly people


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ACB and MMSE scores

% subjects with low MMSE score (≤ 24)

<table>
<thead>
<tr>
<th>SAA (pmol/mL)</th>
<th>% subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable</td>
<td>4.8%</td>
</tr>
<tr>
<td>&lt;2.80</td>
<td>7.6%</td>
</tr>
<tr>
<td>≥2.80</td>
<td>28.6%</td>
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SAA = serum anticholinergic activity
MMSE = Mini-mental state examination

*p<0.05 vs undetectable SAA (logistic regression)

Blood-brain barrier

- Permeability of the blood-brain barrier increases with age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>QAb (mean ± SD)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>20–50</td>
<td>2.42 ± 0.27</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>51–70</td>
<td>3.30 ± 0.30</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>&gt;70</td>
<td>5.87 ± 0.5</td>
<td></td>
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</tbody>
</table>

QAb = albumin permeability index

- Co-morbid conditions such as type 2 diabetes, multiple sclerosis and Alzheimer’s disease can also increase blood–brain barrier permeability

So, what is the problem?

- Use of anticholinergic drugs and higher serum anticholinergic activity have been associated with impaired cognition.
- Both ageing, MCI and Alzheimer’s disease are associated with a central cholinergic deficiency.
- Blockade of muscarinic receptor subtypes can increase amyloidogenic processing of amyloid precursor protein and promote tau phosphorylation.
- The cholinergic system in the central nervous system (CNS) exerts a major influence on cognitive processes:
  - Memory mediated by M1 cholinergic receptors.
  - M2 receptors mediate cognitive function.
- Cognitive dysfunction a concern:
  - Older patients
  - Mild cognitive impairment
  - Dementia.
- Increased blood–brain barrier permeability may also facilitate CNS access of antimuscarinic agents.
• penetration of the blood-brain barrier is highest for oxybutynin, lower for tolterodine, and lowest for trospium chloride; limited data are available for propiverine.

• The spectrum of anticholinergic CNS adverse effects
  – drowsiness
  – hallucinations
  – severe cognitive impairment,
  – delirium
  – coma

What’s the scope of the potential problem?

• About 10% of community dwelling adults and 30% of patients in nursing homes receive anticholinergic drugs

• Up to 17% of long-term care residents aged ≥65 years in nursing homes (1011/5902), could have received three or more anticholinergic agents concurrently during a year

• Nearly 35% of patients on cholinesterase inhibitors receive a concurrent prescription for an anticholinergic.

Serum anticholinergic levels

Ranked according to frequency of prescriptions in older adults

<table>
<thead>
<tr>
<th>Medication</th>
<th>Atropine Equivalents (ng/mL)</th>
</tr>
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<tbody>
<tr>
<td>Furosemide*</td>
<td>0</td>
</tr>
<tr>
<td>Digoxin*</td>
<td>0.2</td>
</tr>
<tr>
<td>Dyazide</td>
<td>0.4</td>
</tr>
<tr>
<td>Dipryidamole</td>
<td>0.6</td>
</tr>
<tr>
<td>Theophylline*</td>
<td>0.8</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1</td>
</tr>
<tr>
<td>Prednisolone*</td>
<td></td>
</tr>
<tr>
<td>Nifedipine*</td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td></td>
</tr>
<tr>
<td>Cimetidine*</td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td></td>
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<tr>
<td>Ranitidine*</td>
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Medications with the five highest levels of anticholinergic activity.
Drugs With Anticholinergic Properties, Cognitive Decline, and Dementia in an Elderly General Population

The 3-City Study

- 520/6912 participants (7.5%) were taking anticholinergic drugs at baseline
- 36 participants (6.9%) were taking 2 anticholinergic drugs
- 8 (1.5%) were taking 3 drugs.
- 1.6% of the participants were taking bladder drugs.

Women reporting use of anticholinergic drugs at baseline showed greater decline over 4 years in

- verbal fluency scores (odds ratio [OR], 1.41; 95% confidence interval [CI], 1.11-1.79)
- global cognitive functioning (OR, 1.22; 95% CI, 0.96-1.55)

than women not using anticholinergic drugs.

In men, decline in

- visual memory (OR, 1.63; 95% CI, 1.08-2.47)
- executive function (OR, 1.47; 95% CI, 0.89-2.44).

A 1.4- to 2-fold higher risk of cognitive decline was observed for those who continuously used anticholinergic drugs but not for those who had discontinued use.

The risk of incident dementia over the 4-year follow-up period was also increased in continuous users (hazard ratio [HR], 1.65; 95% CI, 1.00-2.73).

Patients with an Increased Risk of Cognitive Deficit

- Alzheimer's disease and related dementias (including mild cognitive impairment, age-associated memory impairment)¹
- Parkinson's disease²
- Type 2 diabetes in the elderly³
- Multiple sclerosis⁴
- Alcohol dependence⁵

Dementia – prevalence in women in Europe

Prevalence of dementia in Canada by age

Subtypes of dementia

Minimal cognitive impairment

- the transitional phase between normal aging and dementia

- Definition:

  "a condition characterized by newly acquired cognitive decline to an extent that is beyond that expected for age or educational background, yet not causing significant functional impairment"
Sub types of MCI

- Amnestic MCI single domain: objective impairment in memory but not in another cognitive domain.
- Amnestic MCI multiple domain: objective impairment in memory and in at least 1 other cognitive domain.
- Non-amnestic MCI single domain: objective impairment in a single cognitive domain other than memory.
- Non-amnestic MCI multiple domain: objective impairment in at least 2 cognitive domains other than memory.

Stockholm criteria (2005)

- Cognitive complaints coming from the patients or their families
- Report of a decline in cognitive functioning relative to previous abilities during the past year by the patient or informant
- Cognitive disorders as evidenced by clinical evaluation (impairment in memory or in another cognitive domain)
- Absence of major repercussions on daily life (the patient may, however, report difficulties concerning complex day-to-day activities)
- Absence of dementia

Prevalence of MCI

<table>
<thead>
<tr>
<th>Age and Sex-Specific Prevalence of any MCI</th>
<th>Prevalence (%)</th>
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<tbody>
<tr>
<td>70-74</td>
<td>10</td>
</tr>
<tr>
<td>75-79</td>
<td>20</td>
</tr>
<tr>
<td>80-84</td>
<td>30</td>
</tr>
<tr>
<td>85-89</td>
<td>40</td>
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http://discoverysedge.mayo.edu/de08-4-age-roberts/index.cfm accessed 20.1.11

MCI

- random sample of 2,719 participants aged between 70 and 89
- Baseline cognitive state in 2004

http://discoverysedge.mayo.edu/de08-4-age-roberts/index.cfm
Annual transition to dementia

• approximately 2% to 25% of those carrying the diagnosis of MCI convert to AD per year
• Wide variation due to different populations

What is known about drugs for the bladder?

• Published data exist for the following drugs in cognitively intact older adults
  - darifenacin
  - solifenacin
  - oxybutynin transdermal gel
  - tolterodine (abstract only)
  - trospium chloride
  - oxybutynin

Oxybutynin

• A double-blind, placebo-controlled cross-over study.
• A convenience sample of 12 volunteers, average age 69.17 years.
• Baseline assessment was followed by randomized administration of a placebo, oxybutynin hydrochloride (5 and 10 mg), and diphenhydramine hydrochloride (50 mg) in test sessions separated by 1 week.
• Evaluation of cognitive performance with a 1-hour battery of pencil and paper, interviewer-administered, and computer-administered tests beginning 90 minutes after drug (or placebo) administration.
• oxybutynin caused significant cognitive decrements on seven of 15 cognitive measures


Solifenacin

• 12 pts, >65, cognitively intact
• Standard cognitive battery
• Single 10mg dose
• decline in mean values for Quality of Working Memory at 2 and 4 h post-dose with solifenacin
• the decline was less than that seen with oxybutynin
• by 6 h post-dose the effects of solifenacin were similar to placebo

Darifenacin
- 129 pts >65
- Cognitively intact
- 14 days therapy, 7 days washout
- There were no statistically significant differences compared to placebo for the mean change from baseline in memory scanning sensitivity, speed of choice reaction time and word recognition sensitivity.


Tolterodine
- 17 subjects, >65, cognitively intact
- Tolterodine ER (4 mg) had no effect on the primary outcome measure (delayed recall on the Name-Face Association Test) or on other measures in the cognitive function test battery at any time point.
- There was no decline, relative to baseline, in cognitive test performance when subjects were taking tolterodine ER.
- There was a significant decline in delayed recall on the Name-Face Association Test for oxybutynin ER 20 mg.

Oxybutynin gel
- 152 subjects, mean age 68.2, cognitively intact
- 1 weeks therapy
- Performance on the primary endpoint, Name-Face Association delayed recall, showed no significant treatment effect (p=0.273).
- The Misplaced Objects Test showed a significant treatment effect (p=0.023), with placebo and OTG scores both improving and OXY-IR decreasing.
- Analysis of Reliable Change scores in the HVLT-Total Free Recall (i.e., a decline ≥ 6 from Baseline) indicates that 10 subjects showed a significant decline on OXY-IR, compared to 6 subjects on Placebo and 5 subjects on OTG.

Neurourol Urodyn 2009;28:711-712

Trospium chloride ER
- 12 subjects, cognitively intact
- No total or delayed recall individual HTLV-R score indicated a significant decline in learning or memory on trospium chloride.
- No measurable trospium (<40 pg/ml) was found in CSF at any sampling time in any subject.

Delirium is an idiosyncratic event

- Case reports
  - Tsao JW, Heilman KM. Transient memory impairment and hallucinations associated with tolterodine use. NEJM. 2003; 349(23): 2274-5.

Brenda

- Brenda was started on solifenacin 5mg and her dose was increased at 8 weeks to 10mg
- Her MMSE did not change – evidence is that this is not sensitive to change in the areas in which we might expect impact.

In a large study of antimuscarinic medication for the bladder in European elderly:

- MMSE Scores similar
- 1 patient discontinued active drug due to cognitive problems (related),
- 1 patient discontinued due to amnesia (unrelated),
- 1 patient discontinued due to confusional state (unrelated).

Conclusion

- For the majority of older people, antimuscarinics should provide symptom relief with minimal SE
- Cognitive safety needs to be taken into account for those who are cognitively vulnerable
- The long terms effects of the use of such drugs in terms of cognitive safety and dementia is unknown.