

# OREGON DUR BOARD NEWSLETTER<sup>®</sup>



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## Quantities of Carisoprodol (Soma<sup>®</sup>) to be Restricted

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The Oregon DUR Board has recommended to the State of Oregon Office of Medical Assistance Programs (OMAP) that carisoprodol (Soma<sup>®</sup>) be subject to prior authorization after the dispensing of 56 tablets in 90 days.

Carisoprodol drug abuse is a public health problem nationwide, with many cases of overdose reported to poison control centers. A DUR Board report suggests carisoprodol is continuing to be used outside recommended guidelines in Oregon. The routine review suggested that 13.5% of carisoprodol prescriptions were dosed at greater than 1400mg per day, based on the day's supply and the number of tablets dispensed. The review of OMAP Fee for Service (FFS) patients showed that 17.6% of the total 6469 prescriptions of carisoprodol issued over a 10-month period in 1999 were for doses greater than 1500 mg/day. Of 1689 patients, 57.5% received more than one prescription for carisoprodol and the average number of days between the first and last prescription was 128 days (SD±89). Results of the review indicate 2 areas of inappropriate use: patients taking high doses of carisoprodol who have chronic pain problems and patients with multiple prescriptions whose prescription history is suggestive of drug seeking behavior.

Carisoprodol has limited efficacy in the short-term and is not effective for the treatment of chronic pain. No evidence exists for a clinically significant effect other than sedation.<sup>1</sup> In addition, carisoprodol is associated with dependence when used on a long-term basis. This lack of efficacy and potential for abuse led the Portland VA Medical Center Formulary Committee to completely remove carisoprodol from its formulary in 1997. Many prescribers may still be unaware of carisoprodol's potential for abuse and dependence.

The exact mechanism of action of carisoprodol is unknown. It does have an effect on the reticular system, but its effects are believed to be due to sedation rather than any direct effect on the muscle. Drowsiness is reported in 40% of patients taking carisoprodol and it is also reported to cause dizziness, lightheadedness and euphoria. Some of the effects of carisoprodol

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## Alosetron (Lotronex<sup>®</sup>): A New Treatment for Irritable Bowel Syndrome

By: **Dean Haxby**, Pharm.D., **Cisco Jorgensen**, B.S. Pharmacy Clerkship Student & **Helen Varley**, B. Pharm., Dip. Clin. Pharm., M.R.Pharm.S.

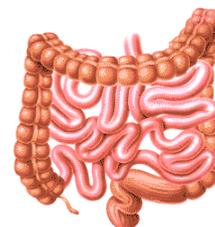
### Introduction

Irritable Bowel Syndrome (IBS) is a common chronic gastrointestinal disorder. IBS is a "functional" GI disorder, not explained by structural or biochemical abnormalities. The predominant symptoms of IBS are abdominal pain plus diarrhea, constipation or both. Other symptoms may include cramping, gas, abdominal distension and nausea.<sup>1</sup> Pain often is worsened soon after eating, and improved by having a bowel movement or passing gas. Symptoms tend to wax and wane, and can vary from mildly annoying to debilitating.<sup>2</sup> The etiology of IBS is poorly understood, although the syndrome has been attributed to a variety of factors, including altered motility, abnormal visceral perception, psychological stress, food intolerance and infection.<sup>1,2,3</sup>

The prevalence of IBS in adults in the United States is approximately 20%. Women account for about 70% of cases. While it is estimated that IBS is responsible for about 3.5 million doctor visits annually in the United States, only about 10% of patients actually consult a physician.<sup>2</sup> Studies have shown that about half of patients with IBS have a concurrent psychiatric disorder, with depression and generalized anxiety being most common.<sup>2</sup> While psychological factors are not implicated in the cause of IBS, they may exacerbate symptoms.

### Traditional IBS Therapy

As there is no cure for IBS, treatment focuses on alleviating symptoms. The ability to evaluate treatments is confounded by the high placebo response rate (up to 40-70%).<sup>3</sup> Because many patients attribute their symptoms to specific foods, dietary modification may be the initial intervention. Foods that may aggravate symptoms include: chocolate, dairy products, alcohol, caffeine, fructose, sorbitol, fatty foods, and gas-producing foods (i.e. legumes, onions, broccoli, cabbage, apple and grape juices, bananas, nuts, raisins)<sup>3</sup> While some patients may see marked improvement in their symptoms with diet modification, others may not. Evidence supporting the relationship between diet and IBS symptoms is limited.<sup>4</sup>



Fiber supplements or bulk-forming laxatives, such as methylcellulose (Citrucel<sup>®</sup>) or psyllium (Metamucil<sup>®</sup>), may be useful for patients with constipation-predominant IBS. While effective at alleviating constipation, some patients may experience bloating or an increase in symptoms.<sup>5</sup> If a fiber supplement is initiated, it should be administered with adequate fluids. Prokinetic agents, such as metoclopramide, are also used in the treatment of IBS patients with constipation and bloating as their primary symptoms. Unfortunately, the benefits of metoclopramide are marred by unpleasant side effects, thus it is not considered a first line treatment. The FDA is currently reviewing tegaserod (Zelmac<sup>®</sup>), a 5-HT<sub>4</sub> agonist, for use in constipation-predominant IBS. Preliminary data on efficacy are not impressive.<sup>6</sup>

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may be due to its major metabolite, meprobamate (Miltown®, Equanil®), a Schedule IV drug pharmacologically similar to barbiturates. Repeated dosing with carisoprodol may lead to substantial steady-state levels of meprobamate and could give rise to habituation and withdrawal effects.<sup>1</sup>

Cases of carisoprodol dependence have been reported to the FDA's Adverse Event Reporting System and in the medical literature.<sup>2,3,4</sup> Carisoprodol withdrawal has been described as having both physical and psychological components. Carisoprodol, in doses of 350-1050 mg, causes general relaxation and drowsiness. Higher doses of carisoprodol, 1400-3500 mg, produce a hypomanic state that is characterized by undue cheerfulness, psychomotor excitement, increased self confidence, increased socialization and disinhibited behavior. Even higher doses cause disorientation, confusion, perseveration, ataxia and partial amnesia.<sup>4</sup>

Non-medical use of carisoprodol is an increasing problem. Carisoprodol is frequently used by poly-drug abusers, particularly those dependent on opioids. It may be used as a substitute when narcotics are not available in order to combat opioid withdrawal. It may also be used to prolong the effects of a narcotic or alcohol, to enhance the effect of a primary drug of abuse, to "take the edge off the jittery feeling of cocaine", and to terminate a "cocaine binge".<sup>4,5,6</sup> A 1997 FDA review showed 72,000 carisoprodol tablets were seized by law enforcement personnel between 1980 and 1996 in 224 seizures. Carisoprodol was frequently encountered in cases where other controlled substances were being trafficked. The data indicated that carisoprodol is sought by patients who go from doctor to doctor in order to obtain supplies. Recreational use of carisoprodol has been noted in Oregon, with stories circulating of a Central Oregon "Soma clique" that keeps its members supplied through the sharing of prescriptions.

An annual survey of hospital emergency departments revealed that in the first half of 1998, there were 4,438 emergency department drug episodes involving the non-medical use of carisoprodol, a 50% increase compared

with the first half of 1997.<sup>7</sup> Carisoprodol alone is rarely fatal in overdose, but when taken with other CNS depressants, respiratory depression and death can result. Ethanol is reported to be a frequent co-intoxicant with carisoprodol, as are diazepam, propoxyphene, hydrocodone and alprazolam.<sup>8</sup> An Alabama investigation into 24 carisoprodol-related deaths showed that carisoprodol was never detected alone, but with various co-intoxicants. Seventeen victims had a history of drug abuse and intoxication was the cause of death for each (8 accidental, 6 suicide, 3 undetermined). The authors believed the effects of carisoprodol on respiratory depression probably played a role in 14 of these deaths (82%).<sup>3</sup>

Carisoprodol is not a federally-controlled drug, but it is a Schedule IV drug in Oregon. While this may affect potential abuse problems, further measures are needed to limit its use. Prior authorization is being recommended by the DUR Board so that carisoprodol is only prescribed for short periods of time. It is important that prescribers are aware of the problems associated with this drug.

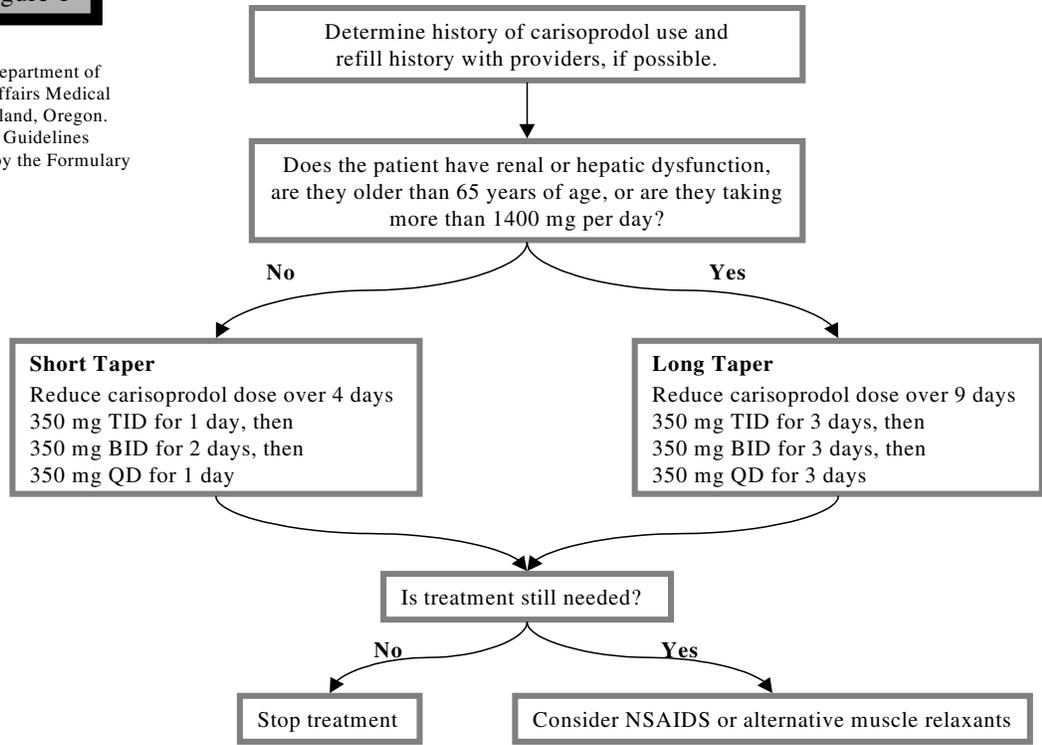
**Recommendations**

- Carisoprodol and other oral skeletal-muscle relaxants should only be considered for the short-term treatment of acute, painful musculoskeletal conditions. Little evidence supports efficacy for these agents whose primary effect is sedation. Many clinicians are skeptical about the use of oral skeletal-muscle relaxants even for acute musculoskeletal conditions. If prescribed, oral skeletal-muscle relaxants should be an adjunct to rest and physical therapy, and they should not be used for more than two weeks at a time.
- Carisoprodol is metabolized to meprobamate, a federal Schedule IV drug associated with dependence. Use caution when prescribing carisoprodol for patients who are known abusers of alcohol, narcotics or benzodiazepines and for new patients whose prescription history is unknown.<sup>1</sup> Patients requesting carisoprodol for long-term use should be evaluated for addictive disorders.

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**Tapering carisoprodol (Soma)**

**Figure 1**  
From the Department of Veterans Affairs Medical Center Portland, Oregon. Medication Guidelines Approved by the Formulary Committee



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- Skeletal-muscle relaxants are not indicated for the treatment of chronic pain and there is very little data supporting their long-term use.

#### Safe discontinuation of carisoprodol

Prescribers should discuss the need to discontinue carisoprodol with their patients. Many patients with chronic pain may not be getting pain relief from the drug but may still be reluctant to discontinue it because of its effects on associated problems such as depression, anxiety and sleeping difficulties. If relief of pain or associated symptoms is indicated, an alternative agent may be introduced while carisoprodol therapy is tapered. This allows carisoprodol to be discontinued without causing any unnecessary discomfort to the patient.



Alternative skeletal-muscle relaxants for the treatment of muscle spasm include cyclobenzaprine (Flexeril®), tizanidine (Zanaflex®), and dantrolene (Dantrium®). Cyclobenzaprine is a centrally acting skeletal-muscle relaxant which is pharmacologically related to the tricyclic antidepressants. Cyclobenzaprine acts on the central nervous system at the level of the brain stem. Tizanidine is an alpha2-adrenergic agonist with skeletal-muscle relaxant properties, but very

little effect on blood pressure. Tizanidine is said to have minimal abuse potential.<sup>9</sup> Dantrolene is indicated for the treatment of spasticity associated with spinal cord injury, stroke, cerebral palsy, and multiple sclerosis. It is unique among the muscle relaxants in that it acts directly on skeletal muscle, interfering with the release of calcium.

If there is no requirement for an alternative treatment, carisoprodol therapy should be tapered and stopped. There is no justification for ongoing use of carisoprodol. To assist in the tapering process, the algorithm in Figure 1 was produced at the Portland VA Medical Center. Upon the discontinuation of high doses of carisoprodol, patients may suffer withdrawal symptoms such as body aches, increased perspiration, palpitations and psychological symptoms such as sadness, restlessness, anxiety and insomnia.<sup>4</sup> A withdrawal program similar to one used for alcohol withdrawal may be required for these patients and the advice of an addiction specialist may be necessary. A suggested tapering schedule for such patients is to reduce the dose daily by 25% of the previous day's dose. (

#### Useful resources

##### Treatment Guidelines

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<http://www.medicalinterface.com/resources/miclinical298.html> and  
<http://www.medicalinterface.com/resources/miclinical398.html>

##### Patient Information Leaflets

Many patient guides to low back pain are available on the internet. These can be downloaded and printed for patients, e.g., American Family Physician, Acute Low Back Pain.

<http://www.aafp.org/afp/20000315/1789ph.html>

**Article Reviewers:** Brett Stacey, M.D., Director, Pain Management Center, Associate Professor, OHSU Department of Anesthesiology & Sue Millar, Pharm.D., Clinical Pharmacy Coordinator, Portland VA Medical Center

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## Phenylpropanolamine Health Advisory

By: **Joseph Jordan, Pharm.D.**

The Food and Drug Administration (FDA) has issued a public health advisory concerning phenylpropanolamine (PPA), a common ingredient in over-the-counter (OTC) cough/cold and weight-loss products.<sup>1</sup> Phenylpropanolamine may increase a patient's risk of hemorrhagic stroke, according to an epidemiologic study requested by the FDA and funded by a trade group of OTC manufacturers.<sup>2</sup> The case-controlled study of 2078 subjects found a statistically significant increased risk of hemorrhagic stroke among users of PPA products. Based on these findings, an FDA advisory committee has recommended that PPA products should no longer be available over-the-counter.<sup>1</sup> The FDA is working to remove PPA from all OTC and prescription drug products and has requested drug manufacturers to stop marketing products containing PPA.<sup>1</sup>

PPA is commonly found in OTC weight-loss products, including Acutrim and Dexatrim, as well as cough/cold products including some forms of Allerest, Contac, Coricidin, DayQuil, Dimetapp, Dristan, Entex LA, Guaifenesin LA, Phenylphenesin, Tavist-D, Tussin CF, Triaminic, and ULR LA. PPA is one of several OTC decongestants used in cough/cold preparations, but it is the only approved active ingredient for OTC diet products.<sup>3</sup>

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## Soy: A Viable Alternative to HRT?

By: *Michele Koder, Pharm.D.*

It is increasingly apparent that interest in the health effects of soy, among women in particular, is growing at a rapid pace. This can be attributed to frequent promotion in the media, lay literature, and Internet and is substantiated by a booming industry of soy-containing food products and supplements. A lack of consensus on the benefits and risks of conventional hormone replacement therapy (HRT) is also fueling interest in the alternative management of menopause. The intent of this review is to aid primary care providers and pharmacists in answering common questions about the role of soy in menopause.

### What are phytoestrogens?

Although often used interchangeably, it is important to distinguish between the soy-related terms. Soy is vegetable protein found in the soybean, a legume, containing iron, B vitamins, calcium, fiber, low levels of saturated fat and no cholesterol. The soybean and soy-food products are also high in phytoestrogens. Phytoestrogens, commonly called "natural estrogens", are plant-derived compounds similar to 17,  $\beta$ -estradiol that bind to estradiol receptors where they function as weak agonists and/or antagonists.<sup>1</sup> Phytoestrogens are divided into several classes including isoflavones, lignans and coumestans.<sup>2</sup> Isoflavones are primarily found in soybeans while coumestans and lignans are found in sunflower seeds, bean sprouts, red clover and seed oils. Ipriflavone is a synthetic isoflavone. Isoflavones are inactive in their natural state and require intestinal bacterial metabolism for activation so their activity is subject to wide variability. The primary active metabolites of isoflavones are genistein and daidzein.<sup>1-3</sup>

### Proposed Benefits

The majority of proposed health effects are derived from epidemiologic studies which discovered significantly lower rates of coronary heart disease (CHD), hot flashes and hormonal malignancies of the breast, ovaries, endometrium and colon in women in Asian countries.<sup>1-3</sup> This was attributed to a soy-based diet, high in phytoestrogen content, in Asian women, who ingest on average 20 to 80 mg of isoflavones daily, compared to an average of less than 5 mg/d in Americans. Further clinical investigations have revealed the following:

#### • Menopausal Symptoms

Three 12-week, randomized, double-blind, placebo-controlled trials evaluated the frequency and severity of hot flashes in postmenopausal women ingesting isolated soy protein, soy flour, or isoflavone extract containing 45 to 76 mg isoflavones daily.<sup>4-6</sup> Only one trial resulted in a reduction of hot flashes that achieved statistical significance. A 9-week study in nearly 200 women taking soy tablets failed to produce significant differences in hot flash frequency and severity versus placebo.<sup>7</sup> Anecdotal experience and reports suggesting the contrary may be largely the result of a strong placebo effect seen in studies of hot flashes. However, clinical studies do not support a consistent or significant hormonal effect of phytoestrogens in postmenopausal women.

#### • Coronary Heart Disease

Phytoestrogens derived from a diet high in soy-protein and low in fat and cholesterol may reduce the risk of CHD.<sup>8</sup> Studies show that an average of 47 g/d soy-protein lowers total cholesterol, LDL-cholesterol, and triglycerides by 10-13% in postmenopausal women.<sup>8-10</sup> Reductions are greatest in patients with moderate to severe hypercholesterolemia. Limited clinical data also suggest soy-protein may possess additional cardiovascular benefits on HDL, LDL oxidation, systemic arterial compliance, vascular and endothelial function, platelet aggregation, and blood pressure.<sup>1-3</sup> To date, no clinical trials have directly



assessed whether soy-protein can reduce cardiovascular morbidity and mortality. Available data are limited by inconsistent trial results among different soy/phytoestrogen sources and small sample sizes. Based on the LDL-lowering benefit, the FDA approved a health claim for CHD reduction

for foods containing at least 6.25 g of soy-protein and recommends consumption of such products 4 times daily to equal 25 g/d.<sup>8</sup>

#### • Osteoporosis

Several small clinical trials of short duration have been conducted and the majority have been with ipriflavone. A recent review of randomized, controlled trials concluded that ipriflavone in doses of 400 to 600 mg/d preserves bone mineral density in postmenopausal women.<sup>10</sup> Available data suggest the effect may be more pronounced in trabecular (e.g. vertebral) bone than cortical (e.g. hip) bone in a fashion similar to conventional estrogen. No studies have been conducted with outcomes such as fracture incidence. Additional data are needed to draw conclusions about the potential of isoflavones to prevent osteoporosis.

### Many Unanswered Questions Remain

1) What is the long-term safety of isoflavones and are they safe in women with contraindications to conventional estrogen replacement? 2) Is there a risk of causing endometrial hyperplasia with isoflavones as there is with unopposed estrogen? 3) What is the relationship between isoflavones and estrogen-dependent malignancies such as breast cancer? 4) What is the therapeutic dose? 5) Are benefits due to the isoflavone content or other components of whole soy foods and what are the safety and benefit differences among soy foods and soy supplements? 6) Is there a role for isoflavones in the prevention of CHD or osteoporosis and how does this compare to conventional estrogen replacement?

### Selecting Among Various Soy Products

Patients should be educated that differences may exist among phytoestrogens and soy-products in the form of tablets, powders and drinks. They need to read labels carefully. "Soy-protein concentrate", commonly found in vegetarian and soy burgers, contains negligible amounts of isoflavones, whereas in "soy-protein isolate or ISP" the isoflavone content is higher. Products containing the latter are preferred. Many soy milk products contain negligible amounts of calcium. Additionally, limited data suggest that absorption of calcium from fortified soy milk may be up to 75% less than that from cow's milk. To achieve the standard 300 mg of calcium per serving, patients should select fortified soy milk products containing 500 mg of calcium per serving.<sup>11</sup> If selecting a supplement in tablet or liquid form, caution patients that product ingredients are not subject to regulation and may not be consistent or comparable to agents used in clinical trials.



### Conclusion

The available literature regarding soy and isoflavones is inconsistent and limited by small samples, differences among samples, and short study durations. The majority of data do not support a significant benefit for the use of phytoestrogens or isoflavones to decrease hot flashes. Preliminary data suggest that isoflavones confer beneficial effects on serum lipids and bone metabolism. However, the data are inconclusive on cardiovascular and fracture outcomes. Although the products evaluated in clinical trials were well-tolerated, there is a significant lack of long-term safety data, particularly on breast and other female cancers. This is of particular concern in women who have contraindications to conventional estrogen. In such women, precautions should be observed until data prove otherwise.

**Article Reviewer:** Lisa Dodson, M.D., Assistant Professor, OHSU Department of Family Medicine

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## Treating PMS: A Review of Current Strategies

By: **Ann Hamer, Pharm.D.**

**P**remenstrual syndrome (PMS) is a condition characterized by physical and emotional symptoms occurring 7 to 10 days prior to menstruation, and disappearing a few hours after the onset of menstrual flow. PMS is relatively common, affecting as many as 85% of menstruating women. Approximately 2-10% of these women may be classified as suffering from premenstrual dysphoric disorder (PMDD); a more severe form of PMS characterized by impairment of daily functioning. Common symptoms of PMS include breast tenderness, bloating, muscle pain, depression, anxiety, lethargy, irritability, and changes in appetite, concentration and sleep. A diagnosis of PMDD requires that at least five symptoms be present (confirmed by daily rating scales during two consecutive cycles), with at least one being a mood symptom.<sup>1</sup>



While the true pathophysiology of PMS is yet to be determined, there is significant evidence to suggest an interaction between sex hormones and neurotransmitters, specifically serotonin. With the recent addition of PMDD to the list of FDA-approved indications for fluoxetine (Sarafem<sup>®</sup>, Prozac<sup>®</sup>), it is appropriate to review the efficacy of various PMDD treatment strategies.

### Nonpharmacological Interventions

Methods of nonpharmacological intervention consist of changes in exercise, diet and sleep regimens. Suggested modifications include:

increasing aerobic activity (increases endorphin levels, reduces fluid retention), increasing consumption of carbohydrate-rich foods (improves mood and alleviates food cravings), reducing salt intake (minimizes bloating, weight gain, and breast tenderness), restricting caffeine intake (reduces irritability and insomnia) and maintaining a regular sleep schedule (minimizes insomnia). Small studies of aerobic activity and consumption of carbohydrate-rich, protein-poor meals have shown moderate efficacy.<sup>2</sup>

### Pharmacological Interventions

It should be noted that, in general, studies of pharmacological interventions for PMS are limited by small numbers and a large placebo effect.

#### Dietary Supplements

Serum levels of calcium and magnesium have both been shown to fluctuate with the menstrual cycle, with troughs occurring during the luteal phase.<sup>3</sup> Both minerals have demonstrated moderate efficacy in the reduction of physical (fluid retention, headache and menstrual pain) and mood symptoms associated with PMS. Doses of 1000-1500 mg/day calcium daily and 200-400 mg/day magnesium, daily or during luteal phase only, have been recommended. The use of vitamin A, vitamin E, vitamin B6, evening primrose oil, or potassium have not proven to be effective.<sup>4</sup>

#### Non-Steroidal Anti-Inflammatory Drugs

NSAIDs have known benefit in the treatment of dysmenorrhea. Benefit may also be seen in the treatment of PMS when agents are started approximately one week prior to menses onset. Agents within this class have been shown to reduce headache, pain, tension, fatigue, and mood swings compared to placebo.<sup>5</sup> Studies have been done using standard dosing of ibuprofen and naproxen, but other NSAIDs would be expected to work as well.

#### Diuretics

Studies evaluating the effectiveness of diuretics have conflicting results. Women most likely to respond are those who suffer from weight gain as a predominant symptom of PMS. Spironolactone may be beneficial in the treatment of PMS, and is typically dosed 100 mg/day during the luteal phase or daily throughout the cycle. Spironolactone's demonstrated effects include the reduction of bloating, breast tenderness, irritability and food cravings.

#### Hormonal Suppression

Oral contraceptives (OCs) are often touted for their ability to reduce the symptoms of PMS. Although they provide a reasonable option for the reduction of physical symptoms, controlled studies have failed to prove their benefit in the reduction of mood symptoms.<sup>2</sup> In fact, some patients may experience a worsening of mood symptoms while on OCs. Gonadotropin-releasing hormone (GnRH) agonists (i.e. leuprolide and goserelin), while possibly effective in some patients, are both costly and associated with troublesome side effects, including the induction of menopause.

#### Antidepressants

Serotonin has become increasingly acknowledged as important in the pathogenesis of PMS. While fluoxetine is the only SSRI with a PMDD indication (marketed as Sarafem<sup>®</sup>), other SSRIs, including citalopram, sertraline, and paroxetine, have been studied for the same purpose. Each has demonstrated superiority to placebo in controlled trials of patients with severe PMS (meeting criteria for PMDD).<sup>6</sup> Patients on SSRI therapy typically notice improvement in psychosocial functioning by the second menstrual cycle of treatment. It should be noted that patients may not require daily therapy. In studies comparing the use of intermittent (given during luteal phase only) versus daily SSRI therapy, intermittent therapy appears to be equally, if not more effective than continuous therapy.<sup>7</sup> However, SSRIs are not innocuous, and are associated with considerable adverse effects including agitation, insomnia, GI upset, headache and sexual dysfunction. Optimal dosing, as well as long-term side effects of these agents are yet to be determined.

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### Conclusion

PMS or PMDD symptoms vary in type and severity from woman to woman. Treatment should be based on symptom severity, patient preference, adverse effect profile, as well as cost. No definitive therapy exists for the treatment of PMS. Reasonable first-line interventions include lifestyle modifications and calcium supplementation. The treatment of PMS and PMDD are not covered by the Oregon Health Plan.

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## Alosetron (Lotronex®): A New Treatment for Irritable Bowel Syndrome

- continued from page 1

For diarrhea-predominant IBS, loperamide has been shown to improve stool consistency, decrease stool frequency, and reduce pain.<sup>1</sup> Antispasmodic agents such as antimuscarinics (i.e. belladonna alkaloids, hyoscyamine) and smooth muscle relaxants (dicyclomine) have been used in the treatment of IBS associated with abdominal pain and spasm. They can be used on an as needed basis.<sup>5</sup> Tricyclic antidepressants (TCAs) are useful, particularly for patients with more severe or refractory symptoms, impaired daily function or associated depression. In addition to their antidepressant effects, TCAs also exert analgesic and anticholinergic effects.<sup>2</sup> Effectiveness is established in patients with diarrhea-predominant IBS, however they may worsen constipation.<sup>7</sup> Secondary amine TCAs such as desipramine have an improved side effect profile over older TCAs like amitriptyline, and may be preferred for many patients.

### Alosetron

Alosetron (Lotronex®) has recently been approved for the treatment of irritable bowel syndrome in women whose predominant symptom is diarrhea. Alosetron is a selective 5-HT<sub>3</sub> antagonist. Serotonin (5-HT) released in the gut wall initiates a process that increases secretory and peristaltic reflexes and also sends signals to the brain causing sensations of nausea, bloating or pain. Alosetron decreases sensitivity to, but not perception of colonic distension. It also enhances jejunal sodium and water absorption and slows colonic transit.<sup>7</sup>

### 7 Effectiveness

Two phase III clinical trials compared alosetron 1mg bid with placebo over a 12-week period in 1273 non-constipated women with IBS.<sup>8</sup> Criteria defining a response were fairly liberal in these trials. Responders were defined as patients with "adequate relief" of IBS pain and discomfort for at least 2 weeks in each 4 week study period. The 2 trials found 41% and 41% response to alosetron compared to 29% and 26% on placebo. Alosetron patients reported a statistically significant reduction in urgency, stool frequency, and improved stool consistency compared to patients on

placebo.<sup>8</sup> Onset of effect was detected between 1 and 4 weeks of treatment. Earlier phase II studies demonstrated that alosetron was not effective in men.

### 7 Adverse Effects

During clinical trials, the most common adverse effect seen with alosetron was constipation, reported in 28% of patients (placebo rate 5%). Results from long-term studies (6 and 12 months) involving approximately 600 patients revealed a 31% incidence of constipation and a dropout rate of approximately 40%.<sup>8</sup> The most serious adverse event reported in clinical trials was 4 cases of ischemic colitis (reduced blood flow to the intestines) which resolved after discontinuation of treatment; a clear cause and effect could not be established.<sup>8</sup>

Since the approval and marketing of alosetron in February 2000, the FDA has received reports of serious adverse events with its use, some leading to hospitalization, surgery and death.<sup>9</sup> As of October 2000, the FDA had recorded 21 cases of severe constipation, with 2 deaths, and 49 cases of ischemic colitis, with 3 deaths.<sup>10</sup> The FDA is currently evaluating these reports and its options for alosetron, from convening an advisory committee meeting or changing labeling, to withdrawal of the drug from the market.<sup>11</sup> It is now evident that there is a clear link between the use of alosetron and ischemic colitis, with an estimated occurrence of 1 in 700 patients.<sup>9</sup> Prompt discontinuation of alosetron may lead to a resolution of the condition, but possible consequences of ischemic colitis include life-threatening hemorrhage, necrosis, bowel perforation and death.<sup>9</sup> Patients prescribed alosetron should know the early symptoms of ischemic colitis: new or worsening abdominal pain, bloody diarrhea or blood in the stool.

### 7 Dosage and Cost

The recommended dose of alosetron is 1 mg twice daily. Higher doses do not improve the therapeutic response. The average wholesale cost of Lotronex® is \$2.38 per tablet. Table 1 compares the monthly cost of drugs commonly prescribed for IBS.

### Conclusion

Alosetron offers an expensive new approach for the management of IBS, with modest effectiveness. Once the placebo response is factored in, only 12% to 15% of patients treated show a true response. However, the greatest concern with alosetron is the serious adverse effects that have been reported. While IBS can negatively impact quality of life, it does not result in serious complications or increase mortality. Clinicians and patients must carefully weigh the potential risks and benefits of alosetron therapy.

Table 1

Cost of Common Drug Therapies for IBS			
Generic	Brand	Usual Adult Dosage <sup>3</sup>	Avg. OMAP Cost/Month
calcium polycarbophil	Konsyl Fiber	1-6 g/day polycarbophil in divided doses	\$6.49
loperamide	Imodium	2.4 mg up to QID prn	\$11.90
amitriptyline	Elavil, Endep	10-100 mg QHS	\$12.61
desipramine	Norpramin	50-150 mg QHS	\$12.61
dicyclomine	Bentyl	10-20 mg TID-QID prn	\$19.25
alosetron	Lotronex	1 mg BID	\$110.94

Article Reviewer: Sandra B. Earle, Pharm.D., BCPS, OSU College of Pharmacy

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- **Alosetron** continued from page 6

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## Influenza Vaccination Programs Delayed

By: **Lori Syed, Pharm.D.**

This year's influenza vaccine will contain the following strains: A/Panama, A/New Caledonia, and B/Yamanashi. Vaccination supplies for this influenza season have been delayed due to two manufacturing issues.<sup>1</sup> First, the yield for this year's influenza vaccine appears to be lower than expected. Manufacturers have reported that the influenza A (H3N2) strain, or "A/Panama" has not grown nearly as well as the strain that was used in last year's vaccine. This unfortunate situation has been confounded by the fact that the FDA took regulatory action against two of the four companies licensed to manufacture influenza vaccine in this country. Both of these companies have stepped up efforts to correct the situation.



The influenza vaccine is recommended for those who are at increased risk of developing complications due to influenza. These include:

- persons who are 65 years old and older
- residents of nursing homes or other long-term care facilities
- adults and children aged 6 months or older who have chronic pulmonary or cardiovascular conditions, such as asthma
- adults or children 6 years of age or older who have required medical follow-up or hospitalization during the past year for a chronic condition such as diabetes, kidney dysfunction, blood disorders, or immune system deficiencies such as HIV, or immunosuppression from chemotherapy or radiation therapy
- children and teenagers (aged 6 months to 18 years) who are receiving long-term aspirin therapy and who are at increased risk of developing Reye's Syndrome secondary to influenza infections

- pregnant women who will be in their second or third trimester during the influenza season;
- healthcare workers, caregivers or any other close contacts of the above high-risk individuals (including children aged 6 months and older) who may transmit influenza virus

In April 2000, the CDC and the Advisory Committee on Immunization Practices (ACIP) issued new influenza vaccination guidelines.<sup>2</sup> In these guidelines, ACIP increased its target groups to include all persons between 50-64 years old. The intention of this was to encompass greater participation in this age group and to provide greater guarantees that those individuals with high-risk conditions would be vaccinated.

In addition, the CDC and ACIP offered the following points to remember:

- Influenza vaccinations administered after mid-November can still offer protection. While past recommendations have suggested that vaccinations take place from October to mid-November, this was only done to balance the period of protection as much as possible. Due to this year's delay many mass vaccination campaigns will be scheduled well into December. It is important to remember that it takes about two weeks for full immunity to develop, and protection can last anywhere from about 6 months to a year.
- There are **no new recommendations** for the use of influenza antiviral drugs. The newer drugs, zanamivir (Relenza<sup>®</sup>) and oseltamivir (Tamiflu<sup>®</sup>) can limit the severity and duration of types A and B influenza. They have **not been approved** for the prevention of influenza. In the event of an influenza vaccine shortage, the CDC and ACIP do not endorse the routine, widespread use of any influenza antiviral medication for chemoprophylaxis as they are untested for this, are expensive and could place large numbers of people at risk for experiencing adverse drug events.

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## Address Changes:

Oregon Medicaid providers and pharmacies can provide OMAP with change of address information by fax at: (503) 945-6873 or by calling: 1-800-422-5047.

We hope you found this issue of the Oregon Drug Use Review Board Newsletter useful as well as thought-provoking and interesting. We welcome your questions, concerns, comments or ideas regarding the newsletter. Address correspondence to the managing editor:

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