In the pharmacologic treatment of overactive bladder (OAB), antimuscarinics are the first line of drug therapy. There are currently 6 antimuscarinic agents used in the treatment of OAB. They all have proven efficacy and can provide significant benefit for the patient. However, mode(s) of elimination (i.e., hepatic metabolism, renal excretion or both) as well as active metabolites (resultant from metabolism) can affect their pharmacokinetic and pharmacodynamic profiles.

**Pharmokinetics** is defined as n. (used with a sing. verb)1
The process by which a drug is absorbed, distributed, metabolized, and eliminated by the body.
The study of this process.

**Pharmacodynamics** is defined n. (used with a sing. verb)2
The study of the action or effects of drugs on living organisms.

Patients with OAB commonly have comorbidities with the resultant need in polypharmacy.3,4 Therefore, the choice of the correct medication should be based not only on efficacy, dose flexibility and adverse event profiles, but also on potential drug-drug interactions.5 Drug-drug interactions can result in alterations in efficacy of one or more of the drugs involved, and can also cause bothersome and potentially life-threatening adverse effects. The purpose of this CME activity is to take a closer look at the potential drug-drug interactions as the educated provider strives to make an informed decision.

**QUESTION 1:** What defines a drug-drug interaction?
A. One drug affecting the pharmacokinetics of another drug
B. One drug affecting the pharmacodynamics of another drug
C. Both A and B

**QUESTION 2:** Which of the following factors do not affect the metabolism and/or elimination of anticholinergics?
A. Age
B. Sex
C. Presence of concomitant disease
D. Other medications
E. Site of metabolism/excretion and presence or absence of active metabolites

**QUESTION 3:** Which of the following is true regarding hepatic metabolism or renal excretion of medications?
A. The CYP450 hepatic microsomal system only deals with a small number of the medications used by the average patient
B. The majority of drugs undergoing metabolism are metabolized by three of the 12 families in the CYP450 system (CYP1, CYP2 and CYP3)
C. 15-20% of Caucasians are devoid of the isozyme CYP2D6
D. Many drugs are dependent on active tubular secretion for their elimination

**QUESTION 4:** As a class, all antimuscarinics are metabolized the same?
A. True
B. False

**QUESTION 5:** What is true about pharmacodynamic effects?
A. Similar to pharmacokinetic drug-drug interactions, pharmacodynamic interactions are easy to predict
B. Most potential pharmacodynamic interactions that are relevant to anticholinergic drugs result from concomitant use of other drugs with anticholinergic effects
C. Many classes of drug other than anticholinergic agents exhibit anticholinergic properties because they interfere with the action of acetylcholine in some way
D. A and B
E. B and C

**LEARNING OBJECTIVES:**
1. Awareness of the metabolism and/or excretion of medications used in the treatment of overactive bladder
2. Understanding how the effect of a medication can be altered in patients on multiple medications or with hepatic or renal issues
The answer is C.

It is essential to define what constitutes a drug-drug interaction. A drug-drug interaction involves one drug altering the pharmacokinetics or pharmacodynamics of another drug. Plasma concentrations are determined by the dosing of the drug and rate of metabolic clearance. Unbound (free) plasma concentrations determine the drug concentration at the receptor site and the resultant pharmacodynamic effect. A pharmacokinetic drug-drug interaction occurs when the concentration of one drug is altered (increased or decreased) based on the influence of another drug. This would occur if there is an effect of the metabolism/clearance of the initial drug. For example, if the affecting drug induces the metabolizing enzyme, then the plasma concentration and effect of the initial drug is lessened. Likewise, if the enzyme was inhibited, the clearance would be decreased and the pharmacodynamic effect would be increased. Obviously, these alterations in plasma concentrations could result in changes in adverse reactions and efficacy. These changes may not always be bad. In fact, an important example of a therapeutically beneficial drug-drug interaction would be that of probenecid and beta-lactam antibiotics, whereby probenecid increases beta-lactam antibiotic concentrations and, therefore, efficacy.

Pharmacokinetic drug-drug interactions may also include situations in which the one drug modifies access of another drug to the receptor site(s), but does not alter metabolic clearance(s). Pharmacodynamic drug interactions occur when one drug alters the therapeutic response of another but there is no change in the pharmacokinetics of either drug. This can be beneficial by working synergistically or can be adverse by limiting the response or increasing the adverse effects.

The answer is B.

Age, concomitant disease and other medications could alter hepatic and/or renal function thereby affecting the metabolism and/or elimination of anticholinergic agents. For example, the terminal elimination half-life of oxybutynin may be increased in elderly patients due to a decrease in the hepatic metabolism of the parent compound. Likewise, its active metabolite (N-desethyloxbutynin) may have a decrease if renal function is impaired.

The sites of metabolism/elimination, the metabolic pathway(s) involved, and the presence/absence of active metabolites generated from the parent compound not only influence the incidence of adverse events, but also that of drug-drug interactions. Drug-drug interactions may enhance or attenuate the efficacy of anticholinergic agents as well as the efficacy of interacting concomitant medications.

The correct answer is B.

Table 1 shows the clearence mechanism of the various antimuscarinics. Tropium hydrochloride is renally excreted, whereas all the others are heptatically metabolized. Of those that are heptatically metabolized there are differences with the pathways of the cytochrome P450 system. The following text will provide further detail.

Oxybutynin undergoes first-pass hepatic metabolism by the CYP3A4 isozyme. This is extensive and results in a much higher plasma concentration of the active metabolite (N-desethyloxbutynin) than the poorly bioavailable parent drug. In vitro studies, using human microsomal enzymes, have shown that there is also some contribution from CYP3A5. Tolterodine is metabolized primarily through oxidation by CYP2D6. This results in 5-hydroxymethyl tolterodine (5-HMT), which is a pharmacologically active metabolite. 5-HMT contributes significantly to the effects of tolterodine as it has similar potency. As a result of this similar potency the pharmacokinetics and pharmacodynamics of tolterodine are expressed as the sum of the two active moieties. In patients who are poor metabolizers of CYP2D6, tolterodine metabolism is dealkylation by CYP3A4 to N-dealkylated tolterodine. Studies have shown that this results in an approximate 7-fold increase in serum concentrations of tolterodine and in negligible concentrations of 5-HMT compared with patients with normal CYP2D6 function. Tolterodine is considered a pro-drug. Upon absorption, fesoterodine is rapidly hydrolyzed to its active metabolite, 5-HMT, by nonspecific esterases in the gut wall and bloodstream. There are also other metabolites that do not have antimuscarinic activity. Metabolism is primarily mediated by the CYP3A4 and CYP2D6 isozyme similar tolterodine. A significant benefit of its metabolic profile, is that the interindividual variability in the exposure (Cmax) of fesoterodine is less than that observed with tolterodine. In contrast to tolterodine, which requires CYP2D6 for conversion to its active metabolite, 5-HMT, the conversion of fesoterodine to 5-HMT is CYP2D6 independent.
The primary pathway for elimination of solifenacin succinate is poor metabolizers of CYP2D6 have a 2.5-fold increase in exposure.\(^3\) Unfortunately, these effects can be difficult to predict. To complicate matters, each patient must be evaluated individually. True, there may be this interaction and it may lessen the effects of the medications, but may not be practical in this population. Despite the controversy regarding the potential pharmacodynamic drug-drug interactions, each patient must be evaluated individually. True, there may be this interaction and it may lessen the effects of the medications, but it may be more susceptible to such potential antagonistic interactions.\(^5\)

The studies themselves are not consistent in their findings. In one small retrospective study of 69 patients with Alzheimer’s disease, it was observed that chronic concomitant therapy with the cholinesterase inhibitor donepezil and anticholinergics may be associated with significant deleterious effects of donepezil in terms of reduced efficacy. The mean Mini Mental State Examination (MMSE) scores at 2 years were significantly worse for patients receiving concomitant anticholinergic medication than those who were not (\(P=0.032\)).\(^4\) However, another retrospective study of 303 patients showed that the differences in MMSE scores were much less pronounced, not statistically significant at 2 years and were consistent with disease progression. It has been speculated that patients with a higher anticholinergic load may be more susceptible to such potential antagonistic interactions.\(^4\)

Since the conversion of 5-HMT is also CYP2D6 dependent, in the face of CYP2D6 deficiency, 5-HMT is approximately doubled in the patient taking fezolestin.\(^5\) The elimination of darifenacin is mediated primarily by CYP2D6 and CYP3A4, with a small amount (3%) being excreted unchanged in urine and feces.\(^4\) The mean Mini Mental State Examination (MMSE) scores at 2 years were significantly worse for patients receiving concomitant anticholinergic medication than those who were not (\(P=0.032\)).\(^4\) However, another retrospective study of 303 patients showed that the differences in MMSE scores were much less pronounced, not statistically significant at 2 years and were consistent with disease progression. It has been speculated that patients with a higher anticholinergic load may be more susceptible to such potential antagonistic interactions.\(^4\) The studies themselves are not consistent in their findings. In one small retrospective study of 69 patients with Alzheimer’s disease, it was observed that chronic concomitant therapy with the cholinesterase inhibitor donepezil and anticholinergics may be associated with significant deleterious effects of donepezil in terms of reduced efficacy. The mean Mini Mental State Examination (MMSE) scores at 2 years were significantly worse for patients receiving concomitant anticholinergic medication than those who were not (\(P=0.032\)).\(^4\) However, another retrospective study of 303 patients showed that the differences in MMSE scores were much less pronounced, not statistically significant at 2 years and were consistent with disease progression. It has been speculated that patients with a higher anticholinergic load may be more susceptible to such potential antagonistic interactions.\(^4\)

The correct answer is E.

**DISCUSSION OF QUESTION 5**

The correct answer is _E._

As mentioned earlier, pharmacodynamics refers to a drugs effect on the body. Drug-drug interactions may alter the usual pharmacodynamics which may result in additive or synergistic beneficial or adverse effects, or even an increase in symptoms caused by one of the drugs. Unfortunately, these effects can be difficult to predict. To complicate the issue, many classes of drug other than anticholinergic agents exhibit anticholinergic properties as they interfere with the action of acetylcholine in some way. The result of these interactions may be an increase in the frequency and/or severity of adverse effects.\(^5\)

A concern amongst many providers is the drug-drug interaction of anticholinergic drugs is with cholinergic agonists (direct or indirect) as these two agents have opposing mechanisms of action and concomitant use may reduce the efficacy of one or both agents. As the population ages, arguably the most important cholinergic agonists used are the cholinesterase inhibitors for the treatment of cognitive impairment in patients with dementia.\(^4\) It could be expected that use of the medications together may result in mutual antagonism.\(^5\)

---

**TABLE 1. PHARMACOKINETIC CHARACTERISTICS OF ANTIMUSCARINICS FOR OVERACTIVE BLADDER**

(used with permission Rosenberg, Guay, paper in submission)

<table>
<thead>
<tr>
<th>Route of metabolism and active metabolites</th>
<th>Darifenacin</th>
<th>Festosterodine</th>
<th>Oxybutynin</th>
<th>Solifenacin</th>
<th>Tolterodine</th>
<th>Trosipium Chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic via CYP3A4, CYP2D6</td>
<td>Hepatic via CYP3A4, CYP2D6</td>
<td>Hepatic, predominantly via CYP3A4 and CYP3A5</td>
<td>Hepatic primarily via CYP3A4</td>
<td>Hepatic primarily via CYP2D6, or via CYP3A4 in CYP2D6 poor metabolizers</td>
<td>Renal elimination of parent compound</td>
<td></td>
</tr>
<tr>
<td>CYP2D6 substrates</td>
<td>CYP3A4 substrates</td>
<td>CYP3A4 inhibitors</td>
<td>CYP3A4 inhibitors</td>
<td>CYP3A4 inhibitors</td>
<td>CYP3A4 inhibitors</td>
<td></td>
</tr>
<tr>
<td>CYP3A4 inhibitors</td>
<td>CYP3A4 inhibitors</td>
<td>CYP3A4 inhibitors</td>
<td>CYP3A4 inhibitors</td>
<td>CYP3A4 inhibitors</td>
<td>Other drugs that are eliminated by active real tubular secretion</td>
<td></td>
</tr>
</tbody>
</table>

5-HMT, 5-hydroxymethyl tolterodine; CYP, cytochrome P450

The mean Mini Mental State Examination (MMSE) scores at 2 years were significantly worse for patients receiving concomitant anticholinergic medication than those who were not (\(P=0.032\)).\(^4\) However, another retrospective study of 303 patients showed that the differences in MMSE scores were much less pronounced, not statistically significant at 2 years and were consistent with disease progression. It has been speculated that patients with a higher anticholinergic load may be more susceptible to such potential antagonistic interactions.\(^4\) The studies themselves are not consistent in their findings. In one small retrospective study of 69 patients with Alzheimer’s disease, it was observed that chronic concomitant therapy with the cholinesterase inhibitor donepezil and anticholinergics may be associated with significant deleterious effects of donepezil in terms of reduced efficacy. The mean Mini Mental State Examination (MMSE) scores at 2 years were significantly worse for patients receiving concomitant anticholinergic medication than those who were not (\(P=0.032\)).\(^4\) However, another retrospective study of 303 patients showed that the differences in MMSE scores were much less pronounced, not statistically significant at 2 years and were consistent with disease progression. It has been speculated that patients with a higher anticholinergic load may be more susceptible to such potential antagonistic interactions.\(^4\)
SUMMARY

Currently there are 6 anticholinergic agents approved for the management of OAB. Darifenacin, fesoterodine, oxybutynin, solifenacin succinate, tolterodine and trosipium chloride all demonstrate similar efficacy and tolerability in the treatment of this disease state. Providers must be cognizant of that these agents differ in their pharmacodynamic and pharmacokinetic profiles due to structural and molecular differences. As a result, there is the potential for drug-drug interactions which can increase the frequency and severity of adverse events or decrease drug efficacy. These interactions may be more pronounced in the elderly, patients with numerous co-morbidities or those on multiple medications.

Supported by an education grant from Pfizer and Astellas.

ENDNOTES

ACTIVITY TITLE: Treating Overactive Bladder: Drug-Drug Interactions
DATES VALID: August 17, 2011 – August 17, 2012
CREDITS AVAILABLE: 1 Category 2B, AOA; 1 Category 1 AMA PRA™

INSTRUCTIONS: Please complete this form and return it to the address or fax number below.

PLEASE PRINT CLEARLY
FULL NAME: [ ]
Last 4 digits of SSN: (for tracking) [ ]
MAILING ADDRESS: [ ]
PHONE: [ ]
FAX: [ ]
E-MAIL: [ ]

QUESTION RESPONSES

<table>
<thead>
<tr>
<th>Q#</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

PROGRAM EVALUATION

LEARNING OBJECTIVES

<table>
<thead>
<tr>
<th>Scale:</th>
<th>P=Poor</th>
<th>F=Fair</th>
<th>G=Good</th>
<th>VG=Very Good</th>
<th>E=Excellent</th>
</tr>
</thead>
</table>

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Awareness of the metabolism and/or excretion of medications used in the treatment of overactive bladder</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Understanding how the effect of a medication can be altered in patients on multiple medications or with hepatic or renal issues</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

CONTENT

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>To what extent this activity is fair and balanced.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>Likelihood that you will implement change in your practice based on information from this activity.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>Your OVERALL rating of this activity.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

PRACTICE

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>How will you use the information presented to improve the care of your patients?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SIGNATURE [ ] DATE [ ]