

# WYOMING DRUG UTILIZATION REVIEW



Edited by  
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## Two New Drugs for the Treatment of Painful Diabetic Peripheral Neuropathy

*Kendra Grande, RPh*

It is estimated that painful diabetic peripheral neuropathy affects at least 24% of the US diabetic population or around 3 million people.<sup>1</sup> Two drugs have now been approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy. These are the first drugs with this indication in the U.S. The drugs are duloxetine (Cymbalta®) and pregabalin (Lyrica®).

Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor. Its exact mechanism in treating peripheral neuropathy is unknown. It is dosed orally at 60mg daily. No dosage adjustment is required in the elderly but duloxetine should not be administered to patients with hepatic impairment or end stage renal disease requiring dialysis or with a CrCl <30 ml/min. Start patients with mild renal disease at a lower starting dosage with a gradual increase.<sup>2</sup>

Two studies have been published on the efficacy of duloxetine in peripheral neuropathy. The first studied 20, 60 and 120mg duloxetine versus placebo in 457 patients for twelve weeks. The trial showed a 50% reduction in average 24-hour pain scores for 58% of patients in the 60mg group versus 30% of patients in the placebo group. Secondly, the 60mg group required less supplemental analgesics. While these findings were also true for the 120mg group, no additional clinical benefit was shown at the higher dose.<sup>3</sup>

The second twelve week trial compared duloxetine 60mg QD, 60mg BID or placebo in 348 patients with bilateral peripheral neuropathy due to diabetes. The primary outcome was the average 24-hour pain response rate. Results are shown in Table 1. The difference between the QD and BID dosing was not statistically significant.<sup>4</sup>

Side effects commonly seen with duloxetine include nausea, dizziness, somnolence and constipation. Side

effects are more common in the 120mg dosage. Do not coadminister duloxetine and thioridazine because of the risk of serious ventricular arrhythmias and sudden death.<sup>2</sup> In October 2005, Lilly issued a Dear Health Care Professional letter warning that duloxetine may increase serum transaminase levels, cause hepatotoxicity or mixed liver injury or cause cholestatic jaundice with minimal transaminase elevation. It is possible that alcohol and duloxetine may interact to cause liver disease. Avoid use in patients with substantial alcohol use as well as those with chronic liver disease.<sup>5</sup>

The other drug now approved for neuropathic pain associated with diabetic peripheral neuropathy is pregabalin. While the exact mechanism is unknown, pregabalin binds to the alpha<sub>2</sub>-delta site of voltage gated calcium channels in CNS tissue and reduces the release of excitatory neurotransmitters. Although it is a GABA derivative, it does not bind to GABA or benzodiazepine receptors. The starting dose of pregabalin for diabetic neuropathy is 50mg TID increased to 100mg TID in one week. There is no evidence that higher doses are more effective and may increase the risk of dose-dependent adverse effects. Pregabalin is renally eliminated and doses must be adjusted in renal impairment. A dosing table based on creatinine clearance is located in the prescribing information.<sup>6</sup> Pregabalin is a schedule V medication because some patients experienced euphoria in clinical trials.<sup>7</sup>

Three complete studies have been published on pregabalin in painful diabetic neuropathy. The first was a 5 week trial of 338 patients comparing pregabalin 75mg daily, 300mg daily, 600mg daily or placebo. A ≥50% reduction in pain score was seen in 46% (300mg), 48% (600mg) and 18% (placebo). The 75mg percentage was not provided.<sup>8</sup>

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Reduction in Avg 24-hour Pain Rate	Duloxetine 60mg QD	Duloxetine 60mg BID	Placebo
50%	50%	39%	30%
75%	20%	22%	11%
100%	5%	8%	4%

Table 1: Percentage of patients who achieved the reduction in average 24-hour pain rate on duloxetine<sup>4</sup>

## Atypical Antipsychotic Risks in the Elderly

Scott Johnston, MD

The use of an atypical antipsychotic in the elderly for dementia-related psychosis places the patient at an increased risk of death. The cause of death varied but was primarily from cardiovascular causes, including heart failure and sudden death, or infectious causes such as pneumonia. This increased death rate was seen in studies with aripiprazole (Abilify®), olanzapine (Zyprexa®), quetiapine (Seroquel®), and risperidone (Risperdal®). However, other drugs in the class may also place the patient at increased risk and the entire class is included in this warning.<sup>1</sup> The mortality from analyses of 17 placebo-controlled studies was 4.5% versus 2.6% in the placebo group.<sup>2</sup>

The mechanism of the increased mortality is not yet clear. Theories include thrombogenic mechanisms, hypotensive episodes and oversedation leading to aspiration pneumonia.<sup>1</sup> It does not appear to be dose-related and could not be conclusively tied to a concurrent medication. Some concurrent medications taken by patients in olanzap-

ine studies were benzodiazepines, aspirin, diuretics and narcotics. Potential risk factors that may predispose patients to an increased risk of death include age >80 years, sedation, concomitant use of benzodiazepines and the presence of pulmonary conditions.<sup>3</sup>

The atypical antipsychotics are not approved for the treatment of dementia-related psychosis in any population; however, they have been widely used for this indication. Controlled-trial evidence for this indication is limited.<sup>1</sup>

FDA is currently reviewing data for the typical antipsychotics also. Preliminary data suggest there is a possibility that this warning will be expanded to include that class also.<sup>2</sup>

### References

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The second trial was an 8 week trial of 146 patients comparing placebo to pregabalin 300mg daily. 40% of the pregabalin group achieved a  $\geq 50\%$  reduction in mean pain score versus 14.5% of the placebo group.<sup>9</sup>

The third 8 week trial compared pregabalin 150mg or 600mg with placebo. Only the 600mg group achieved a statistically significant reduction of baseline pain versus placebo.<sup>10</sup>

The most common adverse events with pregabalin are dizziness, somnolence and peripheral edema. These side effects appear to be dose-dependent. Peripheral edema and weight gain are more common in patients taking both pregabalin and a thiazolidinedione such as rosiglitazone or pioglitazone. Pregabalin should be used with caution in Class III or IV congestive heart failure patients. Pregabalin may increase creatine kinase. Patients should be monitored for markedly elevated creatine kinase levels or myopathy.<sup>6</sup>

No direct comparisons of duloxetine or pregabalin with any other drug for diabetic peripheral neuropathy are available. Because all the available trials are of short duration, the long-term efficacy of duloxetine and pregabalin in painful diabetic neuropathy is still unclear.

Complete guidelines for treatment of painful diabetic neuropathies have not yet been issued since the approval of duloxetine and pregabalin. Begin treatment of diabetic neuropathy by excluding nondiabetic causes and then stabilizing glycemic control. Observational studies suggest that

neuropathic symptoms improve both with increased blood glucose control and by avoidance of extreme fluctuations in blood glucose levels. Pharmaceutical agents are often required to treat neuropathic symptoms after these initial steps.<sup>11</sup> A technical review of neuropathies and older agents is available in *Diabetes Care* 2004;27:1458-1486. Unfortunately, duloxetine and pregabalin were not available for inclusion in that review.

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# Selective Serotonin Reuptake Inhibitors (SSRIs) and Bleeding Risk

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The use of selective antidepressants, such as SSRIs, has increased significantly in the past few years. This phenomenon may be due to the reduced incidence of adverse effects and low toxicity associated with SSRIs. Evidence has shown an increase in the risk of gastrointestinal (GI) bleeding associated with the use of SSRIs.<sup>1</sup>

Serotonin promotes platelet aggregation. SSRIs decrease the uptake of serotonin from the blood by platelets leading to decreased aggregation and clotting activity and an increased bleeding risk.<sup>2</sup> The risk of bleeding has been shown, in a retrospective cohort study, to increase with concomitant use of NSAIDs, acetylsalicylic acid, glucocorticoids, anticoagulants, H2 blockers, and PPIs; increased age, particularly those patients over 80 years of age; a history of previous gastrointestinal bleeding; and increased degree of serotonin reuptake inhibition.<sup>3</sup> SSRIs that exhibit a high degree of serotonin inhibition include fluoxetine (Prozac), sertraline (Zoloft), clomipramine (Anafranil), and paroxetine (Paxil), and have been shown to double the risk of GI bleeding. Other SSRIs, such as citalopram (Celexa) and fluvoxamine (Luvox), produce a lower degree of inhibition and are associated with a lower risk of abnormal bleeding.<sup>4</sup>

Drug interactions need to be considered when prescribing an SSRI. Fluoxetine is a CYP2C9 substrate, and levels of this drug may be increased when taken in combination with a CYP2C9 inhibitor, such as fluconazole, lovastatin and amiodarone, among others. Fluvoxamine, paroxetine and sertraline are CYP2C9 inhibitors, and when taken in combination with CYP2C9 substrates, such as warfarin, may increase the levels of those other medications. When a patient is on one of these SSRIs, they may experience drug interactions that can increase their risk of a GI bleed. Combinations such as this should be avoided if possible. If these therapies are necessary,

patients should be advised to report any bruising, black tarry stools, blood in urine or stools, or petechiae.<sup>4</sup>

There have been few studies suggesting beneficial effects of SSRIs in patients with cardiovascular disease. Although the antiplatelet effect may seem desirable, unless the patient is experiencing both depression and cardiovascular disease, this should not prompt prescribers to use SSRIs for this purpose.<sup>5</sup> However, there is some evidence showing a possible additive antiplatelet effect when using SSRIs in combination with aspirin or clopidogrel (Plavix) in patients with cardiovascular disease.<sup>4</sup>

The risks and benefits need to be evaluated when using SSRIs for treatment of depression. If a patient is experiencing cardiovascular symptoms and depression, it may be beneficial to use an SSRI for the additive effect with aspirin or clopidogrel. The combination of these drugs, however, may increase a patient's risk of abnormal bleeding, especially if the patient is elderly, particularly over 80 years of age, or has a history of gastrointestinal bleeding. SSRIs with a lower degree of serotonin reuptake inhibition, such as citalopram (Celexa) or fluvoxamine (Luvox), have a lower incidence of gastrointestinal bleeding associated with their use, and may be a good option for patients refractory to other treatments for depression.

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## Wyoming Medicaid Pharmacy Program Preferred Drug List

Effective 12/1/2005

### Long Acting Opioids

Methadone  
Morphine Sulfate

### ACE Inhibitors

Captopril  
Enalapril  
Lisinopril

### Skeletal Muscle Relaxants

Cyclobenzaprine

### Calcium Channel Blockers

Verapamil  
Felodipine  
Diltiazem

### Statins

Lescol (fluvastatin)  
Pravachol (pravastatin)

### NSAIDs

Ibuprofen  
Naproxen

### Proton Pump Inhibitors

Prilosec OTC (omeprazole)  
Protonix (pantoprazole)

### 2nd Generation Antihistamines

Loratadine  
Loratadine-D

### Overactive Bladder Agents

Oxybutynin  
Detrol (tolterodine)

*Drugs listed are preferred and do not require prior authorization. All other medications within the classes are non-preferred and require prior authorization.  
For comparative cost information, please visit our website at [www.uwyo.edu/PDL](http://www.uwyo.edu/PDL).*

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