The Pharmacologic Management of Gastroesophageal Reflux Disease

A collaborative effort of the
Veteran's Health Administration
Pharmacy Benefits Management
Strategic Healthcare Group (PBM)
and the Medical Advisory Panel (MAP)

This pocket card should be used to highlight the PBM-MAP treatment guideline on the pharmacologic management of gastroesophageal reflux disease developed as a joint venture with experts practicing at Veterans Affairs Medical Centers. The complete VHA PBM-MAP document can be found at www.vapbm.org.

This document should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. The ultimate judgement regarding the propriety of any course of conduct must be made by the clinician in light of individual patient situations.

Department of Veterans Affairs
Veterans Health Administration
Publication No. 98-0010
September 1998 (Pending Approval)
Updated March 2000

Considerations for the Pharmacologic Management of Gastroesophageal Reflux Disease (GERD)

- GERD is a common disorder; severity ranges from mild non-erosive disease to severe complicated disease (i.e., Barrett's metaplasia, erosive esophagitis, esophageal strictures, and extraesophageal complications).
- Goals of treatment are to relieve patient symptoms, heal esophagitis, manage or prevent complications, avoid recurrence.
- Treatment should be based upon patient symptomatology, although symptoms do not always reflect disease severity.
- Diagnostic evaluation is warranted in patients with atypical symptoms, at high risk for Barrett's metaplasia,have failed pharmacologic therapy, or have signs or symptoms of complicated disease. Esophagogastroduodenoscopy (EGD) is the best test to evaluate mucosal damage.
- Lifestyle modifications are recommended in all patients with GERD throughout therapy.
- Pharmacologic therapy should be considered in patients who do not adequately respond to lifestyle modifications or have moderate to severe symptoms or evidence of esophageal damage.

- Options for pharmacotherapy include an antacid (AA), histamine$_2$ receptor antagonist (H_2RA), or a proton pump inhibitor (PPI); refer to Tables 3 and 4 for appropriate selection and dosing. Prokinetic agents should be reserved for patients who fail other therapies due to their potential for serious and potentially life-threatening drug and disease interactions (refer to www.vapbm.org The Pharmacologic Management of GERD for precautions and contraindications); cisapride is restricted to use through the manufacturer's patient enrollment program.

- Surgical intervention may be necessary in a minority of patients and is based on individual patient considerations and preferences. A gastroenterologist should be consulted to help determine the appropriateness of antireflux surgery in patients with severe esophagitis, intractable symptoms, recurrent symptoms despite maintenance antisecretory therapy, or in patients requiring maintenance therapy with a PPI. Surgery may be the preferred therapy in these patients, especially if they are young and otherwise healthy.

Table 1. Symptoms and Potential Complications of GERD

Classification	Patient Presentation
Typical Symptoms	Heartburn, regurgitation, waterbrash
Extraesophageal Manifestations	Chronic cough, noncardiac chest pain, hoarseness, globus sensation, respiratory symptoms, dental disease
Complications of Advanced Disease	Difficulty swallowing (dysphagia), painful swallowing (odynophagia), esophageal stricture, Barrett's metaplasia, perforation, hemorrhage, anemia, weight loss

Table 2. Nonpharmacologic Measures to Reduce GERD Symptoms

Dietary	Decrease fat intake, reduce/eliminate intake of foods or beverages which exacerbate symptoms (e.g., alcohol, caffeinated beverages, peppermint/spearmint, chocolate, citrus, high fat content, milk, onions, garlic, spicy foods, tomato juices), consume meals of smaller volume, avoid recumbent position for 3 hours after a meal
Lifestyle	Elevate head of bed 6-8 inches, avoid tight clothing, weight reduction if appropriate, smoking cessation

Table 3. Pharmacotherapeutic Agents for GERD Management

Class	Antacid	H_2RA	PPI
Place in Therapy	Initial therapy: mild or infrequent reflux symptoms	Standard dose: inadequate response to diet/lifestyle modification, antacids, or nonprescription H_2RAs High dose: inadequate response to standard dose therapy, or as initial treatment for moderate to severe symptoms	Complicated GERD: ulcerative esophagitis, stricture, Barrett's esophagus, atypical symptoms; refractory to high dose H_2RAs

Table 4. Recommended Dosages of Medications Used in GERD/Reflux Esophagitis[a]

Drug[b]	Recommended Dosing (Oral)		Dose Adjustment in Renal/Hepatic Impairment		Comments
H_2RA	**Standard Dose**	**High Dose**	**CrCl**	**Dose**	
Cimetidine	400mg BID or 800mg QHS	400mg QID or 800mg BID	> 30ml/min 15-30ml/min < 15ml/min	800mg QHS 600mg QHS 300-400mg QHS	More frequent dosing results in greater symptomatic improvement and healing in patients with more severe disease. Recommended duration of therapy is 8 to 12 wks.
Ranitidine	150mg BID or 300mg QHS	150mg QID or 300mg BID	< 50ml/min	150mg QHS	
Proton Pump Inhibitor					
Lansoprazole	Treatment: 30mg QD x 8 wks. Maintenance: 15mg QD		Dosage adjustment should be considered in patients with severe hepatic disease		Patients with difficulty swallowing should be instructed that the capsule can be opened and sprinkled on applesauce or mixed with juice for administration in patients with an NG tube.

[a] Antacids: dose equivalent to 80mEq neutralizing capacity (most products, approximately 15ml to 30ml) administered QID (eg., after meals and at bedtime) for 2 to 4 weeks then as needed; sucralfate has also been used for the treatment of mild to moderate GERD

[b] National Formulary

Table 5. Drug Interactions With Cimetidine

Interacting Drugs With Cimetidine[a,b,c]	Effect
Warfarin[d], Benzodiazepines (diazepam, chlordiazepoxide, alprazolam and triazolam), ß-blockers (propranolol, metoprolol, labetalol, and pindolol), Calcium channel blockers (verapamil, diltiazem, nifedipine, nimodipine, nisoldipine and nitrendipine), Carbamazepine, Cisapride, Clozapine, Flecainide, Lidocaine, Meperidine, Nicotine, Sulfonylureas (glyburide, glipizide, tolbutamide), Paroxetine, Phenytoin, Praziquantel, Procainamide, Propafenone, Quinidine, Tacrine, Theophylline, Tricyclic antidepressants (desipramine, doxepin, imipramine, nortriptyline)	↑ serum levels of interacting drugs; cause potentiation of therapeutic effects and in some cases, symptoms of toxicity Monitor concurrent therapy with H_2RAs; draw serum levels of interacting drugs if appropriate; consider alternative to cimetidine if appropriate
Fluconazole, Ketoconazole, Itraconazole	↓ serum levels of interacting drugs

[a] Adapted from: Hansten PD, Horn JR. Drug interactions analysis and management. Vancouver:Applied Therapeutics;1997
[b] Adapted from: Hebel SK ed. Drug facts and comparisons, St. Louis, MO: Facts and Comparisons;1997
[c] More commonly cited drug interactions; this list is not wholly comprehensive
[d] Use combination only if benefit outweighs risk

Table 6. Drug Interactions With Lansoprazole or Omeprazole[a-d]

Precipitant Drug	Interacting Drugs	Effect
Omeprazole	Benzodiazepines	↓ clearance and ↑ half-life of diazepam[e]
Omeprazole	Phenytoin	↓ clearance and ↑ half-life of phenytoin[e]
Omeprazole	Warfarin	Prolonged elimination of warfarin[e]
Lansoprazole	Theophylline	10% ↑ in the clearance of theophylline
Lansoprazole and Omeprazole	Sucralfate	Delayed absorption and ↓ bioavailability of PPI
Lansoprazole and Omeprazole	Itraconazole, Ketoconazole, Digoxin	May interfere with absorption of medications where bioavailability is affected by gastric pH

[a] Adapted from: Hansten PD, Horn JR. Drug interactions analysis and management. Vancouver:Applied Therapeutics Inc;1997
[b] Adapted from: Hebel SK ed. Drug facts and comparisons. St. Louis: Facts and Comparisons;1997
[c] Spencer CM, Faulds D. Lansoprazole: A reappraisal of its pharmacodynamic and pharmacokinetic properties and its therapeutic efficacy in acid-related disorders. Drugs 1994;48:404-30
[d] More commonly cited drug interactions; this list is not wholly comprehensive
[e] Monitor concurrent therapy with omeprazole; draw serum levels of interacting drugs if appropriate; change interacting drug if needed

Table 7. Follow-up and Maintenance Therapy

Response	Step-Down Therapy	Chronic Therapy
Symptoms Resolve: Complete course of therapy; then discontinue agent or maintain at lowest dose to control symptoms. Relapse in symptoms: Treat with another course of therapy (similar to or more potent than initial therapy); if on maintenance, dose should be reassessed or agent changed.	Response to standard dose H_2RA: Trial p.r.n. H_2RA or antacid. Response to high dose H_2RA: Trial standard dose H_2RA for maintenance. Response to PPI: Attempt trial on H_2RA, with maintenance at lowest effective dose. Not responding to step-down: Maintenance therapy with agent that originally provided symptom control. Higher grade esophagitis: Relapse more likely to occur, step-down may not be appropriate. Control symptoms with least number of medications, at lowest possible dose; some may respond to repeated short courses of treatment.	Due to the chronicity of GERD, high % patients will require long-term therapy to control symptoms or prevent recurrence of esophagitis. Patients on long-term (≥ 5 years) antisecretory therapy for symptom control may be referred for EGD to determine presence of Barrett's esophagus or malignancy.

Table 8. Selected Costs for GERD Drug Therapy

Drug	Daily Regimen	FSS[a] Cost Per Month
Antacids	15ml QID	$6.12
Cimetidine	400mg BID[b]/400mg QID[c]	$2.72 - $4.13
Ranitidine	150mg BID[b]/150mg QID[c]	$1.93 - $3.20
Lansoprazole	15-30mg QD	$37.50
Sucralfate	1gm suspension QID	$52.44

[a] Federal Supply Schedule; for current prices, refer to www.vapbm.org
[b] Example of standard dose H_2RA
[c] Example of high dose H_2RA

Lansoprazole BID Dosing for GERD

Lansoprazole* 30mg BID is appropriate in the following GERD scenarios:

1. Treatment of complicated GERD† (eg., ulcer bleeding, esophageal ulcer, strictures, and extraesophageal manifestations of GERD). Re-evaluate at 8 weeks to determine if dose may be decreased to 30mg QD.

2. Documented Barrett's metaplasia if inadequate acid suppression on 30mg QD.

3. Persistent symptoms despite an adequate trial of alternate GERD regimens listed below.

*** Lansoprazole is currently the only PPI on the VA National Formulary**

† In PPI naïve patients,treatment dose should begin at lansoprazole 30mg QD.

Note: PBM-MAP recommends that prescriptions for lansoprazole 30mg BID be channeled through a prior authorization process (i.e., GI or drug usage review group). Medical centers may consider limiting this to a 60-day supply with an automatic decrease to 30mg QD by pharmacy, **unless appropriate justification is documented by the prescriber.**

Suggested alternatives for uncomplicated GERD with inadequate symptom control on lansoprazole 30mg/day

1. Add QHS H_2-receptor antagonist and titrate dose as needed (eg., ranitidine 150-300mg QHS, particularly for nocturnal symptoms)‡ $

2. Add prokinetic agent if symptoms associated with motility disorder (refer to GERD guideline at www.vapbm.org) $$

3. Increase lansoprazole dose to 30mg BID for no more than 60-day supply and re-evaluate in 8 weeks. $$$

‡ based on histamine's hypothesized role in the circadian nocturnal acid secretion profile and decreased number of actively secreting acid pumps during the night in the absence of meal stimulation.

$ denotes relative cost of each alternative but does not reflect actual value

Note: Since omeprazole is a non-formulary agent, submission of the proper Non-Formulary Drug Request form should be executed in the event a patient is switched to omeprazole due to intolerance to or inadequate response with lansoprazole therapy.

[a] GERD-Gastroesophageal reflux disease; GI-gastrointestinal; H_2RA-histamine2 receptor antagonist; PPI-proton pump inhibitor; EGD-esophagogastroduodenoscopy

[b] Refer to Table 1; patients with complications of advanced disease should be referred immediately to a GI specialist. Some experts also recommend referral to rule-out Barrett's esophagus in patients with a long history of symptoms. However, it is unclear if early diagnosis influences outcome.

[c] Refer to Table 2.

[d] Some medications may decrease lower esophageal sphincter pressure or cause direct injury to the esophageal mucosa.

[e] Symptoms do not always correlate with disease severity; symptom assessment should take into consideration impact on quality of life. Referral to a GI specialist may occur at any time depending on patient symptoms and clinician preference; some practitioners embrace the approach of early referral for once in a lifetime EGD in all patients requiring chronic pharmacologic therapy.

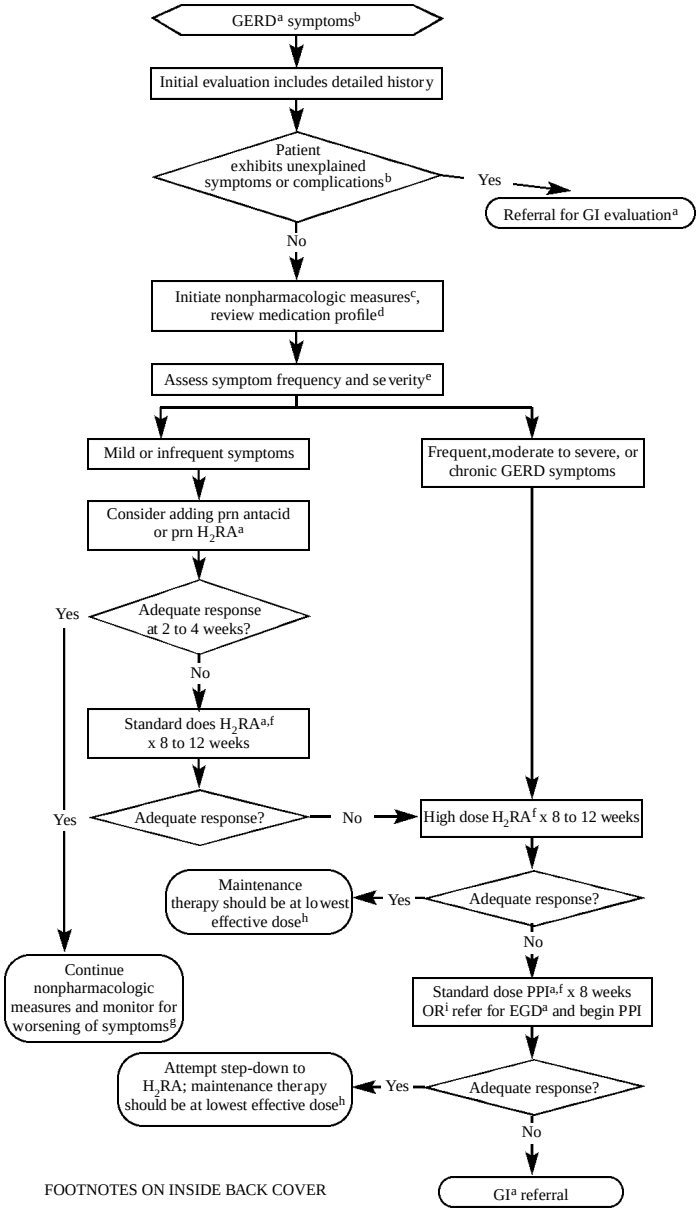
[f] Refer to Table 4.

[g] Consider prn H_2RA or antacids for symptom control. Reinstitute therapy if patient relapses; consider maintenance for frequent relapses.

[h] Consider step-down therapy if appropriate; reinstitute therapy if patient relapses. Refer to Table 7.

[i] Evidence not conclusive to recommend preferred strategy. EGD will rule-out Barrett's esophagus or malignancy, assess degree of mucosal injury, and in patients with esophagitis, identify those likely to need maintenance PPI. Choice of therapy should take into account age and lifespan, availability and risk of EGD, patient preference, and additional clinic visits to step-down therapy.

Algorithm 1



FOOTNOTES ON INSIDE BACK COVER