

# WYOMING DRUG UTILIZATION REVIEW

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Edited by  
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## Off-Label Use of Gabapentin (Neurontin)

Scott Johnston, M.D.

Gabapentin is structurally related to the neurotransmitter GABA. It is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Its mechanism of action is unknown. Side effects are dose dependent and are common when starting or increasing the dosage with both dizziness and somnolence occurring in about 20% of patients, diplopia and amblyopia in about 5%. Many patients will develop withdrawal symptoms that can be severe if gabapentin is abruptly stopped. The FDA has approved gabapentin for both post-herpetic neuralgia and as adjunctive therapy for partial seizures. Recently gabapentin has been used for mostly off-label indications. In Wyoming an approved indication could be identified in less than three percent of MEDICAID patients. Most of the randomized placebo controlled trials (RCT's) have failed to show any benefit of gabapentin for these off-label uses. I attempted to identify all RCT's by contacting the manufacturer and through a MEDLINE search. I have summarized the data below.

**Peripheral neuropathy:** There is fair evidence of the utility of the medication in some studies<sup>1,2</sup>, but those studies only decrease the pain by 0.5 points over placebo on a 11 point pain scale (statistically significant but I doubt the clinical significance of 0.5 point decrease on a pain scale). One study revealed no benefit over placebo<sup>3</sup>. A recent Cochran database review of anti-seizure medication use for neuropathic pain concluded that carbamazepine worked better and had fewer side effects<sup>4</sup>. Another study showed amitriptyline to be as effective as gabapentin<sup>5</sup>.

**Back pain:** There is evidence of no benefit over placebo<sup>6</sup>. One poorly designed randomized placebo controlled study that showed a benefit (0.5 points on a 11 point scale) in low back pain but not the associated leg pain<sup>7</sup>. A retrospective chart review revealed no change in low back pain with gabapentin<sup>8</sup>. One randomized open-label study of gabapentin versus imipramine suggested the two medications worked about the same for lower back pain<sup>9</sup>.

**Bipolar, depressive affective, schizo-affective disorders:** The companies own study showed placebo better than gabapentin<sup>10</sup>. Placebo controlled studies have failed to show any benefit over placebo<sup>11, 12</sup>.

**Panic/anxiety disorders:** A randomized placebo-controlled trial showed no difference over placebo<sup>13</sup>.

**Seizure as a single agent:** The manufacturer failed to show a benefit over placebo as a single agent and was refused that indication by the FDA.

**Multiple sclerosis:** One good placebo controlled trial showing a benefit in reduction of the pain from spasticity in MS patients<sup>14</sup>.

**Headache:** The American Academy of Neurology evidence-based guidelines for the treatment of headache rates amitriptyline, divalproex sodium, timolol, and propranolol higher than gabapentin and rates several beta-blockers, several NSAIDs, fluoxetine, feverfew, magnesium, and B-12 on the same level as gabapentin<sup>15</sup>. Two placebo controlled studies showed some efficacy when the study used a modified intention to treat population but no efficacy when the study used an efficacy evaluable patient population<sup>16, 17</sup>. Two placebo controlled studies showed some benefit over placebo<sup>18, 19</sup>. Divalproex sodium was less expensive and just as effective<sup>20, 21</sup>. Two open label studies revealed some efficacy.

**Hot Flashes:** A placebo controlled trial revealed some benefit over placebo<sup>22</sup>, and one small open-label trial showed some benefit over placebo<sup>23</sup>.

### Conclusions on the use of gabapentin:

**Effective:** partial seizures as adjunctive therapy, post-herpetic neuralgia, and spasticity.

**Effective but other medications work better:** headache.

**Possibly effective but other medications work better:** peripheral neuropathy, hot flushes.

**Ineffective:** back pain.

**No evidence of benefit and evidence of harm:** psychiatric diagnosis.

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# GERD and the Use of PPIs

Whitney Buckley, Pharm.D.

There are currently two different strategies for the treatment of GERD: step-up and step down therapy (Figure 1). Step-up therapy involves three main phases. Phase I involves the treatment of mild, intermittent heartburn<sup>1</sup> and should be continued for at least four weeks.<sup>2</sup> Treatment involves lifestyle changes, which should be started initially and continued throughout the course of treatment, and OTC antacids. OTC antacids have a rapid onset of action; however, relief only lasts about 60 minutes. H<sub>2</sub>RAs may take up to 90 minutes to reach the full effect and the relief lasts for about nine hours.<sup>2</sup>

While lifestyle changes may help to improve some of the symptoms, they are not effective enough to be considered for therapy alone without the concomitant use of medications.<sup>3</sup> A low dose, 1/2 of the standard adult dose, of an OTC H<sub>2</sub>RA may be added and taken up to twice daily if needed.<sup>1</sup> Up to 67% of patients who initially require and have symptom control with H<sub>2</sub>RAs and lifestyle modifications will be controlled with the intermittent use of H<sub>2</sub>RAs for maintenance therapy. It is appropriate to begin treatment at Phase II if these modifications have already been tried by the patient.<sup>2</sup>

In Phase II, lifestyle modifications are continued and standard doses of H<sub>2</sub>RAs should be tried for six to twelve weeks. Mild GERD can be managed effectively with H<sub>2</sub>RAs; however, patients exhibiting more moderate to severe symptoms should begin treatment with standard dose PPIs or double dose H<sub>2</sub>RAs for at least eight to twelve weeks. PPIs are the most effective treatment for those patients with atypical symptoms, complicated symptoms, or erosive disease.<sup>1</sup>

Symptom relief and control achieved with any of the recommended agents should lead to maintenance therapy with the effective agent on an as-needed basis for the treatment of symptoms in the future. For symptoms that reoccur frequently, maintenance therapy should be considered with the use of the lowest effective dose. Many patients will require standard doses of H<sub>2</sub>RAs or PPIs for maintenance therapy.<sup>1</sup> For those patients who do not get symptom relief during phase II with standard doses of PPIs or double doses of H<sub>2</sub>RAs, it is important to perform an endoscopy to evaluate the mucosa of the esophagus if the procedure has not already been performed.<sup>2</sup>

The step-down approach is based on the belief that the most clinically effective initial therapy is also the most cost effective. This may be due to the increase in physician visits and use of other medical resources associated with beginning treatment with less effective forms of therapy such as lifestyle modifications and H<sub>2</sub>RAs.<sup>3</sup> There have also

been numerous clinical trials to demonstrate a marked increase in healing rates and symptom relief with PPIs compared with H<sub>2</sub>RAs.<sup>4</sup> Some of the advantages associated with step-down treatment include maximum symptom relief that is seen more rapidly than with lifestyle modifications and OTC treatments, fewer treatment failures, and fewer physician consults.<sup>5</sup>

One of the main arguments for the use of PPIs at the beginning of therapy is to gain complete relief of symptoms as soon as possible. The control, or complete relief, of heartburn is also associated with the healing of the esophagus and is seen more often when using PPIs.<sup>3</sup> The initiation of therapy begins with a full dose PPI for eight to twelve weeks. After the initial course of treatment, the medication may be reduced to a half dose PPI or further down to a standard dose H<sub>2</sub>RA (Fig. 1). The goal is to provide complete healing of the esophagus and then to decrease the amount of medication being taken to the most clinically and cost effective dose for maintenance therapy. Five to ten percent of patients suffer from severe esophagitis. For those patients any medical treatment other than a full dose PPI is unlikely to prevent the relapse of esophagitis or strictures.<sup>4</sup>

There are currently two recommended methods for maintenance therapy in GERD patients: intermittent and on-demand therapy.<sup>5</sup> Intermittent therapy involves the use of a PPI in blocks of two to four weeks for those patients with clear-cut relapses and remissions. On-demand therapy with a PPI should be initiated when symptoms reappear and should continue until the patient has been symptom free for at least 24 hours. It is also recommended that all patients undergo a trial withdrawal of long-term therapy to reassess the need for continuous drug treatment.<sup>3,5</sup> Because the majority of the PPIs have been studied for up to twelve months by the manufacturers<sup>6</sup>, trial withdrawals or step-down therapy may be initiated on an annual basis.

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# NSAID-Induced Gastroduodenal Ulcers

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NSAIDs are among the most frequently prescribed agents in North America and Europe.<sup>1</sup> Symptoms of dyspepsia, nausea, and abdominal pain are frequently associated with the use of NSAIDs; however, the severity of symptoms do not necessarily correlate with the potential severity of ulcer complications such as bleeding. There are several factors that have been associated with the development of upper gastrointestinal (GI) toxicity including age (>65 years old), history of peptic ulcer disease (PUD), co-morbidities, the type and number of NSAIDs being used, and combining the use of NSAIDs and corticosteroids.<sup>2</sup> Patients taking NSAIDs who experience dyspeptic symptoms should discontinue the medication if possible. If discontinuation is not possible, patients should be treated with 12 weeks of an H<sub>2</sub>RA at the usual adult dose or 8 weeks with a PPI at the usual adult dose (Figure 1).<sup>3</sup>

There have been numerous studies conducted to compare the efficacy of medications in the prevention and treatment of NSAID-induced ulcers. Misoprostol, 400 mcg/day and 800 mcg/day, is the only prophylactic agent currently documented to reduce the complications associated with NSAID-induced ulcers. A dose of 800 mcg of misoprostol daily was associated with a 40 % risk reduction and appeared to be superior to the 400 mcg/day dose in the prevention of gastric ulcers. The higher dose was also associated with higher rate of adverse events such as nausea, diarrhea, and abdominal pain.<sup>2</sup>

Both H<sub>2</sub>RAs and PPIs have been used in the treatment of NSAID-induced ulcers. Regular adult doses of H<sub>2</sub>RAs are effective in the reduction of duodenal ulcers but have little effect on gastric ulcers.

Because standard doses of H<sub>2</sub>RAs are effective in reducing the symptoms associated with upper GI toxicity but do not prevent serious complications, they are not recommended for the prevention of NSAID-related toxicities. Double doses of H<sub>2</sub>RAs and standard doses of PPIs were as effective as and better tolerated than misoprostol for the reduction of NSAID related gastric and duodenal ulcers.<sup>2</sup>

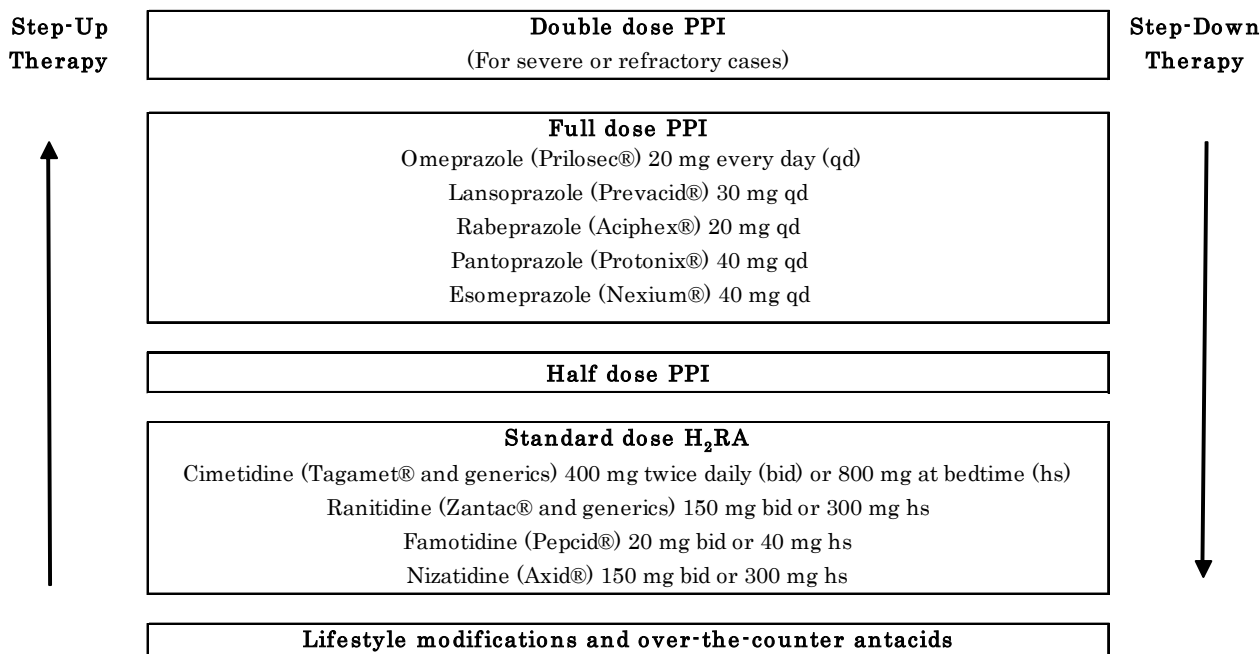
Patients with a history of PUD who require treatment with NSAIDs may benefit from a combination of a non-selective NSAID with a PPI. At this time, the combination is not known to be superior or inferior to treatment with cyclooxygenase-2 (COX-2) inhibitors alone.<sup>3</sup>

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**Figure 1**



Modified from Dent J, Brun J, Fendrick AM, Fennerty MB, et al. An evidence-based appraisal of reflux disease management – The Genval workshop report. *Gut* 1999; 44 (Suppl2): S1–S16.

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