Medical Advisory Panel
Drug Class Review
H_2-Receptor Antagonists

This review was adapted from the VISN #12 P&T review written by Dayna Mitchell, Pharm.D., edited by Stephanie Davis, Pharm.D., Patricia Barriuso, Pharm.D. and Peter Glassman, M.D. for the MAP

OBJECTIVE

To review the efficacy, safety, and administration of the currently available H_2-receptor antagonists (H_2RAs) in the treatment of peptic ulcer disease. This review has been expanded from the original review used at the time of national contracting to assist the VISN groups in understanding the decisions made for the national contract on H_2RAs.

Table 1. Agents Available in the U.S.

GENERIC NAME	TRADE NAME	GENERIC AVAILABLE	MANUFACTURER
Cimetidine	Tagamet ®	Yes	SKB & various
Famotidine	Pepcid ®	No	Merck
Nizatidine	Axid ®	No	Eli Lilly
Ranitidine	Zantac ®	Pending	Glaxo

I. INDICATIONS[1]

There are currently four main indications for the use of H_2RAs; they include: duodenal ulcer (treatment and maintenance), benign gastric ulcer (treatment and maintenance), gastroesophageal reflux disease (GERD) including erosive esophagitis and the treatment of pathologic hypersecretory conditions. Table 2 summarizes the clinical status of the H_2RAs and their indications.

Table 2 FDA Approved Indications

GENERIC NAME	DUODENAL ULCER		BENIGN GASTRIC ULCER		GASTROESOPHAGEAL REFLUX DISEASE (including erosive esophagitis)	PATHOLOGIC HYPERSECRETORY CONDITIONS
	Treatment	Maintenance	Treatment	Maintenance		
Cimetidine	Yes	Yes	Yes	No	Yes	Yes
Famotidine	Yes	Yes	Yes	No	Yes	Yes
Nizatidine	Yes	Yes	Yes	No	Yes	No
Ranitidine	Yes	Yes	Yes	Yes	Yes	Yes

II. PHARMACOLOGY[1,2]

H_2RAs bind competitively to gastric H_2 receptors to reversibly inhibit acid secretion. Blockade of parietal cell histamine receptors inhibit all phases of gastric acid secretion induced by histamine, gastrin and acetylcholine. The net effect is an increase in the pH of the stomach.

III. PHARMACOKINETICS [1,3]

Although the absorption for cimetidine, ranitidine and famotidine is rapid, the bioavailability for these agents is diminished due to extensive first-pass hepatic metabolism. Nizatidine undergoes little first-pass and as a result bioavailability reaches close to 100% in normal patients. Only minimum protein binding occurs with these agents (range 15 - 35%). All are eliminated by a combination of hepatic metabolism, renal tubular secretion and glomerular filtration. Cimetidine, ranitidine and famotidine are primarily eliminated through hepatic metabolism. Because cimetidine has a high affinity for the cytochrome P_{450} it may reduce the hepatic metabolism of drugs metabolized through the cytochrome P_{450} system. Ranitidine weakly binds to the cytochrome P_{450} system whereas famotidine and nizatidine have little to no interaction with this pathway. Only nizatidine is primarily eliminated by renal excretion, however dosage adjustments are required for all agents in renal dysfunction. When severe hepatic disease is present with renal dysfunction a further dosage reduction may be necessary.

Table 3 Summary of Pharmacokinetic Parameters[1,3]

	CIMETIDINE	FAMOTIDINE	NIZATADINE	RANITIDINE
Absorption				
Bioavailability (%)	60 - 70	40 - 45	> 90	50 - 60
Time to peak serum concentration (hr)	1 - 2	1 - 3.5	1 - 3	1 - 3
Distribution				
Volume (L/kg)	0.8 - 1.2	1.1 - 1.4	0.8 - 1.5	1.2 - 1.9
Protein-binding in serum (%)	13 - 25	15 - 20	26 - 35	15
Elimination				
Half-life (hr)	1.5 - 2.3 [a,b]	2.5 - 4 [a]	1.1 - 1.6 [a]	1.6 - 2.4 [a]
Hepatic clearance (%) Oral	60	50 - 80	22	73
Renal clearance (%) Oral	40	25 - 30	57 - 65	27

[a] increased in renal impairment
[b] increased in hepatic impairment and in the elderly

IV. CLINICAL EFFICACY

Numerous studies comparing the individual H_2RAs in the treatment of gastrointestinal disease can be found in the medical literature. The majority of trials evaluate the use of H_2RAs in the treatment or maintenance of duodenal ulcers or gastric ulcers; there is considerably less published literature comparing H_2RAs in the treatment of GERD or pathological hypersecretory conditions.

In the clinical trials, there is great variation in blinding and randomization techniques, number of enrolled patients, duration of therapy, patient characteristics, locale of investigation, and appropriateness of statistical analysis. However, very few differences in efficacy and safety have been identified within the H_2RAs class. Although data exists suggesting one agent may be more potent than another, the increase in potency has not resulted in a parallel increase in healing efficacy.[4]

A. Active Treatment of Duodenal Ulcer

All H_2RAs have been shown to be effective in the treatment of duodenal ulcers. When used in the appropriate doses, H_2RAs, heal duodenal ulcers to approximately the same degree.[5] Recommended dosages of these agents for 4 – 6 weeks achieve a healing rate of 70 - 95%.[6], and after 8 weeks 85 - 90% .[7] No consistent data has been published to suggest an advantage of any one of the H_2RAs.[4,6]

Numerous studies have compared famotidine to ranitidine in the treatment of active duodenal ulcers.[8-16] and have found little difference in efficacy between these agents. Similarly, trials of ranitidine versus nizatidine,[17-20] cimetidine versus famotidine,[21,22] and cimetidine versus nizatidine [23] have yielded similar rates of ulcer healing. Table 4 reports healing rates
for duodenal ulcers with H_2RAs.

Table 4 Healing of Duodenal Ulcers with H_2Ras

DRUG	DOSE (mg)	DURATION OF TREATMENT	
		4 weeks	8 weeks
Cimetidine	800 hs	80.2%	96.0%
Famotidine	40 hs	82.4%	
Nizatidine	300 hs	76.6%	92.0%
Ranitidine	300 hs	84.1%	95.0%

Source: Adapted from reference 4.

B. Maintenance Therapy of Duodenal Ulcer

Maintenance therapy given at reduced dosages at bedtime have been shown to be effective in preventing ulcer relapses.[5] All H_2RAs have been proven to prevent symptomatic and asymptomatic recurrence of ulcer.[24] [5] Maintenance therapy, usually not necessary after eradication of H. *pylori* infection, may be used for patients who experience frequent recurrences and/or who have a history of ulcer complication such as bleeding.

A review of the literature by Freston (1990) found little difference in recurrence rates of duodenal ulcers treated with maintenance doses of these agents. Reported relapse rates were 25 - 30% as compared to 70% with placebo.[4,24,26] Comparisons of cimetidine to ranitidine [27,28] generally demonstrate similar relapse rates between the two drugs. Studies comparing ranitidine to nizatidine [29-31] and ranitidine to famotidine [8,312,33] also describe comparable relapse rates. Eradication of H. pylori has been shown to reduce occurrence to less than 10% per year and benefits to patients with duodenal ulcer are greater than for patients with gastric ulcer. [67]

C. Treatment and Maintenance of Gastric Ulcer

All H_2RAs have been shown to be effective for the treatment of gastric ulcers. Gastric ulcers heal more slowly than duodenal ulcers, and may require an increased duration of treatment.[5] Healing rates also tend to be slightly lower for gastric ulcers and are dependent upon ulcer size.[7] Fewer studies describe the efficacy of these agents in gastric ulcer treatment, however, in one review of H_2RAs average healing rates are 63%, 75%, and 88% after four, six and eight weeks respectively.[5] Trials of ranitidine versus nizatidine [34] and ranitidine versus famotidine[35] have demonstrated approximately equivalent healing rates. Debas et al.[2] found both ranitidine and cimetidine to be effective in the acute and maintenance treatment of this condition. Miyoshi et al.[36] found famotidine to be slightly more effective than cimetidine in the treatment of gastric ulcer patients. Overall healing rates with all recommended doses of H_2RAs is approximately 80% at 8 weeks and 90% at 12 weeks with duration of treatment remaining the deciding factor in the healing rate.[4,6] Maintenance with 50% of the acute dosage was found to reduce the rate of relapse to 20 - 30% from 50 - 70% with placebo.[4,6]

Table 5 Healing Rates of Gastric Ulcer with H_2RAs

DRUG	DOSAGE (mg)	DURATION OF TREATMENT	
		4 weeks	8 weeks
Cimetidine	800 hs	43%	91%
Famotidine	40 hs	52.2%	81.7%
Nizatidine	300 hs	65%	87%
Ranitidine	300 hs	60.9%	90.8%

Source: Adapted from reference 4

D. Gastroesophageal Reflux Disease (GERD)

All H_2RAs have been shown to be effective in the treatment of GERD.[37-39] Overall 50 - 70% of symptomatic patients will have resolution of their symptoms on H_2RAs depending on the severity of disease and the duration of treatment and dosage used.[38-41] Published guidelines for the diagnosis and treatment of GERD from the American College of Gastroenterology recently reviewed the many trials of H_2RAs conducted in GERD patients.[36] Most are dose-comparison studies of the same drug or are comparative with placebo or omeprazole. Results of esophageal healing and improved symptoms vary greatly by study and are generally dose and frequency dependent. Superior efficacy has not been clearly demonstrated by any of the individual agents, however, improved symptoms and increased healing have been identified with these drugs as a class when compared to placebo. Healing rates of these trials averaged 50% with H_2RAs in 1003 patients as compared to 24% with placebo in 433 patients.[37]

Very few direct comparison studies exist for the H_2RAs in the treatment of GERD. In one study famotidine (40 mg bid and 20 mg bid) was compared to ranitidine (150 mg bid) in 440 patients with endoscopic evidence of esophagitis.[42] Healing rates were adjusted for baseline differences due to significantly more patients with grade III in the famotidine 40mg group. No significant differences in healing rates were noted between the treatment groups at week 6. Healing rates at week 12 were significantly different ($p \leq 0.05$) for the famotidine 40 mg bid group (70.6%) vs ranitidine 150mg bid (60.1%). No significant difference was seen between the famotidine 20 mg bid (67.7%) group and the ranitidine or high dose famotidine group. Other comparative studies were published in abstract form and/or used dosing regimens not widely used.

In an article published in Gastroenterology, Tytgat and associates[43] reviewed the efficacy of cimetidine in the treatment of reflux esophagitis in 3 large, double blind controlled trials in which more than 1100 patients participated. Patients with endoscopic evidence of esophagitis (Grades I-III) were eligible and randomized to different treatment regimens depending on the study (cimetidine 400 mg qid vs 800 mg bid; or 400 mg qid vs 800 mg hs or 800 mg hs vs 800 mg at dinnerttime). All cimetidine regimens provided rapid relief of symptoms especially during the first 2 weeks, however the regimens with increased dosing frequency were the most efficacious. The healing rates for grade I ranged from 54% and 86% after 6 weeks and 79% and 92% after 12 weeks. For more severe esophagitis (grade III), healing rates ranged from 18-32% at 6 weeks and 41-54% at 12 weeks.

The following tables (8-11) summarize studies of dose comparisons between H_2RAs or versus placebo. Although many more studies exist, they report similar results.[44-51] In general, most of the studies excluded patients with concurrent duodenal or gastric ulcers, previous esophageal or gastric surgery, concurrent use of medications known to cause ulcers and/or recent use of H_2RAs. Some studies included more severe esophagitis such as Barrett's ulcer. Other studies had higher number of patients with moderate to severe esophagitis which may account for some differences in the healing rates. Overall, all H_2RAs had comparable results.

Table 8 Cimetidine in GERD

STUDY	CRITERIA	RESULTS	DOSE
Cimetidine vs Placebo (Palmer)[52] n =250 pts parallel, multicentered, RDBPC	Endoscopic evidence of moderate to severe esophagitis	Cumulative symptomatic improvement at 12 weeks: cimetidine 800 mg bid = 66% (p < 0.05 vs placebo); cimetidine 400 mg qid = 75% (p < 0.01 vs placebo); placebo = 49% Total cumulative healing at 12 weeks: cimetidine 800 mg bid = 60% (p < 0.05 vs placebo); cimetidine 400 mg qid = 66% (p < 0.01 vs placebo); placebo = 42% Mean proportion of pts with complete freedom from heartburn during days 1-7 : (daytime) cimetidine 800 mg bid = 22%; cimetidine 400mg qid = 32% (p<0.01 vs placebo for both groups) (nighttime) cimetidine 800 mg bid = 35%; cimetidine 400 mg qid = 47% (p<0.05 vs placebo)	cimetidine 800 mg bid (n = 85) cimetidine 400 mg qid (n = 83) placebo (n = 80)
Cimetidine Vs Placebo (Wesdorp)[53] n=24 RDBPC	Endoscopic evidence of moderate to severe esophagitis	Total cumulative healing at 8 weeks (p<0.01) cimetidine group 8/12 (6 moderate, 2 severe) 4/12 remained unchanged (1 moderate 3 severe-of the 4, 2 had Barrett's esophagus and 2 had marked distal stricturing of the esophagus) placebo group none healed or improved (9 moderate, 3 severe) 10/12 remained unchanged and 2 became worse Histological improvement:(p<0.001) cimetidine 9/12 improved vs 0/12 in placebo The difference in frequency of heartburn attacks during the day & night between groups was not significant	cimetidine 400mg tid (n-12) placebo (n=12)

Table 9 Nizatidine in GERD

STUDY	CRITERIA	RESULTS	DOSE
Nizatidine vs Placebo (Cloud)[54] n = 515 pts parallel multicentered, RDBPC intent to treat	Endoscopic evidence of esophagitis GERD 3 mos; symptoms present for 5 of 7 days prior Failure of standard antireflux regimen	Total cumulative healing at 3 weeks (defined as Grade 0 or no esophagitis): nizatidine 300 mg bid = 17.2% (p =0.070); nizatidine 150 mg bid = 19.6%(p = 0.023 vs placebo); placebo=11.8% Total cumulative healing at 6 weeks (defined as Grade 0): nizatidine 300 mg bid = 38.5%(p = 0.006 vs placebo); nizatidine 150 mg bid = 41.1% (p = 0.001 vs placebo ;p>0.05 vs nizatidine300mg bid) Majority of pts had Grade III baseline: nizatidine 150mg group (41.7%); 300mg group (43.8%) placebo (44.9%) In patients with grade IV esophagitis, the incidence of healing was > with nizatidine 300 mg bid vs nizatidine 150 mg bid (p = 0.021) or placebo (p = 0.040) Greater reduction in heartburn severity nizatidine 300mg (p=0.033) or 150mg (p=0.019) vs placebo Heartburn frequency also ↓ with nizatidine 300mg (p=0.018) and 150mg (p=0.003) vs placebo Nighttime heartburn was significantly relieved with nizatidine 300mg after day 1. Nizatidine 150mg had a significant ↓ only on the day 1 vs placebo	nizatidine 150 mg bid (n = 168) nizatidine 300 mg bid (n = 169) placebo bid (n = 178)
Nizatidine vs Placebo (Quik)[55] n=325 pts multicentered RDBPC	Endoscopic evidence of esophagitis Symptoms present for ≥ 3 mos	Overall healing at week 6 nizatidine 300mg qhs =30% (p=0.071 vs placebo); nizatidine 300mg bid =40% (p<0.05) placebo=26% Overall healing at week 12 nizatidine 300mg qhs=44%; nizatidine 300mg bid=50% (p<0.05 vs placebo) placebo=34% Healing rate for moderate to severe esophagitis at 12 weeks: nizatidine 300mg qhs=36%, nizatidine 300mg bid =45%, (p<0.05 vs placebo) placebo 27% Overall endoscopic improvement of one grade or more: nizatidine 300mg qhs=78% (p<0.07 vs placebo); nizatidine 300mg bid=82% (p<0.05 vs placebo) placebo=64% Majority of pts had grade II baseline: nizatidine 300mg qhs (47%); 300mg bid (48%) placebo (46%) Symptomatic healing (complete disappearance) at week 6 nizatidine 300mg qhs (17%) ; nizatidine 300mg bid (25%); placebo (15%) Treatment effect seen with nizatidine 300mg bid reaching significance at both week 6 and 12 in pts with moderate and severe GERD upon entry (p<0.05)	nizatidine 300mg hs (n=109) nizatidine 300mg bid (n=109) placebo (n=107)

Table 10 Ranitidine in GERD

STUDY	CRITERIA	RESULTS	DOSE
Ranitidine vs Placebo (Sontag)[56] n=237 pts multicentered RDBPC	Endoscopic evidence of esophagitis positive Berstein test ≥ 7 episodes of heartburn/week	Complete healing rate at 6 weeks ranitidine =56% vs placebo=41%(p=0.09) Among pts endoscopically abnormal at entry, overall change in endoscopic classification indicated a significant advantage for ranitidine therapy (p=0.03) At final endoscopy ranitidine group had ↓ incidence of erosion (p=0.02), ulcerations (p=0.08) compared with baseline 35% of ranitidine group & 40% of placebo group were not evaluable with respect to their esophageal histology (62% of normal biopsy specimens among patients randomized to placebo) Only 18% or ranitidine-treated patients had negative Berstein test response after 6 weeks vs 23% in placebo (p=0.47) Heartburn frequency and severity (day and nights) significantly reduced (p<0.05) by ranitidine group vs placebo	ranitidine 150mg bid (n=119) placebo (n=118)
Ranitidine vs Placebo (Euler)[57] n = 328 pts parallel, multicentered, RDBPC	Endoscopic evidence of esophagitis (grades 2-4)	Healing rate at 4 weeks: (p = 0.001 vs placebo for both ranitidine groups) ranitidine 150 mg qid = 45%; ranitidine 300 mg qid = 47%; placebo = 19% Healing rate at 8 weeks: (p = 0.001 vs placebo for both ranitidine groups) ranitidine 150 mg qid = 69%; ranitidine 300 mg qid = 62%; placebo = 28% Healing rate at 12 weeks: (p = 0.001 vs placebo for both ranitidine groups)) ranitidine 150 mg qid = 79%; ranitidine 300 mg qid = 74%; placebo = 40% Majority of pts with Grade II baseline: ranitidine 150mg group (58%); ranitidine 300mg group (59%); placebo (48%) Daytime and nighttime heartburn severity scores were also significantly lower within 24 hrs of receiving either ranitidine dosage then placebo (p≤0.01)	ranitidine 150 mg qid (n = 106) ranitidine 300 mg qid (n = 106) placebo (n = 116)

Table 11 Famotidine in GERD

STUDY	CRITERIA	RESULTS	DOSE
Famotidine (Wesdorp)[58] n=443pts multicentered, RDBCT	Endoscopic evidence of esophagitis Barrett's ulcer eligible	Healing rate at 6 weeks famotidine 20mg bid=43%; famotidine 40mg bid=58%; (p<0.05) Healing rates per severity of esophagitis famotidine 20mg group Grade I (57%); Grade II (44%); Grade III (26%); Grade IV (0%) famotidine 40mg group Grade I (71%); Grade II (39%)*; Grade III (39%); Grade IV (15%) Healing at 12 weeks famotidine 20mg bid =67%; famotidine 40mg bid 76% (p<0.05) Healing rates at 12 week per severity of esophagitis famotidine 20mg group Grade I (81%); Grade II (75%); Grade III (38%); Grade IV (0%) famotidine 40mg group Grade I (87%); Grade II (74%); Grade III (68%)*; Grade IV (46%)* *significantly better (p<0.05) than famotidine 20mg group Treatment with an additional 12 weeks improved healing but not significantly Healing rate in Barrett's esophagus at 6 weeks: famotidine 20mg group 7/12pts; at 12 weeks 10/12 at 6 weeks: famotidine 40mg group 13/28pts; at 12 weeks 20/28 Relief of symptoms was significant for all patients after 6 & 12 weeks, no difference between groups	famotidine 20mg bid (n=220) famotidine 40mg bid (n=223)

Famotidine vs Placebo (Seymour)[59] n = 338 pts multicentered, RDBPC intention to treat	Endoscopic evidence of esophagitis (grades 2-4) <u>without evidence</u> (+) Bernstein test; heartburn for 5 of 7 days erosive esophagitis & Barrett's esophagus eligible	<u>Healing rate at 6 weeks: (</u> p≤ 0.05 for both famotidine groups) famotidine 40 mg hs = 28.6%; famotidine 20 mg bid = 34.4%; placebo = 6.5% <u>Healing rate at 12 weeks: (</u> p≤ 0.05 for both famotidine groups) famotidine 40 mg hs = 49.8%; famotidine 20 mg bid = 54.5%; placebo = 36.6% Majority of pts had Grade 3 baseline: famotidine 40mg (39.3%), famotidine 20mg (36.5%) placebo (37.9%) Symptom relief was significantly improved for famotidine groups (p<0.02). No difference between famotidine groups In famotidine 20mg bid group a greater proportion of patients had complete relief of daytime heartburn by the end of the study than in famotidine 40mgqhs (p<0.02), but no significantly difference seen in nighttime relief	famotidine 40 mg hs (n = 135) famotidine 20 mg bid (n = 137) placebo bid (n = 66)

E. Pathological Hypersecretory Conditions

Few studies are available comparing the H_2RAs in pathological hypersecretory conditions such as Zollinger-Ellison Syndrome. Due to the high acid production state of these patients, most will require treatment with the more potent proton pump inhibitors.

V. ADVERSE EFFECTS [1,3,60]

The overall incidence of serious side-effects with H_2RAs is very low. These effects include headache, dizziness, diarrhea, constipation, and mental status changes with an overall incidence of less than 7%. Bone marrow suppression, hepatotoxicity, and renal damage occur far less frequently. [1]

Cimetidine, and to a lesser extent, ranitidine, may induce breast swelling and galactorrhea, or gynecomastia in men. High dose, long-term therapy with cimetidine has been associated with impotence. CNS symptoms have rarely been a problem with any of the oral H_2RAs in ambulatory patients. With cimetidine, they occur most often in the elderly and in patients with renal and/or hepatic dysfunction in whom the dosage has not been appropriately reduced. Reported with all H_2RAs, mental confusion in the elderly may be alleviated with dosage reduction.

Table 9 Adverse Effects of the H_2RAs [1]

ADVERSE REACTION		CIMETIDINE	FAMOTIDINE	NIZATADINE	RANITIDINE
CNS	Headache	1%	4.7%	+	+
	Somnolence/Fatigue	1%	+	2.4%	Rare
	Dizziness	1%	1.3%	+	Rare
	Confusion	1%	+	Rare	Rare
	Hallucinations	1%	+		Rare
GI	Diarrhea	1%	1.7%	+	+
	Nausea/vomiting/discomfort		+	+	+
	Constipation		1.2%	+	+
	Pancreatitis	Rare [a]			Rare
	Cholestatic/Hepatocellular effects	Rare to 1% [a]			+
Heme	Agranulocytosis	Rare			Rare
	Granulocytopenia	Rare			+ [a]
	Thrombocytopenia	Rare	+	+	+ [a]
	Autoimmune hemolytic/ aplastic anemia	Rare			Rare
Derm	Exfoliative dermatitis/ Eythroderma	+		+	
	Alopecia	Rare [a]	+		Rare
	Rash	+	+	+	+
	Erythema multiforme	Rare			Rare
	Pruritus/Urticaria		+	0.5%	
Other	Gynecomastia	0.3 - 4%		Rare	+
	Impotence	1%	+	+	+
	Loss of libido		+	+	+
	Arthralgia	Rare [a]	+		Rare
	Bronchospasm	+	+		
	Hypersensitivity reaction	Rare [a]			Rare
	Arrhythmia(rapid IV) or arrest	Rare		rare	Rare
	Transient pain injection site (IM)	+	+	na	+

+ occurs, no incidence reported or not well established

[a] reversible

VI. DRUG INTERACTIONS[1,61-66]

Cimetidine is associated with the most significant drug interactions due to inhibition of the cytochrome P450 enzyme (CYP) system, although ranitidine also has an intermediate affinity for the CYP system.[61,62] Inhibition of this enzyme system may inhibit the oxidative metabolism of other drugs, resulting in decreased clearance but the degree of inhibition is subject to interpatient variability. Maximum inhibition with CYP inhibitors, occurs when the inhibiting drug reaches steady state, frequently within 24 hours. Agents with narrow therapeutic windows, like warfarin, phenytoin, and theophylline, have the most clinically significant interactions with cimetidine.[1,63] Famotidine and nizatidine do not appreciably bind to the CYP system and their potential to cause significant inhibition of the CYP system is thereby greatly reduced.[61] All of the H_2RAs may change the rate or extent of absorption of other agents by altering gastric pH.[1]

Table 10 Cimetidine Drug-Drug Interactions

DRUG	EFFECT	SIGNIFICANCE
Warfarin	Dose related ↑ in INR; if adding cimetidine and patient INR at high therapeutic range 2.8 may consider warfarin dose by 30%	major
Theophylline	Dose related ↑ in serum theophylline; if adding cimetidine ↓ theophylline dose by 30 - 50%. New steady state levels usually occur in 2 - 3 days	major
Tricyclic Antidepressants	↑ serum level of TCA	moderate
Benzodiazepines	↑ serum level of diazepam, chlordiazepoxide, desmethyldiazepam alprazolam and triazolam.	moderate
Beta blockers	↑ serum level of propranolol, alprenolol, oxprenolol	moderate
Calcium channel blockers	↑ levels of verapamil and diltiazem.	moderate
Carbamazepine	Transient ↑ in serum level; if adding cimetidine monitor for carbamazepine toxicity which usually occurs during first few days	moderate
Ketoconazole	↓ serum level of ketoconazole	moderate
Lidocaine	↑ serum concentration of lidocaine	moderate
Meperidine	Potentiation of sedation and respiratory depression	moderate
Phenytoin	↑ serum concentration of phenytoin; if adding cimetidine monitor for phenytoin toxicity and obtain serum levels	moderate
Procainamide	↑ serum concentration of procainamide and NAPA; if adding cimetidine monitor for procainamide toxicity and obtain serum levels	moderate
Quinidine	↑ serum concentration of quinidine; if adding cimetidine monitor for quinidine toxicity	moderate
Paroxetine	Serum level of paroxetine may ↑ by about 50%; may achieve therapeutic effects at lower doses	minor

VII. DOSING AND ADMINISTRATION

Table 11 H_2RAs Dosing Regimens [a (1,3)]

DRUG	DUODENAL ULCER		GASTRIC ULCER	GASTROESOPHAGEAL REFLUX DISEASE (Erosive)		DOSE ADJUSMENT IN RENAL IMPAIRMENT per day
	Acute	Maintenance		Oral	Parenteral (iv)	
Cimetidine	300 mg qid 400 mg bid 800 mg hs	400 mg hs	300 mg qid	300 mg qid 400 mg qid 800 mg bid	300mg q6h	CrCl > 30mil/min 800mg CrCl 15-30ml/min 600mg CrCl< 15ml/min 300-400mg
Ranitidine	150 mg bid 300 mg hs	150 mg hs	150 mg bid	300 mg bid	50mg q8h	CrCl < 50ml/min 150 mg
Famotidine	40 mg hs	20 mg hs	20 mg bid 40 mg hs	20 mg bid 40 mg bid	20mg q12h	CrCl < 10 ml/min 20 mg hs or 40 qod
Nizatidine	300 mg hs 150 mg bid	150 mg hs	150 mg bid[b]	300 mg bid	not available	CrCl 20-50ml/min 150mg CrCl <20ml/min 150mg

[a] Average daily doses used in clinical practice.
[b] Acute dose required to heal a duodenal or gastric ulcer

VIII. CONCLUSION

Based on the review of the literature at the time of the national H_2RA contract the MAP concluded the following:

All H_2RAs are therapeutically equivalent in treating duodenal and gastric ulcer disease when used in appropriate doses. Single dose therapy at bedtime at half the treatment dose has also been shown to be equally efficacious when given as maintenance therapy.

All H_2RAs have been shown to be efficacious in the treatment of GERD. H_2RAs are most effective for mild to moderate esophagitis. In general, efficacy improves at higher and more frequent doses for more severe esophagitis, although more potent agents such as proton pump inhibitors may be needed for severe cases of GERD.

Although very few differences have been seen in some studies (most likely due to various study designs and/or inclusion criteria), when the body of literature is viewed as a whole, these small differences found in a few individual studies are not likely to have a clinical impact on the selection of H_2RAs.

IX. RECOMMENDATION

It should be noted that since the publication of the NIH consensus panel statement and the practice guidelines from the American College of Gastroenterology on the treatment of H. *pylori* infections in patients with duodenal or gastric ulcers, the need for H_2RAs may be reduced or even stopped by the eradication of this organism [66,67] Guidelines are being developed on a national level to assist clinicians in identifying and treating patients with H. *pylori*. This will improve patient outcomes while decreasing drug costs due to decrease use in chronic H_2RAs use.

The major difference between these agents is their side effect/drug interaction profile and their cost. Cimetidine has been available the longest and most practitioners are familiar with its potential drug interactions and side effect profile. Therefore cimetidine, or the lowest cost agent, should be considered a first line agent for treatment and maintenance therapy for peptic ulcer disease based on efficacy and cost.

One of the other agents should be available as a second line agent for those patients who cannot tolerate cimetidine due to intolerable side effects, or have a documented clinically significant drug interaction with cimetidine or have demonstrated a therapeutic failure with its use. The choice of a second line agent should be determined by the best available acquisition cost, as the safety and efficacy of these agents appear to be equivalent.

REFERENCES

1. Histamine antagonists in Facts and Comparisons, Olin BR, ed. St. Louis, MO: Facts and Comparisons, Inc., 1996.

2. Debas HT, Mullholland MW. New horizons in the pharmacologic management of peptic ulceration. Am J Surgery 1986;151(3):422-430.

3. Feldman M, Burton ME. Histamine-2 receptor antagonists. Standard therapy for acid-peptic diseases (first of two parts). NEJM 1990;323 (24):1672-1680.

4. Freston JW. Overview of medical therapy of peptic ulcer disease. Gastroenterol Clin North Am.1990;19:121-140.

5. Feldman M, Burton M. Histamine$_2$-resceptor antagonists: Standard therapy for acid-peptic diseases (second of two parts).NEJM. 1990;323 (25):1749-1755.

6. Hixson LJ, Kelley CL, Jones WN, et al. Current trends in the pharmacotherapy for peptic ulcer disease. Arch Int Med 1992;152:726-732.

7. Borne RF. Therapeutic management of peptic ulcer disease. Drug Topics. July 6 1992.80-89.

8. Brogden RN, Carmine AA, Heel RC, et al. Ranitidine: A review of its pharmacology and therapeutic use in peptic ulcer disease and other allied diseases. Drugs 1982;24:267-303.

9. Rohner HG, Gugler R. Treatment of active duodenal ulcers with famotidine. Am J Med 1986;81(Suppl. 4B):13-16.

10. Reynolds JC, Schoen RE, Maislin G, et al. Risk factors for delayed healing of duodenal ulcers treated with famotidine and ranitidine. Am J Gastroenterol 1994;89(4):571-580.

11. Bank S, Greenberg RE, Magier D, et al. The efficacy and tolerability of famotidine and ranitidine on the healing of active duodenal ulcer and during six-month maintenance treatment, with special reference to NSAID/aspirin-related ulcers. Clin Ther 1991;13(2):304-318.

12. Bianchi PG, Lazzaroni M, Barbara L. Famotidine versus ranitidine H.S. in acute duodenal ulcer: A multicentre endoscopic trial. Ital J Gastroenterol 1991;23(2):65-69

13. Alcala-Santaella R, Guardia J, Pajares J, et al. A multicenter, randomized, double-blind study comparing a daily bedtime dose of famotidine and ranitidine in short-term treatment of active duodenal ulcer. Digestion 1989;42(2):79-85.

14. Marks IN, Wright JP. Comparison of famotidine 40 mg with ranitidine 300 mg at night in short-term duodenal ulcer healing: A South African multicentre study. S Afr Med J 1987;72(1):18-20.

15. Dobrilla G, De Prentis G, Piazzi L. Comparison of once-daily bedtime administration of famotidine and ranitidine in the short-term treatment of duodenal ulcer: A multicenter, double-blind, controlled trial. Scan J Gastroenterol 1987;134:21-28.

16. McCullough AJ. A multicenter, randomized, double-blind study comparing famotidine with ranitidine in the treatment of active duodenal ulcer disease. Am J Med 1986;81(4B):17-24

17. Simon B, Cremer M, Dammann HG, et al. 300 mg nizatidine versus 300 mg ranitidine a night in patients with duodenal ulcer. Scan J Gastroenterol 1987;22(Suppl. 136):61-70.

18. Battaglia A, DiMario F, Vigneri S. Peptic ulcer disease in the elderly - a double-blind, short-term study comparing nizatidine 300 mg with ranitidine 300 mg. Aliment Pharmacol Ther 1993;7(6):643-645.

19. Pace F, Colombo E, Ferrara A. Nizatidine and ranitidine in the short-term treatment of duodenal ulcer: A cooperative double-blind study of once-daily bedtime administration. Am J Gastrenterol 1988;83(6):643-645.

20. Bovero E, Poletti M, Boero A. Nizatidine in the short-term treatment of duodenal ulcer: An Italian Multicenter Study. Hepato-Gastroenterol 1987;34(6):269-271

21. Rodrigo L, Viver J, Conchillo F. A multicenter, randomized, double-blind study comparing famotidine with cimetidine in the treatment of active duodenal ulcer disease. Digestion 1989;42(2):86-92.

22. Hartmann H, Folsch UR. Famotidine versus cimetidine in the treatment of acute duodenal ulcer: Double-blind randomized clinical trial comparing nocturnal administration of 40 mg famotidine to 800 mg cimetidine. Digestion 1988;39(3):156-161.

23. Cherner JA, Cloud ML, Offen WW, Latz JE. Comparison of nizatidine and cimetidine as once-nightly treatment of acute duodenal ulcer. Nizatidine Multicenter Duodenal Ulcer Study Group. Am J Gastroenterol 1989;84(7):769-774.

24. Earnest DL. Maintenance therapy in peptic ulcer disease. Med Clin of North Am 1991 75(4):1013-1038.

25. Sontag SJ. Current status of maintenance therapy in peptic ulcer disease. Am J Gastroenterol 1988;83(6)607-617.

26. Freston JW. H2 receptor antagonists and duodenal ulcer recurrence: analysis of efficacy and commentary on safety, costs, and patient selection. Am J Gastroenterol 1987;82(12):1242-1249.

27. Bolin TD, Davis AE, Billington B. Prevention of duodenal ulcer occurrence: Double-blind comparison of ranitidine and cimetidine. J Clin Gastroenterol 1987:9(3):310-313.

28. Hui WM, Lam SK, Lok AS, et al. Maintenance therapy for duodenal ulcer: A randomized controlled comparison of seven forms of treatment. Am J Med 1992;92:265-274.

29. DiMario F, Battaglia G, Saggioro A, et al. A comparison of nizatidine and ranitidine in the maintenance treatment of duodenal ulcer: A randomized, double-blind, multicentre, 2-year study. Ital J Gastroenterol 1991;23(5):253-256

30. Hentschel E, Schutze K, Reichel W. Nizatidine versus ranitidine in the prevention of duodenal ulcer relapse: Six-month interim results of a European multicentre trial. Scan J Gastroenterol 1987;136:84-88.

31. Cerulli MA, Cloud ML, Offen WW, et al. Nizatidine as maintenance therapy of duodenal ulcer disease in remission. Scand J Gastroenterol 1987, 22(suppl 136), 79-83.

32. Deventer GM, Elashoff JD, Reedy TJ, et al. A randomized study of maintenance therapy with ranitidine to prevent the recurrence of duodenal ulcer. NEJM 1989; 320:113-9.

33. Texter EC, Navab F, Mantell G, Berman R. Maintenance therapy of duodenal ulcer with famotidine. Am J Med 1986;81(suppl 4B),

34. Naccaratto R, Cremer H, Dammann, et al. Nizatidine versus ranitidine in gastric ulcer disease. Scan J Gastroenterol 1987;22(Suppl 136):71-78.

35. Brazer SR, Tyor MP, Pancotto FS. Randomized, double-blind comparison of famotidine with ranitidine in treatment of acute, benign, gastric ulcer disease: Community-based study coupled with a patient registry. Dig Dis Sci 1989;34(7):1047-1052.

36. Miyoshi A, Yachi A, et al. Clinical evaluation of famotidine for gastric ulcer: comparison with cimetidine by double blind method. Jap Arch Int Med 1984;31:109-127.

37. De Vault KR, Castell DO. Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Arch Int Med 1995;155:2165-2173.

38. Fennerty MB, Castell D, Fendrick M, et al. Reflux disease in a managed care environment: Suggested disease management guidelines. Arch Intern Med 1996;156;477-484.

39. Johnson DA. Medical therapy for gastroesophageal reflux disease. Am J Med 1992;92(suppl 5A);88s97s.

40. Klinkenberg EC, Festen H, Meuwissen S. Pharmacological management of gastro-oesophageal reflux disease. Drugs 1995;49(5):695-710.

41. Garnett WR. Efficacy, safety, and cost issues in managing patients with gastroesophageal reflux disease. AJHP 1993;50(Suppl. 1):S11-S18.

42. Simon TJ, Berlin RG, Tipping R, Gilde L, for the Famotidine Erosive Esophagitis Study Group. Efficacy of twice daily doses of 40 or 20 milligrams famotidine or 150 milligrams ranitidine for treatment of patients with moderate to severe erosive esophagitis. Scand J Gastroenterol 1993;28:375-380.

43. Tytgat GNJ, Nicolai JJ, Reman FC. Efficacy of different doses of cimetidine in the treatment of reflux esophagitis: A review of three large, double-blind controlled trials. 1990;99:629-634.

44. Wesdorp ICE, Dekker W, Klinkenberg-Knol EC. Treatment of reflux oesophagitis with ranitidine. GUT 1983;24:921-924.

45. Bovero E, Poletti M, Iaquinto G, Giardulo N, et al. Famotidine in the management of acid-reflux oesophagitis. Hepato-gastroenterol 1990;37(suppl 11):145-158.

46. Koelz HR, Birchler R, Bretholz A. et al. Healing and relapse of reflux esophagitis during treatment with ranitidine. Gastroenterol 1986;91:1198-1205.

47. Sherbaniuk R, Bailey W, Grace T, et al. Ranitidine in the treatment of symptomatic gastroesophageal reflux disease. J Clin Gastroenterol 1984; 6:9-15.

48. Johansson KE, Beoryd B, Johansson K et al. Double-blind crossover study of ranitidine and placebo in gastro-oesphageal reflux disease. Scand J Gastroenterol 1986, 21,769-778.

49. Robinson MR, Decktor DL, Stone RC, et al. Famotidine (20mg) b.d. relieves gastro-oesophageal reflux symptoms in patients without erosive oesophagitis. Aliment. Pharmacol. Therap. 1991;5:631-643.

50. Johnson NJ, Boyd EJS, Mills JG, Wood JR. Acute treatment of reflux oesophagitis: a multicentre trial to compare 150mg ranitidine b.d. with 300mg ranitidine q.d.s. Aliment Pharmacol therap 1989;3:259-266.

51. Cloud ML, Offen WW, Robinson M, et al. Nizatidine versus placebo in gasto-oesophageal reflux disease: a 12 week multicentre, randomized, double-blind study. Am J Gastroenerol 1991;86(12):1753-42.

52. Palmer RH, Miller DM, Hedrich DA, et al. Cimetidine qid and bid in rapid heartburn relief and healing of lesions in gastroesophageal reflux disease. Clin Ther 1993;15:994-1001

53. Wesdorp E, Bartelsman J, Pape K, et al. Oral cimetidine in reflux esophagitis: a double blind controlled trial. Gastroenterol 1978;74:821-824.

54. Cloud ML, Offen WW, and the Nizatidine Gastroesophageal Reflux Disease Study Group. Nizatidine versus placebo in gastroesophageal reflux disease: A six-week, multicenter, randomized, double-blind comparison. Dig Dis Sci 1992;37(6):865-874.

55. Quik RFP, Cooper MJ, Gleeson M, et al. A comparison of two doses of nizatidine versus placebo in the treatment of reflux oesophagitis. Aliment Pharmacol Therap 1990;4:201-211.

56. Sontag S, Robinson M, McCallum RW, et al. for the USA Glaxo Gastroesophageal Reflux Disease Study Group. Ranitidine therapy for gastroesophageal reflux disease: Results of a large double-blind trial. Arch Int Med 1987;147:1485-1491.

57. Euler AR, Murdock RH, Wilson TH, et al. Ranitidine is effective therapy for erosive esophagitis. Am J Gastroenterol 1993;88(4):520-524.

58. Wesdorp ICE, Dekker W, Festen HPM. Efficacy of famotidine 20mg twice a day versus 40mg twice a day in the treatment of erosive or ulcerative reflux esophagitis. Dig Dis Sci 1993;38(12):2287-2293.

59. Sabesin SM, Berlin RG, Humphries TJ, et al. and the USA Merck Gastroesophageal Reflux Disease Study Group. Famotidine relieves symptoms of gastroesophageal reflux disease and heals erosions and ulcerations: Results of a multicenter, placebo-controlled, dose-ranging study. Arch Int Med 1991;151;2394-2400.

60. Resnick N. Geriatric medicine. In: Current medical diagnosis and treatment. 35th ed. Tierney LM, McPhee SJ, et al., eds. Stamford CT: Appleton & Lange; 1996:53.

61. Smith C. Upper Gastrointestinal Disorders. In: Applied Therapeutics: The Clinical Use of Drugs. Young LY, Koda-Kimble MA, eds. Vancouver, WA: Applied Therapeutics. 1995; 23.1-23.24.

62. Somogyi A, Muirhead M. Pharmacokinetic interactions of cimetidine. Clin Pharmacokinetics 1987;12:321-366.

63. H_2 receptor antagonists. In: Drug Interactions and Updates. Hansten PD, Horn JR, Koda-Kimble MA, Young LY eds. Vancouver, WA: Applied Therapeutics. 1996:539-549.

64. Reynolds J. The clinical importance of drug interactions with antiulcer therapy. J Clin Gastroenterol 1990;12(Suppl 2): 54s-63s.

65. Hansten P, Horn J. The top 40 drug interactions. Drug interactions newsletter. 1991;11(1):483-490.

66. NIH consensus Development Panel on Helicobacter *pylori* in Peptic Ulcer Disease. Helicobacter *pylori* in peptic ulcer disease. JAMA 1994;272:65-69.

67. Soll AH. Medical treatment of peptic ulcer disease: practice guidelines. JAMA 1996;275(8):622-629.