

Wyoming Drug Utilization Review

Histamine-2 Receptor Antagonists and Proton Pump Inhibitors

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Today we have a number of agents in our arsenal to combat gastrointestinal disorders. However, two families of medications continue to be our go-to weapons. With their reliable pharmacokinetics and good safety profiles, histamine₂ receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs) are first and second line agents for a number of GI hypersecretory disorders. This article will discuss the pharmacology of H₂RAs and PPIs in the treatment of acid-related disorders, and give a brief

review of H₂RAs and PPI claims from Wyoming State Medicaid data.

H₂RAs

Cimetidine was the first H₂RA released in the U.S. in 1977.^{1,2} Currently all four H₂RAs are available in both prescription and lower-strength OTC products (Cimetidine-Tagamet[®], ranitidine- Zantac[®], famotidine-Pepcid[®], nizatidine-Axid[®]).³

The H₂RAs competitively inhibit histamine₂ receptors of parietal cells decreasing gastric acid secretion, gastric volume, and hydrogen ion concentration. Major indications include peptic ulcer disease (PUD), uncomplicated gastroesophageal reflux disease (GERD), and prevention of stress ulcers.¹⁻³

Side effects usually are minor and include diarrhea, headache, drowsiness, fatigue, muscular pain, and constipation.^{1,3} Additionally, cimetidine may cause gynecomastia in males, loss of libido and impotence, all

of which are reversible upon discontinuation.⁴ The most important safety concern regarding the H₂RA class is CYP-450 inhibition by cimetidine, and the potential drug interactions that ensue.¹⁻³

H₂RAs are dosed once to twice daily and require no dose adjustment for hepatic dysfunction. However if the patient has renal insufficiency, doses typically need to be reduced by 50%.¹⁻³

PPIs

Introduced in the 1980s, PPIs are the most potent inhibitors of gastric acid secretion.¹ Available PPIs include: omeprazole-Prilosec[®], Rapinex[®], Zegerid[®]; esomeprazole-Nexium[®]; lansoprazole-Prevacid[®]; rabeprazole-Aciphex[®]; pantoprazole-Protonix[®].³ Omeprazole is also currently available OTC. The Preferred Drug List for Wyoming Medicaid includes Prilosec OTC[®], Protonix[®], and Prevacid[®] for children under the age of eight.

All PPIs are prodrugs requiring an acidic environment for activation before the medication can inhibit the proton pump (H-K-ATPase enzyme), located in parietal cells in the secretory canaliculus of the stomach. The active moiety concentrates up to 1000-fold higher in the canaliculus compared to the rest of the body, accounting for PPI's high potency and limited side effects.² Major indications include: PUD, GERD, Zollinger-Ellison syndrome, H. pylori infections, and stress ulcer prophylaxis and treatment.²

Side effects are typically mild including nausea, abdominal pain, constipation, flatulence and diarrhea.¹⁻³ While metabolized by the CYP-450 system, omeprazole and esomeprazole display inhibition of the 2C9 enzyme, leading to potential drug interactions.^{1,2,3,5} Pantoprazole, another PPI with CYP-450 inhibiting properties inhibits 2C9, causing potential drug interactions with bosentan, dapsone, fluoxetine, glimepiride, glipizide, losartan, montelukast, phenytoin, warfarin, and other 2C9 substrates.⁶

PPIs are most effective when the parietal cell is stimulated to secrete acid postprandially and after a prolonged fast. For this reason, administration before or with the first meal of the day is ideal. Steady-state is

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WY-DUR Board Meeting Update

The DUR Board met for its bimonthly business meeting on May 29, 2008. Highlights of this meeting include:

- The Board approved the following prior authorization criteria for insomnia medications:
 - Zolpidem (immediate release) and Lunesta are the preferred agents and will be approved without prior authorization.
 - Claims for Rozerem will be approved with a history of substance abuse.
 - Claims for other sleep agents will be approved following a 14 day trial of a preferred agent.
 - Dosing will be limited to 150% of the labeled maximum.
 - Utilization of multiple sleep agents will require prior authorization.

Upon implementation of these criteria, existing day supply limits will be removed for all sleep agents.

- At the request of a Cheyenne physician, the Board reviewed the policy for growth hormone utilization for clients over 18 years of age. All medications within the class will be approved for labeled indications with the exception of

fertility-related diagnoses which are exempt from coverage by federal regulation.

- A Casper physician requested exemption from the mandatory generic policy for Trileptal and Zonegran due to adverse effects his patients have experienced with conversion to generic with these agents. The Wyoming Epilepsy Association made public comment and requested that all anticonvulsants being used for seizure be exempt from the mandatory generic policy. The Board asked for data supporting this request. A final decision will be held until additional data can be provided. Until a decision is made, appeals for brand name anticonvulsants with multi-source generics will be approved for clients with a diagnosis of epilepsy who have a history of brand name use.

The next DUR Board meeting will be held July 17, 2008 in Cheyenne. Topics for discussion will include criteria for the therapeutic classes reviewed by the PDLAC on June 4, 2008 including Angiotensin II Receptor Blockers, Triptans, and Antiplatelets. An agenda will be posted approximately two weeks prior to the meeting.

Fibromyalgia Update

In November 2007, the DUR program and Medicaid's Disease Management Contractor, APS Healthcare, began a joint project regarding fibromyalgia. The DUR program sent education letters to 1053 providers while APS contacted members for case management.

APS contacted a total of 101 members identified through the claims system as having a fibromyalgia diagnosis. Of these, 59 reported that they did not have fibromyalgia. 41 clients were engaged in case management for fibromyalgia, and 15 who did not have fibromyalgia were engaged for other diagnoses.

Of the 41 members new to case management, the following comorbid diagnoses (#) were reported: sleep problems (34), depression (28), fatigue (22), headaches (14), cognitive deficits (5), mood disorder (3), diabetes (3), back pain (3), COPD (2), abdominal pain (2). Current medications included Lyrica, Flexeril, Neurontin,

Elavil, Trazodone, Cymbalta, Prozac, Zoloft, Ixel, Tylenol #3, and hydrocodone products. Some members were not taking any medications.

The Nurse Case Managers discussed the nonpharmacologic treatment options with the clients. Very few reported knowledge of the benefits of physical and occupational therapy, exercise or nutrition for relief of pain. Only eight members were doing any type of exercise.

After the initial education session, three members are now swimming, two attending yoga, eight members report an increase in general exercise and two are now attending physical therapy. In regards to nutrition, over 30% of engaged members are focusing on nutrition improvement. Most feel a slight improvement with diet modification.

2007 Education Letter Responses

The Wyoming Drug Utilization Review Program sent out 5 cycles of education alert letters to prescribers during 2007. Each prescriber who received an education alert letter was asked to complete and return a response form. In the response form, we ask the prescriber to classify the information in the letter as *useful*, *neutral*, or *not useful*.

The table shows the following information: the return rate for prescriber response forms for 2007, the percentage of returned provider response forms that fall into each of the 3 classifications (*useful*, *neutral*, and *not useful*), and the percentage of *no class*, which is assigned if the provider fails to classify the information in the alert letter. Return rates range from 53% to 74% and responses are coded as either *useful* or *neutral* by over 55% of the respondents.

The Wyoming Drug Utilization Review Board thanks all practitioners who return the response forms. Your feedback is invaluable to the program.

	Jan 2007	Mar 2007	May 2007	Sep 2007	Nov 2007
Return Rate	53.57	67.65	74.17	59.38	61.04
Useful	51.67	34.78	33.71	35.53	34.04
Neutral	10.00	21.74	21.35	23.68	23.40
Not Useful	15.00	20.29	8.99	17.11	23.40
No Class	23.33	23.19	35.96	23.68	19.15

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reached after five days of once-daily dosing, resulting in inhibition of 66% of the maximal acid output. The initial use of twice-daily dosing for the first 2-3 days may be beneficial in achieving a more rapid inhibition, with the second dose taken before the evening meal.^{1,2}

Simultaneous administration of PPIs with other antisecretory medications (H₂RA, prostaglandins, etc.) should be avoided. Nevertheless, if a patient experiences nocturnal breakthrough symptoms while taking a PPI, a H₂RA can be administered before bed, with the PPI taken before breakfast.¹

Over the past five years, Wyoming Medicaid has seen a trend in prescribing favoring PPIs over H₂RAs. While in 2003-2005 prescription counts for PPIs were steadily growing, prescription counts for H₂RAs were slowly decreasing. In 2006 the prescription count for both H₂RAs and PPIs dropped significantly by almost 50%, with 2007 prescription counts remaining roughly parallel to 2006 for the various H₂RA and PPI medications. The table shows prescription data for these 2 classes for Wyoming Medicaid for 2007.

In summary PPIs and H₂RAs are not only widely prescribed, but also frequently used as OTC products. With both in our arsenal, we can treat a wide variety of hypersecretory GI disorders, as well as provide the necessary counseling to patients so that they may receive the full benefit from their antisecretory treatment.

References

1. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology*. 2000;118:S9-S31.
2. Hoogerwerf WA, Pasricha PJ. Pharmacotherapy of gastric acidity, peptic ulcer and gastroesophageal reflux disease. In: Brunton LL, Parker KL, Buxton ILO, Blumenthal DK(editors). Goodman & Gilman's The Pharmacological Basics of Therapeutics, 11th Edition Online. New York (NY): McGraw-Hill; 2008. Available from: <http://www.accesspharmacy.com>. Accessed: March 26, 2008.
3. Facts and Comparisons 4.0 Online™. Facts & Comparisons 4.0 Online™ [database online]. Indy (IN): Wolters Kluwer Health, Inc.; 2008. Available at: www.online.factsandcomparisons.com. Accessed: March 25, 2008.
4. Spence RW, Celestin LR. Gynaecomastia associated with cimetidine. *Gut*. 1979;20(2):153-157.
5. Prilosec (omeprazole) capsule [prescribing information]. Wilmington (DE): AstraZeneca, April 2007.
6. Protonix (pantoprazole sodium) delayed-release tablets [prescribing information]. Philadelphia (PA): Wyeth Pharmaceuticals Inc., December 2007.

Drug	Rx Count 2007	Total Cost 2007	Percent Cost 2007
cimetidine	90	\$1,002	<1%
rabeprazole	144	\$26,098	2%
nizatidine	356	\$15,965	1%
omeprazole	584	\$33,592	3%
esomeprazole	851	\$164,042	12%
famotidine	1172	\$19,494	1%
lansoprazole	2307	\$282,854	22%
ranitidine	2404	\$97,160	7%
omeprazole Mg ⁺⁺	3291	\$102,872	8%
pantoprazole	4182	\$571,429	44%

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