Family Medicine Clinical Pharmacy Forum

Family Medicine Clinical Pharmacy Forum is a brief bi-monthly publication from the Family Medicine clinical pharmacists distributed to faculty and residents of the Department of Family Medicine. Our intent is to provide timely information on broad-based issues of pharmacotherapy, as well as regulatory and practiced-based issues affecting you as a prescriber. If you have suggestions for things you would like to see, please contact us.

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Pharmacotherapy Issues

Lowering blood pressure through personalized melodies?

It is well known that lifestyle modifications are widely recommended to reduce blood pressure, either alone or with hypertension medications. Slower breathing (<10 breaths/minute) can reduce sympathetic nerve activity and increase arteriolar dilatation, thus causing lowered blood pressure. A new device called RESPeRATE can assist with slower breathing. This portable electronic device consists of a breathing sensor which automatically analyzes an individual breathing pattern and in turn, creates a personalized melody composed of two distinct inhale and exhale guiding tones. By gradually prolonging the exhalation tone to slow breathing, RESPeRATE leads to the recommended breathing rate of less than 10 breaths per minute.

Within minutes, the manufacturer claims the muscles around the blood vessels relax, allowing blood to move more freely, reducing blood pressure. Within 4-6 weeks, the manufacturer claims a significant, lasting reduction in blood pressure.

RESPeRATE’s manufacturer backs up its claims with seven clinical trials, concluding that this device lowers high blood pressure by up to 36 points systolic and 20 points diastolic, with average reductions of 14/8 points. These studies used RESPeRATE for 15 minutes a day for 8 weeks to achieve these results. The study results were similar across gender and medication status.

Clinically, RESPeRATE is indicated to the US FDA for the reduction of stress and as an adjunctive therapy in hypertension that can be combined with standard antihypertensive drugs and non-pharmacologic interventions. RESPeRATE sells for around $290. Routine use of a
A device to assist with slow breathing devoid of adverse reactions may have its place in antihypertensive therapy, particularly in patients interested in nonpharmacologic therapies. Reprints, full indication for use and additional information can be found at www.resperate.com/MD.


New Drugs:

- **Azilect® (rasagiline): New Therapy for Parkinson's Disease**
  Azilect® is a new second generation monoamine oxidase (MAO) type-B inhibitor approved on 5/16/06 for the treatment of Parkinson's disease. MAO-B is involved in regulating the metabolic degradation of catecholamines and serotonin in the CNS and peripheral tissues. The rationale for using MAO inhibitors in Parkinson's disease is enhancement of striatal dopamine activity, resulting in symptomatic motor benefits. A secondary rationale is that MAO-B inhibitors may have antioxidant and antiapoptotic activity in experimental models which may translate into neuroprotective benefits. Azilect® is similar in mechanism to selegiline, although chemically they are metabolized to distinctly different metabolites. Selegiline is metabolized into amphetamine-like metabolites which have been shown to induce neurotoxicity in animal models and may explain the relative lack of neuroprotective effects of the drug.

  In clinical studies, Azilect® has been used as both monotherapy and in conjunction with levodopa therapy, resulting in significant beneficial effect relative to placebo on the primary measure of effectiveness at 6 months of treatment as measured by the UPDRS (a multi-item rating scale that measures the ability of patient’s to perform mental and motor tasks as well as ADLs). When used in conjunction with levodopa in patients experiencing motor fluctuations, Azilect® reduced the mean total daily “OFF” time as reported in patient diaries. UPDRS scores also improved significantly compared to placebo. Azilect® is contraindicated with meperidine, tramadol, methadone, propoxyphene, dextromethorphan, and other MAOIs due to risk of serotonin-syndrome. Patients should be advised to follow a tyramine-restricted diet. Azilect® should be avoided in combination with SSRIs as they have not been studied together. Adverse effects appear mild and are consistent with Parkinson's symptoms such as dyskinesia and postural hypotension. The initial dose is 0.5 mg/day, and may be increased to 1 mg/day. Cost information not yet available. When administered with levodopa, the dosage of levodopa may need to be reduced.


- **Amitiza® (lubiprostone): New Therapy for Constipation**
  Amitiza® (pronounced a-mih-TEE-zah) or lubiprostone was approved by the FDA early this year for the treatment of chronic idiopathic constipation in adults. Unlike Zelnorm®, Amitiza® is approved for use in all adults, including those ≥65 years of age. In two phase III trials of 479 patients, ~60% of patients taking Amitiza™ had a bowel movement within 24 hours compared to ~34% of patients taking placebo. Amitiza™ activates chloride channels in the gut, therefore increasing intestinal fluid and improving motility. It is thought to be only minimally
Amitiza® is absorbed systemically. Studies in renal or hepatic impairment have not been performed. Amitiza® is contraindicated in patients with a history of mechanical gastrointestinal obstruction. Nausea is the most prominent side effect, occurring in approximately 31% of patients. Amitiza® is dosed 24 mcg twice daily, and patients may take it with food to minimize nausea. Cost could not be determined at this time, but it is likely to be priced closely to Zelnorm® at approximately $180 per month.

References:

- **Chantix® (varenicline): New Therapy for Smoking Cessation**
  Chantix® is a new nicotinic receptor agonist approved on 5/10/06 as an aid to smoking cessation treatment. Several clinical trials of 6-12 weeks duration have established the efficacy of Chantix® compared to placebo and to buproprion SR. In these studies, confirmed continuous abstinence rates were observed in approximately 40-50% of patients receiving active treatment, compared to 30% with buproprion SR and 12-18% with placebo. In long-term follow-up (40 weeks post-treatment), continuous abstinence rates for Chantix® treated patients dropped to around 20%. However, rates were even lower in the buproprion SR (16%) and placebo treated patients (4-10%). Adverse reactions are mild and are mostly limited to gastrointestinal such as nausea, dyspepsia, flatulence, and constipation. Chantix® is dosed 0.5 mg/day for days 1-3, followed by 0.5 mg BID for days 4-7, and finally 1 mg BID for day 8 until the completion of 12 weeks of therapy. It can be used with nicotine patches. Although studies have shown that it does not alter the pharmacokinetics of buproprion, the manufacturer does not recommend the combination be used at this time due to lack of data.


**Serotonin Syndrome Revisited**
A recent article was published in Canada that aimed at systematically reviewing documented drug interactions with antidepressants. The authors did MEDLINE and EMBASE searches to compile human studies from 1996-2003. As part of the literature evaluation, the reviewers separately evaluated reports of serotonin syndrome according to Sternbach’s criteria. In order for an interaction to be labeled causative of serotonin syndrome, all of the diagnosis criteria had to be met.

As a result of the literature search, 1478 articles were identified and evaluated, which led to 598 summary interaction reports being collated. Serotonin syndrome was reported in 106 interactions (18%). However, only 34 interactions (6%) successfully met all Sternbach’s criteria (mental status changes ranging from agitation and confusion to stupor and coma, tremor, rigidity, fever, and hyperreflexia).

Definite conclusions could not be made in the review about the frequency of serotonin syndrome related to drug interactions due to many of the reports being incomplete and defined as poor quality (e.g. RCTs with less than 10 subjects, cohort studies, case-control studies, case reports, case series and pharmacokinetic studies). The reviewers also suspected that serotonin syndrome may have been misdiagnosed and underreported.


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Table 1. Drugs and Drug Interactions Associated with the Serotonin Syndrome

<table>
<thead>
<tr>
<th>Drugs associated with the serotonin syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram</td>
</tr>
<tr>
<td>Antidepressant drugs: trazodone, nefazodone, buspirone, domperidone, and venlafaxine</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors: phenelzine, moclobemide, clorgiline, and moclobemide</td>
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<tr>
<td>Anticonvulsants: valproate</td>
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<tr>
<td>Analgesics: meperidine, fentanyl, tramadol, and pentazocine</td>
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<tr>
<td>Antiemetic agents: ondansetron, granisetron, and metoclopramide</td>
</tr>
<tr>
<td>Antihistamines: diphenhydramine, doxepin, and promethazine</td>
</tr>
<tr>
<td>Antibiotics: tetracycline (a monamine oxidase inhibitor) and ribavirin</td>
</tr>
<tr>
<td>(through inhibition of cytochrome P-450 enzyme isofrom 3A4)</td>
</tr>
<tr>
<td>Over-the-counter cough and cold remedies: dextromethorphan</td>
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<tr>
<td>Drugs of abuse: methylphenidate (MDMA, or &quot;ecstasy&quot;), lysergic acid diethylamide (LSD), and methylnaltrexone/bupropion (&quot;foxy methoxy&quot;)</td>
</tr>
<tr>
<td>Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)</td>
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<tr>
<td>Dietary supplements and herbal products: tryptophan, Hypericum perforatum (St. John’s wort), Panax ginseng (ginseng)</td>
</tr>
<tr>
<td>Other lithium</td>
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<tr>
<td>Drug interactions associated with severe serotonin syndrome</td>
</tr>
<tr>
<td>Zolof, Prozac, Sarafem, Paxil, Cedex, Desyrel, Serzone, Buspar, Anafranil, Effexor, Nordit, Serzone, Maprotiline, Depakote, Demerol, Duragesic, Sublimaze, Ultram, Talwin, Zofran, Kylar, Reglan, Imiret, Meridia, Redlux, Pendimine, Zyrac, Norvir, Retime, Tofranil, Remeron</td>
</tr>
<tr>
<td>Phenelzine and meperidine</td>
</tr>
<tr>
<td>Tramadol, and zolpidem</td>
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<tr>
<td>Phenelzine and selective serotonin-reuptake inhibitors</td>
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<tr>
<td>Paroxetine and buspirone</td>
</tr>
<tr>
<td>Linezolid and citalopram</td>
</tr>
<tr>
<td>Moclobemide and selective serotonin-reuptake inhibitors</td>
</tr>
<tr>
<td>Tramadol, venlafaxine, and mirtazapine</td>
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</tbody>
</table>

The table to the left shows the drugs that are commonly associated with serotonin syndrome that was pulled from an article that appeared in *The New England Journal of Medicine* in 2005.


**Glucosamine/chondroitin efficacy revisited**

Results of a recently published study of glucosamine/chondroitin in knee osteoarthritis suggest either agent alone or in combination may not be as effective as previously reported. In an earlier study (Lancet 2001;357:251-6), glucosamine sulphate 1500 mg/day resulted in significant improvement in radiographic and patient-reported measures of disease severity. In the latest study, no significant difference of either agent as monotherapy or in combination was noted. However, in subgroup analysis, those patients with more severe knee pain appeared to respond better with combined therapy compared to placebo. Of note, the most recent study used glucosamine *hydrochloride* whereas the earlier study used the *sulphate* form. It is unknown whether this difference may have contributed to the findings. In addition, the placebo response in the latest study was 60%, much higher than what is usually observed in double-blind, placebo-controlled studies. This phenomenal response rate would make finding a difference between active treatment and placebo difficult in any study.


**Practice-Based Issues**

**Calculating renal function: MDRD equation or Cockcroft-Gault?**

Creatinine clearance (CrCl), as estimated using the Cockcroft-Gault equation, has been widely used to estimate renal function. The National Kidney Foundation now recommends using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation for...
calculation of renal function as a glomerular filtration rate (GFR). A GFR calculator using the MDRD equation can be found at the National Kidney Foundation website (www.kidney.org/kls/professionals/gfr_calculator.cfm). CrCl, from Cockcroft-Gault, and GFR, from MDRD, will not always correlate nicely. It is a good idea to calculate both and evaluate the clinical situation. The MDRD equation has been validated in patients with diabetic renal disease, non-diabetic renal disease, renal transplant, and in Caucasian and African American populations. It has not been validated in children, pregnant women, elderly >70 years, or patients with unimpaired renal function. The Cockcroft-Gault equation was designed to estimate CrCl when renal function is stable. CrCl, from Cockcroft-Gault, is used for most dosing guidelines. Of note, the MDRD equation gives a GFR estimate in ml/min/1.73m\(^2\). This should be corrected for patients with extremes of body surface area.

References:

**Regulatory Issues**

**Medicaid PDL Changes – Xopenex HFA® vs albuterol; Levemir® vs Lantus®**

Effective May 1, some interesting changes are noted to the Medicaid PDL recently. Most notably, Xopenex HFA® (levoalbuterol) inhaler is now preferred over albuterol and Levemir® is now preferred long-acting insulin over Lantus®. Please note that both of these drugs are expensive and do not necessarily offer any therapeutic advantages. The decision to make them preferred drugs in the Medicaid PDL likely reflects contract pricing arrangements. While it is fine to prescribe these to Medicaid patients, keep in mind that other plans may not cover them and your cash-paying patients may not be able to afford them.

**Clinical Pearl**

**Can Aldara® be used for the treatment of actinic keratosis?**

Aldara® (5% imiquimod) was first approved for the treatment of external genital warts. Aldara® is an immune response modifier. In 2004, it also received approval for treatment of actinic keratosis. In two double-blind, vehicle-controlled clinical studies, 436 patients with AK were treated with Aldara cream or vehicle cream 2 times per week for 16 weeks. Patients with 4-8 clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophihc AK lesions of the face or scalp were enrolled. Complete clearance at 8 weeks occurred in 44-46% of patients. 58-60% of patients achieved partial clearance rates (75% or more from baseline). Although liquid nitrogen cryotherapy remains the treatment of choice for single or few scattered small AKs, Aldara® may be preferable when there are multiple AKs present.