USE OF CYCLOOXYGENASE (COX) 2 INHIBITORS *CELECOXIB (CELEBREX)* OR *ROFECOXIB (VIOXX) IN VETERANS*

The following guidelines are based on current literature and expert opinion from clinicians. It is expected that significant, new information will be forthcoming in this drug class. Thus, the following recommendations are dynamic and will be revised as new clinical data becomes available. These guidelines are not intended to interfere with clinical judgement. Rather, they are intended to assist practitioners in providing cost effective, consistent, high quality care.

CELECOXIB AND ROFECOXIB are NSAIDs (non-steroidal anti-inflammatory drugs) that primarily inhibit cyclooxygenase (COX) 2, and avoid inhibition of COX-1 at therapeutic concentrations [1,2]. COX-1 is produced constitutively in most tissues and is responsible for prostaglandin synthesis important for the maintenance of the gastric mucosal barrier and platelet aggregation. COX-2 is an inducible isoform present at sites of inflammation [3-7]. COX-2 is also present in the kidneys, brain, and reproductive organs and may have some physiologic role in these tissues [8-9]. Celecoxib has been reported to produce a lower rate of endoscopically demonstrated gastroduodenal lesions compared to ibuprofen (800 mg tid), naproxen (500 mg bid), and diclofenac SR (75 mg bid) [1]. Administration of rofecoxib, compared to ibuprofen (800 mg tid), was associated with a lower incidence of gastroduodenal erosions or ulcers upon endoscopy [2]. However, the correlation of endoscopic lesions/ulcers and incidence of clinically serious upper gastrointestinal events is unknown. Data on file (Searle) from open-label celecoxib trials, report an annual incidence of clinically significant GI events of 0.18% in nearly 4500 patients**.** The Food and Drug Administration predicts 2-4% of patients, taking NSAIDs on a daily basis for 1 year, will experience a symptomatic GI perforation, ulceration or bleeding [43]. In comparative experimental arthritis studies and in epidemiological studies, the annual incidence of serious gastrointestinal complications in non-NSAID users ranges from 0.1%-0.29% [44-46]. Although infrequent, there have been reports of significant upper gastrointestinal bleeding with celecoxib and rofecoxib in controlled and open-label trials. Recently, there have been reports of several deaths and serious gastrointestinal events (bleeding or ulcers) in patients receiving celecoxib within the first 3 months of marketing. However, the causality of these events is unclear. Although the use of highly selective COX-2 inhibitors may result in a lower incidence of gastrointestinal toxicity, it is not known whether other side effects may arise as a result of specific COX-2 inhibition [8-9]. Clinical trials with celecoxib and rofecoxib have **not** demonstrated any benefit of these agents over currently available NSAIDs with regard to renal effects [1,2,42]. Given the lack of published data, celecoxib and rofecoxib should be considered second-line NSAID therapy for RA and OA, reserved for patients at high risk for adverse outcomes to traditional NSAIDs.

OTHER COX-2 SELECTIVE AGENTS. In addition to the newly marketed COX -2 agents, several other available NSAIDs have relative COX -2 selectivity (e.g. etodolac, nabumetone) [8,13-15]. More importantly, the non-acetylated salicylates (e.g. salsalate) have no measurable effects on COX-1 activity in the stomach [14]. In addition, non-acetylated salicylates do not affect platelet aggregation [16]. Several other factors, aside from selective COX -2 inhibition, may play a role in lessening the risk of GI toxicity of NSAIDs including nonacidic prodrugs (nabumetone), shortened half-life, and low or absent enterohepatic recirculation (etodolac, nabumetone) [10-12]. Endoscopic studies of patients taking salsalate or etodolac (Lodine) indicate low rates of gastric lesions compared to several NSAIDs (Table 1). Fries, et al developed a summary index of drug-induced side effects, laboratory abnormalities, and drug-related hospitalizations referred to as a GI toxicity index (GI TI) [23-25], which has been validated using patients in the Arthritis, Rheumatism and Aging Medical Information System Post Marketing Surveillance Program (ARAMIS PMS) database. The purpose of this database is to prospectively monitor status and outcomes of patients with rheumatoid (RA) and osteoarthritis (OA), drug side effects, and economic impact of illness. The PMS database exists within the ARAMIS database, which is a prospective, observational, noninterventional cohort of patients with chronic disease [27]. Salsalate ranked as having the lowest GI TI [26]. Future ARAMIS PMS reports will include the GI TI for etodolac and nabumetone. Serni reviewed four worldwide postmarketing surveillance studies (4 weeks to 1 year in duration) in nearly 8400 patients with OA or RA receiving etodolac and reported an overall incidence of confirmed ulcers of 0.06% [28]. Data from double-blind and open-label trials (2-6 weeks in duration), enrolling more than 55,000 patients receiving etodolac, demonstrated an incidence of serious gastrointestinal events ranging from 0.04-0.3% [29-30]. Several endoscopic trials have been published supporting nabumetone's safer GI toxicity profile compared to ibuprofen and naproxen [50-52]. However, the dose of nabumetone used in these studies was only 1000 mg daily. A recent randomized trial of 1203 patients with osteoarthritis of the hip or knee and a history of endoscopically documented gastric,

pyloric-channel, duodenal ulcer, or 10 or more erosions in the stomach or duodenum found Arthrotec 75 bid (misoprostol 200 mcg+diclofenac 75 mg) superior to nabumetone 1500 mg qd with regard to 6-week incidence of gastric ulcers (1% vs 9%, $p<0.05$) [53]. Data on file (SmithKline Beecham) from randomized, double-blind, controlled and open label trials with nabumetone show a rate of serious GI complications of 0.10 per 100 patient-years compared to 1.33 per 100 patient-years for traditional NSAIDs. When evaluating the same data, using only randomized controlled trials ranging from 3 to 6 months in duration, in 5,200 patients receiving nabumetone, the incidence of serious GI complications was 0.02% (data on file). In a four week, double-blind, placebo-controlled trial, 270 patients with active osteoarthritis of the knee were randomized to receive etodolac 400 mg bid, nabumetone 1500 mg qd or placebo to compare the safety and efficacy of these agents [54]. The authors found that etodolac had the earliest onset of action and, at the final visit, the greatest improvements in patients' and investigators' global assessments of disease severity ($p<0.05$). There were no differences between groups in side effects with the exception of more frequent hypokalemia with nabumetone. Although head-to-head, long-term clinical trials comparing the efficacy and safety of etodolac and nabumetone are lacking, it appears that both can be considered "safer NSAIDs". Since etodolac has recently become available as a price-competitive generic product and offers a safer alternative to current formulary NSAIDs, it was added to the VA National Formulary for those patients considered to be at moderate risk for NSAID-induced GI injury.

ASSESSING NSAID GI RISK. A simple self-assessment tool, developed from the ARAMIS database, helps to quantify the risk of NSAID-related gastrointestinal complications in patients with OA or RA (G. Singh, see appendix 1). Risk of NSAID-related events is graded from 1 (lowest) to 4 (highest). Patients in risk levels 1 or 2 may receive a nonselective formulary NSAID (ibuprofen, naproxen, salsalate, sulindac, piroxicam, tolmetin). Those in risk group 3, who take NSAIDs for less than 30 days or intermittently, may also receive a nonselective formulary NSAID. Patients in risk group 3, who take NSAIDs chronically, should receive a therapeutic trial of salsalate prior to prescribing a COX-2 inhibitor. Although limited, extant data support etodolac's lower incidence of significant GI complications compared to traditional NSAIDs. Therefore, consideration should be given to using etodolac or salsalate prior to a COX-2 inhibitor in patients in risk group 3 (chronic user). Patients in risk group 4 may receive salsalate or a COX-2 specific agent. Patients with a history of hospital admission for a serious gastrointestinal event or those receiving warfarin may receive salsalate or a COX -2 without having to calculate a GI Score [41]. The efficacy of salsalate in treating rheumatoid arthritis has been documented in several trials (Table 2).

The following individuals are considered to be at a higher risk of upper GI events associated with NSAIDs and may be candidates for acetaminophen (OA), salsalate, celecoxib or rofecoxib [36-40]. **However, no data exist in high-risk patients receiving celecoxib or rofecoxib, so extreme caution must be used, as with other NSAIDs, in these individuals. It is imperative to determine whether patients truly need treatment with a NSAID or COX-2 inhibitor prior to their initiation.** Other options, such as non-pharmacologic aids (e.g. physical therapy, assistive devices), topical analgesics (e.g. capsaicin), and other forms of non-NSAID analgesia (e.g. codeine, propoxyphene) should be considered. NSAID overuse is common and can be dangerous. A recent retrospective chart review included patients treated with NSAIDs or aspirin and admitted with an upper gastrointestinal bleed, perforation or gastric outlet obstruction; an indication for NSAID or aspirin therapy was identified in only 55%[47]. In this study, over 40% of patients receiving NSAIDs or aspirin were at high risk for complications from NSAIDs.

Individuals with a higher risk for NSAID-induced GI injury:

1. Prior history of a **serious** gastrointestinal event (**hospital admission** for gastroduodenal perforation, ulcer or bleed). Patients with osteoarthritis must fail treatment with acetaminophen 4000 mg qd. If an NSAID must be used, treatment options include salsalate, a non-cox-2 selective NSAID (formulary-nonselective NSAID) with cytoprotection (e.g. PPI or alternatively, misoprostol or famotidine-*not on VA National Formulary-see page 5*) or a COX-2 inhibitor.

2. Concurrent use of warfarin (Reinforce to patients to report any signs or symptoms of bleeding. In addition, patients and their INRs should be monitored more closely when any new drug is initiated). Patients should fail acetaminophen (osteoarthritis) 4000 mg qd **and** salsalate 1500 mg bid (osteoarthritis and rheumatoid arthritis) prior to receiving a COX-2 inhibitor. Since marketing, there have been reports of increased INR and subsequent bleeding as a result of using the combination of warfarin and celecoxib. Concurrent use of rofecoxib and warfarin resulted in an 8-11% increase in INR in single and multiple dose studies.

Patients **not** having a history of hospital admission for a significant gastrointestinal event or those **not** receiving warfarin must have a **GI Score** (see appendix 1) calculated in order to identify their risk level prior to receiving a COX -2 inhibitor.

The use of low dose aspirin (equal to or less than 325 mg qd) may reduce or eliminate any gastrointestinal protective benefit of the COX-2 inhibitors (see discussion of the CLASS trial below).

WHEN NOT TO USE A COX-2. Patients with an allergy to sulfonamides should NOT receive celecoxib. Dyspepsia with NSAIDs is not an indication for a COX-2 inhibitor. Cyclooxygenase-2 inhibitors can also cause dyspeptic symptoms. Furthermore, lack of response to NSAIDs is not an indication for COX -2 inhibitors since they have not been shown to be superior to traditional NSAIDs. Patients receiving lansoprazole, omeprazole or misoprostol will **not** be considered for treatment with a cyclooxygenase-2 inhibitor since all of these agents, combined with traditional NSAIDs, have been shown to decrease the risk of NSAID-induced GI toxicity in high-risk patients[39,48-49]. The exception is for patients treated with warfarin that require an NSAID, and have failed a therapeutic trial of salsalate, and require a PPI for GERD, ZE, etc.

LOW DOSE ASPIRIN COMBINED WITH A COX-2. Recently, there have been 2 articles published questioning the gastrointestinal safety of low dose aspirin. In addition, the CLASS (Celecoxib Long-term Arthritis Safety Study) was published. In the CLASS trial, the use of low dose aspirin (for cardioprotection) was permitted in both the celecoxib and NSAID (ibuprofen and diclofenac) groups.

In the first article, Cryer, et al [55], studied the effects of 3 low doses of aspirin in 29 healthy volunteers. The investigators attempted to evaluate whether there was a minimally effective dose of aspirin in which thromboxane was maximally inhibited without causing gastric mucosal injury. Each subject underwent gastroduodenal endoscopy at baseline, 1.5 and 3 months to determine the effects of 10 mg, 81 mg, and 325 mg of aspirin daily. At the time of endoscopy, biopsies were taken from the gastric and duodenal mucosa to determine the prostaglandin content 2 hours after the aspirin dose. Subjects were given the option of also undergoing flexible sigmoidoscopy at baseline and 3 months in order to visualize and obtain biopsy specimens from the rectal mucosa. Serum thromboxane levels were measured at baseline, 1.5 and 3 months.

All three doses of aspirin resulted in gastric injury with one 5-mm gastric ulcer observed in the antrum of the stomach at 1.5 months in a patient receiving 10 mg of aspirin daily. Three other antral ulcers were noted after 3 months in 2 patients receiving 325 mg of aspirin daily (one patient had one 5-mm ulcer, the other had 2 ulcers 8-mm and 6-mm). The authors note that gastric injury appeared to be dose-related, however the differences were not significant. As for the duodenum, injury was only observed with the 325 mg dose. No injury was noted in the rectum with any of the aspirin doses.

When the gastrointestinal prostaglandin content was measured from the gastrointestinal biopsies, all 3 doses of aspirin reduced gastric prostaglandin content similarly (34-44% of baseline levels). Duodenal prostaglandins were reduced significantly only in the 81 mg and 325 mg groups and rectal prostaglandin content was decreased only in the aspirin 325 mg daily group.

Serum thromboxane levels were reduced in the 10 mg, 81 mg, and the 325 mg aspirin groups to 38%, 2% and 3% of baseline values, respectively.

The authors concluded that they were unable to identify a dose of aspirin that would provide maximal inhibition of thromboxane synthesis while minimizing the risk of gastric injury. Furthermore, doses of aspirin as low as 10 mg daily resulted in gastric injury while only modestly reducing thromboxane levels. The authors question the long-term safety of even 10 mg of aspirin daily.

The second article[56] was a meta-analysis undertaken to assess the incidence of gastrointestinal complications associated with long-term aspirin. In addition, to determine whether dose reduction and formulation alter the incidence of those gastrointestinal complications.

Twenty-four randomized controlled trials of aspirin were included in the analysis for a total of 65,987 primarily male patients. Doses of aspirin ranged from 50-1500 mg daily. Indications for aspirin included healthy subjects, atrial fibrillation, myocardial infarction, secondary stroke prophylaxis, etc. In all 24 trials, patients were not included if they had a history of peptic ulcer disease, prior gastrointestinal hemorrhage, or any other contraindication for aspirin therapy.

Overall, gastrointestinal hemorrhage occurred in 2.47% of those taking aspirin versus 1.42% of those taking placebo. The pooled odds ratio for gastrointestinal complications with aspirin was 1.68 (95% CI, 1.51-1.88; $p<0.0001$). The author also noted the number of patients needed to harm, based upon treatment with aspirin for an average of 28 months, was 106.

Data, with lower doses of aspirin (50-162.5 mg daily), were analyzed separately for a total of 49,927 patients. Gastrointestinal hemorrhage occurred in 2.3% of patients taking aspirin versus 1.45% of those taking placebo. The pooled odds ratio for gastrointestinal hemorrhage with aspirin was 1.59 (95% CI, 1.4-1.81; $p<0.0001$).

The authors performed meta-regression to assess for a possible correlation between daily dose of aspirin and risk of gastrointestinal hemorrhage. They were able to determine that for every 100 mg reduction in aspirin dose, the incidence of hemorrhage was reduced by 1.5% which was not statistically significant ($p=0.3$).

The authors concluded, from their review of the literature, that there is no evidence to support the notion that reducing daily aspirin dose or use of a modified-release form of aspirin translates into lower risk of gastrointestinal hemorrhage. Furthermore, providers and their patients need to consider the risk-benefit ratio of long-term aspirin administration.

The CLASS (celecoxib long-term arthritis safety study)[57] included 8000 patients with osteoarthritis or rheumatoid arthritis. These patients were randomized to receive celecoxib 400 mg bid, ibuprofen 800 mg tid or diclofenac 75 mg bid for a minimum of 6 months. The use of low dose aspirin was permitted during the trial with approximately 20% of patients in each group receiving it (data for diclofenac and ibuprofen were grouped together and referred to as the NSAID group). The primary endpoint of the CLASS trial was complicated upper gastrointestinal events (UGI) (defined as perforation, obstruction, or GI bleeding). The secondary endpoint was symptomatic ulcers combined with complicated UGI events.

Overall, there was no statistically significant difference in the incidence of complicated UGI events between the celecoxib and the NSAID group (0.76% vs. 1.45%, respectively; RR 0.53; 95% CI 0.26-1.11; $p=0.09$). There were statistically fewer symptomatic ulcers in the celecoxib versus the NSAID group (2.08% vs. 3.54%, respectively; RR0.59; 95% CI 0.38-0.94; $p=0.02$). Patients not taking low dose aspirin had statistically significantly fewer events in the celecoxib versus the NSAID group (complicated UGI events: 0.44% vs. 1.27%, respectively; RR 0.35; 95% CI 0.14-0.98; $p=0.04$; symptomatic GI events: 1.4% vs. 2.91%, respectively; RR 0.48; 95% CI 0.28-0.89; $p=0.02$). However, patients taking low dose aspirin had no difference in either complicated UGI or symptomatic GI episodes (complicated UGI: 6 events in both groups $p=0.92$; symptomatic GI: 14 events in the celecoxib versus 17 in the NSAID group $p=0.49$). Moreover, the use of low dose aspirin, combined with a nonselective NSAID (ibuprofen or diclofenac), did not significantly increase GI ulcer complications in patients receiving nonselective NSAIDs (ibuprofen or diclofenac) alone. Note that data from the CLASS trial was annualized, based upon 6-month-results. About

57% of patients completed 6 months of the trial with just over 40% of those randomized to celecoxib and 44% of those randomized to the NSAID group withdrawing from the trial early due to adverse events, lack of efficacy, and protocol violation.

Although data are limited, it appears from this trial that the use of low dose aspirin may reduce or eliminate any gastrointestinal protective benefit of the COX-2 inhibitors. Furthermore, the use of low dose aspirin with ibuprofen or diclofenac did not seem to increase the GI toxicity of these agents significantly.

Although well documented in previous studies, it can be concluded from the studies above that the use of low dose aspirin is associated with an increased risk for gastrointestinal hemorrhage compared with nonusers of aspirin. In the investigation by Cryer, et al, doses as low as 10 mg of aspirin daily were associated with a reduction in gastric prostaglandin content and one gastric ulcer, however no placebo group was included. In the CLASS trial, when analyzed separately, users of low dose aspirin did not seem to gain any gastrointestinal protective benefit while receiving the cyclooxygenase 2-inhibitor, celecoxib, compared to those in the NSAID (ibuprofen and diclofenac) groups. Interestingly, no significant increase in gastrointestinal toxicity was noted in those receiving low dose aspirin in combination with a NSAID. Therefore, at present, there is little data to support the argument that patients on aspirin (any dose) will achieve any gastrointestinal protective benefit from the COX-2 inhibitors compared to nonselective NSAIDs. Furthermore, the use of aspirin appears to significantly reduce or eliminate any potential gastric safety benefit of the COX-2 inhibitors. Providers are cautioned to consider the risk-benefit ratio of prescribing prophylaxis with low dose aspirin in their patients.

GASTROINTESTINAL CYTOPROTECTION: REDUCING THE RISK OF NSAID-ASSOCIATED UGI COMPLICATIONS. Several options, to reduce the risk of NSAID-associated GI damage in patients requiring treatment with NSAIDs, currently exist and include combining a proton-pump inhibitor (PPI), misoprostol, or high-dose histamine-2 receptor blockers with a nonselective NSAID or switching to a COX-2 inhibitor. Data from the CLASS (see page 4 for discussion) trial has raised question with regard to the continued GI safety benefit of the COX-2 inhibitors compared to the nonselective NSAIDs in patients receiving treatment with low dose aspirin. Recently, lansoprazole has received FDA approval for the healing and prevention of NSAID-associated ulcers based upon endoscopic data, although the correlation of endoscopically determined ulcers/lesions and incidence of serious upper GI complications is not known.

MISOPROSTOL (CYTOTEC): THE MUCOSA TRIAL [39]

Investigators of the MUCOSA Trial attempted to determine whether misoprostol 200 mcg, administered four times daily, reduced the incidence of serious upper gastrointestinal complications (e.g. perforation, obstruction, GI bleeding) in patients with rheumatoid arthritis taking NSAIDs. This study was a 6- month, randomized, double-blind, placebo-controlled trial in which 8,843 patients were enrolled. Gastrointestinal events were investigated during usual clinical care (no planned endoscopies or other GI procedures) based upon spontaneous reporting. A second objective was to identify whether certain patients were at increased risk for NSAID-associated gastrointestinal events.

Patients in the placebo group experienced more serious ulcer complications documented by surgery, endoscopy, or radiography than those receiving misoprostol (33 of 4439 vs. 16 of 4404, respectively; odds ratio 0.487; [95% CI 0.268 to 0.787; p=0.012]) resulting in a 51% reduction in events. In the misoprostol group, perforated ulcers and ulcer-induced gastric outlet obstruction were decreased 10-fold compared to those patients receiving placebo (1 of 4404 vs. 10 of 4439; odds ratio 0.101[95% CI 0.013-0.787; p=0.012]). Combined events, including complicated events and confirmed, symptomatic ulcers, occurred statistically significantly less often in the misoprostol compared to placebo group (25 of 4404 vs. 42 of 4439; odds ratio 0.598 [95% CI 0.364-0.982; p=0.049]) resulting in a 40% reduction in event risk. When the data was analyzed for bleeding events, with or without confirmation of active ulceration, 33 of 4404 misoprostol vs. 51 of 4439 placebo recipients experienced bleeding episodes resulting in a 35% reduction in bleeding in the misoprostol vs. placebo group (odds ratio 0.650 [95% CI 0.418 to 1.009; p=0.062]) which was not statistically significant.

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The investigators determined that age 75 years or greater, history of peptic ulcer disease, history of gastrointestinal bleeding, and history of cardiovascular disease placed individuals at a greater risk of serious NSAID-associated upper GI events. They were unable to correlate use of corticosteroids, arthritis disability score or gender with increased risk for significant events.

The authors concluded that misoprostol reduces the risk of serious upper GI events including perforation, obstruction or bleeding in older patients with rheumatoid arthritis taking NSAIDs.

Cumulative endoscopic evidence, in patients receiving misoprostol compared to placebo, suggests a dose-response relationship in gastric ulcer formation with misoprostol 800 mcg daily being associated with the lowest risk (RR 0.18; 95% CI 0.11-0.28) and 400 mcg daily with a relative risk of 0.38 (95% CI 0.3-0.49) reaching a statistical difference (p=0.0055). Misoprostol 600 mcg daily was not different than either the 400 or 800 mcg dose [58]. Therefore, a dose of at least 600 mcg daily is needed for gastric protection.

PROTON-PUMP INHIBITORS: Lansoprazole (Prevacid) has recently received FDA approval for the treatment of NSAID-associated gastric ulcer in patients who continue NSAID use. In addition, it was granted FDA approval for reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer and who continue to require treatment with NSAIDs. The recommended dose of lansoprazole for healing is 30 mg qd and for reducing risk of NSAID-associated GI events is 15 mg qd. All of the following studies utilize endoscopy to document their study endpoints recognizing that the correlation of endoscopic ulcers/lesions with the incidence of clinically serious upper gastrointestinal events is not known.

Clinical Trial	Treatment Group	Results	Comments
Yeomans ND, et al[48] I, MC, R, DB 541 patients 4 to 8 weeks 432 patients 6 months (Astra) **Endpoint:** Complete healing of ulcer(s) (gastric or duodenal) or significant ↓ in # of erosions and minimal or no symptoms of dyspepsia.	Inclusion required ulcer(s) or 10 or more erosions in the stomach or duodenum and continued need for NSAID treatment. **Healing Phase:** (4-8 weeks) -RAN 150 mg bid (n=174) -OME 20 mg qd (n=174) -OME 40 mg qd (n=187) **Maintenance Phase:** (6 months) -RAN 150 mg bid -OME 20 mg qd	**Healing Phase:** Treatment was successful in 63% of those receiving RAN compared to 80% and 79% of those receiving OME 20 and 40 mg, respectively (p=or< 0.001). The rate of healing for all types of lesions was statistically faster during the 8 weeks (p<0.001) for both doses of OME compared to RAN. **Maintenance Phase:** At the end of 6 months, there were 59% of patients receiving RAN compared to 72% of those in the OME group in remission (p=0.004). -At 8 weeks, most patients had none or only mild symptoms of dyspepsia. There were no differences between groups. **Healing and Maintenance:** **OME 20 and 40 mg>RAN**	-ADEs were similar between groups. -After 10 days of maintenance therapy on OME, 1 patient developed a bleeding duodenal ulcer and was hospitalized. -Gastric ulcers recurred 5.2% of patients on OME vs. 16.3% of those on RAN. Duodenal ulcer recurred in 0.5% on OME vs. 4.2% on RAN. -This study included patients that had evidence of endoscopic ulcers or lesions at baseline theoretically placing them at a higher risk of NSAID-associated ADE.
ADE=adverse effects, DB= double-blind, I=International, LAN=Lansoprazole, MC=multicenter, MIS=misoprostol, OME=omeprazole, PC=placebo-controlled, PLA=placebo, R=randomized, RAN=ranitidine (Responsible for funding)			

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Clinical Trial	Treatment Group	Results	Comments
Hawkey, CJ, et al [49] I, MC, R, DB, PC (maintenance phase) 935 patients 4 to 8 weeks 732 patients 6 months (Astra) **Endpoint:** same as previous study by Yeomans, et al.	Inclusion required ulcer(s) or 10 or more erosions in the stomach or duodenum and continued need for treatment with NSAIDs. **Healing Phase:** (4-8 weeks) -MIS 200 mcg qid (n=298) -OME 20 mg qd (n=308) -OME 40 mg qd (n=315) **Maintenance Phase:** (6 months) MIS 200 mcg bid OME 20 mg qd PLA qd	**Healing Phase:** At 8 weeks, 71% of MIS, 76% of OME 20 mg, and 76% of OME 40 mg reached the endpoint resulting in no significant difference between groups. **Maintenance Phase:** At 6 months, the percentage of patients in remission was 61% in the OME 20 mg group vs. 48% of those taking MIS vs. 27% of those taking PLA. OME vs. MIS p=0.001 OME and MIS vs. PLA p<0.001 **Healing: OME 20 and 40 mg=MIS** **Maintenance: OME>MIS>PLA**	-ADE occurred in a higher percentage of patients receiving MIS compared to either dose of OME (no p value listed). -1 perforated duodenal ulcer occurred in a patient receiving PLA during the maintenance phase after 31 days. -32% of patients on PLA developed gastric ulcers during the maintenance phase vs. 10% on MIS and 13% on OME. -This study included patients that had evidence of endoscopic ulcers or lesions at baseline theoretically placing them at a higher risk of NSAID-associated ADE. -The authors note a statistically higher percentage of healed gastric ulcers in the OME 20 mg group compared to MIS. Duodenal ulcer healing rates were higher in both OME groups vs. MIS. Erosion healing rates were higher in the MIS vs. OME groups.
Agrawal NM, et al[59] MC, R, DB 353 patients 8 weeks (TAP) **Endpoint:** Complete gastric ulcer healing with no evidence of ulcer crater or erosion at ulcer site.	Inclusion required having a nonmalignant gastric ulcer (> or = to 5 mm) diagnosed by endoscopy in patients receiving stable doses of NSAIDs for 30 days or more who continued to need treatment with NSAIDs. -RAN 150 mg bid -LAN 15 mg qd -LAN 30 mg qd	**Ulcer healing:** At 8 weeks, 53% of those receiving RAN, 69% on LAN 15 mg, and 73% of patients on LAN 30 mg experienced complete ulcer healing (p=0.01 for RAN vs. LAN 15 mg) (p=0.009 for RAN vs. LAN 30 mg). Controlling for H pylori status, gastric ulcer healing was similar in infected vs. non-infected patients, however the healing rates were statistically higher in both LAN groups compared to RAN (p ranged from 0.001 to <0.05). **Ulcer healing in those continuing on NSAIDs:** **LAN 15 and 30 mg>RAN**	-ADEs were similar across treatment groups and no report of ulcer complications. -No significant difference in healing of gastric ulcers was seen between the 2 doses of LAN. -Trend toward better symptom relief with LAN 15 and 30 mg vs. RAN.

ADE=adverse effects, DB= double-blind, I=International, LAN=Lansoprazole, MC=Multicenter, MIS=misoprostol, OME=omeprazole, PC=placebo-controlled, PLA=placebo, R=randomized, RAN=ranitidine
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Clinical Trial	Treatment Group	Results	Comments
Data on File TAP Pharmaceuticals[60] MC, R, DB, PC 535 patients 12 weeks (TAP) **Endpoint:** Reoccurrence of NSAID-associated ulcers.	Inclusion: chronic NSAID users with a history of gastric ulcer but no current gastric or duodenal ulcer and were H. pylori negative with fewer than 25 gastric or duodenal erosions. -MIS 200 mcg qid -LAN 15 mg qd -LAN 30 mg qd -PLA qd	At 4, 8 and 12 weeks, use of MIS resulted in 96, 95, and 93% of patients remaining gastric ulcer free, respectively. As for LAN 15 mg, 90, 86, 80% of patients remained gastric ulcer free at 4, 8, and 12 weeks, respectively. LAN 30 mg resulted in 92, 88, and 82% of patients remaining gastric ulcer free at 4, 8 and 12 weeks, respectively. As for PLA 66, 60, and 51% of patients remained gastric ulcer free at 4, 8, and 12 weeks, respectively while continuing NSAID treatment. $p<0.0001$ for all 3 active groups vs PLA $p<0.05$ for MIS vs. LAN 15 or 30 mg **Patients remaining gastric ulcer free while continuing NSAIDs:** **MIS>LAN 15 and 30 mg>PLA**	-Unpublished data -Included patients with a history of prior ulcer.

ADE=adverse effects, DB= double-blind, I=International, LAN=Lansoprazole, MC=Multicenter, MIS=misoprostol, OME=omeprazole, PC=placebo-controlled, PLA=placebo, R=randomized, RAN=ranitidine
(Responsible for funding)

HIGH DOSE HISTAMINE-2 RECEPTOR (H2R) BLOCKERS: All of the following studies utilize endoscopy to document their study endpoints recognizing that the correlation of endoscopic ulcers/lesions with the incidence of clinically serious upper gastrointestinal events is not known. There are no studies comparing the effectiveness of high-dose H2R blocking agents to misoprostol or PPIs in the prevention of NSAID-associated GI ulcers. To date, only famotidine 40 mg bid has been demonstrated to prevent gastric ulcers associated with NSAIDs.

Clinical Trial	Treatment Group	Results	Comments
Taha AS, et al [62] R, DB, PC 285 patients 24 weeks (Merck) **Endpoint:** Cumulative incidence of gastric or duodenal ulceration at 24 weeks.	Inclusion: patients with RA (82%) or OA (18%) without peptic ulcers receiving chronic NSAIDs. FAM 20 mg bid (n=84) FAM 40 mg bid (n=83) PLA bid (n=81) Endpoints were determined by endoscopy at 4, 12 and 24 weeks.	Cumulative gastric ulcer incidence was 20% in the PLA group, 13% in the FAM 20 mg group, and 8% in the FAM 40 mg group. (p=0.24 FAM 20 vs. PLA) (p=0.03 FAM 40 vs. PLA) Cumulative duodenal ulcer incidence was 13% in the PLA group, 4% in the FAM 20, and 2% in the FAM 40 mg group. (p=0.04 FAM 20 vs. PLA) (p=0.01 FAM 40 vs. PLA) **Prevention of gastric ulcer:** **FAM 40>FAM 20 or PLA** **Prevention of duodenal ulcer:** **FAM 20 and 40>PLA**	-In this study, only 10-16% of patients had a history of a previous ulcer. -No active comparator (misoprostol or a PPI)

ADE=adverse effects, DB= double-blind, FAM=famotidine, I=International, LAN=Lansoprazole, MC=Multicenter, MIS=misoprostol, OA=osteoarthritis, OME=omeprazole, PC=placebo-controlled, PLA=placebo, R=randomized, RA=rheumatoid arthritis, RAN=ranitidine
(Responsible for funding)

USE OF CYCLOOXYGENASE (COX) 2 INHIBITORS *CELECOXIB (CELEBREX)* OR *ROFECOXIB (VIOXX)* IN VETERANS

Clinical Trial	Treatment Group	Results	Comments
Hudson N, et al [63] R, DB, PC **Healing phase:** 104 patients 12 weeks **Maintenance Phase:** 78 patients 6 months (Merck) **Endpoint:** **Healing phase:** Complete healing at 4 and 12 week. **Maintenance phase:** Cumulative incidence of gastroduodenal ulcers .	Inclusion: patients with RA or OA with gastric or duodenal ulcers receiving chronic NSAIDs. Patients were given the option of stopping or continuing their NSAIDs. Healing: FAM 40 mg bid for 12 weeks (n=104), 16 patients stopped NSAIDs, 88 continued. Maintenance: FAM 40 mg bid (n=39) PLA bid (n=39)	**Healing:** At 12 weeks, 89% of ulcers in those continuing NSAIDs healed vs. 100% of those stopping NSAIDs. Differences were not statistically significant. **Maintenance:** Cumulative incidence of gastroduodenal ulcers at 24 weeks was 53.5% (95% CI 36.6%-70.3%) for the PLA group vs. 26% (95% CI 12.1%-39.9%) for the FAM group (p=0.011). **Healing:** Continuing NSAIDs did not delay healing in patients on FAM **Maintenance: FAM>PLA** for preventing recurrence of gastroduodenal ulcers.	-Gastric ulcer incidence was 41.4%(95% CI 24%-58.7%) in the PLA compared to 19.1% (95% CI 6.3%-31.9%) in the FAM group (p=0.026). -Incidence of duodenal ulcer showed a trend toward reduced incidence in the FAM group vs. PLA but was not statistically significant. -No active comparator -Patients all with current ulcer theoretically placing them at higher risk for NSAID-induced GI injury.
WoldeS, et al [64] R, DB, PC 30 patients 12 months (Glaxo) **Endpoint:** Recurrence of gastric or duodenal ulcer	Inclusion: patients with RA and a history of gastric and/or duodenal ulcers who required regular use of NSAIDs. Endoscopy was performed at baseline, 6 and 12 months. PLA bid Ranitidine 300 mg bid	**Duodenal ulcers** recurred in 4 of the 10 patients on PLA but none of the 10 patients receiving RAN (p=0.04; 95% CI –0.88 to –0.12). **Gastric ulcers** recurred in 6 patients in the PLA group and 3 patients in the RAN group (p=0.18; 95% CI –0.72-0.12). **Prevention of:** **duodenal ulcers: RAN>PLA** **gastric ulcers: RAN=PLA**	Recruitment was slower than anticipated so study was stopped after 3 years. No active comparator. Small sample size.

ADE=adverse effects, DB= double-blind, FAM=famotidine, I=International, LAN=Lansoprazole, MC=Multicenter, MIS=misoprostol, OA=osteoarthritis, OME=omeprazole, PC=placebo-controlled, PLA=placebo, R=randomized, RA=rheumatoid arthritis, RAN=ranitidine
(Responsible for funding)

COX-2 INHIBITORS: CLASS [57] AND VIGOR [61] TRIALS

For discussion of the CLASS trial, please see the section regarding use of a COX-2 combined with low dose aspirin starting on page 3.

The VIGOR or Vioxx Gastrointestinal Outcomes Research Trial is a study in which 8,076 patients with rheumatoid arthritis were enrolled and randomized to receive treatment with rofecoxib 50 mg qd or naproxen 500 mg bid for 1 year (median follow up was 9 months). The primary endpoint was confirmed upper GI events (e.g. gastroduodenal perforation or obstruction, upper GI bleeding, and symptomatic ulcers). A secondary endpoint was confirmed complicated events (e.g. perforation, obstruction and severe upper GI bleeding). The use of low dose aspirin was not allowed.

The efficacy of rofecoxib vs. naproxen was found to be similar and withdrawal due to lack of efficacy was not significantly different between groups.

The number of confirmed upper GI events was 2.1/100 patient-years in those receiving rofecoxib vs. 4.5/100 patient-years in those receiving naproxen (relative risk, 0.5; 95% CI 0.3-0.6; p<0.001). The rate of

confirmed complicated events was 0.6/100 patient-years taking rofecoxib vs. 1.4/100 patient-years in those taking naproxen (relative risk, 0.4; 95% CI 0.2-0.8; p=0.005) resulting in both endpoints occurring significantly less often in the group receiving rofecoxib compared to naproxen.

During the trial, an unexpected higher number of myocardial infarctions (MI) were observed in the rofecoxib arm of the study compared to the naproxen arm (0.4 vs. 0.1, relative risk 0.2; 95% CI 0.1-0.6). However, there was no significant difference in the rate of mortality between groups being 0.5% in the rofecoxib vs. 0.4% in the naproxen group. There was also no difference in the rate of mortality from cardiovascular causes occurring at a rate of 0.2% in both groups. Ischemic cerebrovascular events were reported in 0.2% of patients for either group. Investigators noted that 4% of patients, participating in VIGOR, met the FDA criteria for secondary cardiac prophylaxis with aspirin (e.g. prior myocardial infarction, angina, stroke, transient ischemic attack, cardiac bypass or angioplasty), however were not taking aspirin. Of the patients experiencing a myocardial infarction, that 4%(with a prior cardiac history) accounted for 38% of the patients having an MI during the study. When the data was evaluated, excluding that 4% of patients, there was no observed statistical difference in the incidence of MI between groups (0.2% rofecoxib vs. 0.1% naproxen). The authors comment that there was no correlation between hypertension and MI, noting that only 1 patient experienced both. They attribute the lower risk of MI, seen in the naproxen group, to naproxen's ability to inhibit the production of thromboxane (by 95%) and inhibit platelet aggregation (by 88%) and maintain this effect throughout its dosing interval.

The authors concluded that although efficacy was similar, treatment with rofecoxib resulted in a significantly lower incidence of clinically meaningful upper GI events compared to naproxen in patients with rheumatoid arthritis. Furthermore, the reduced incidence of myocardial infarction, observed in the naproxen group, requires further evaluation in larger studies.

CONCLUSION. Misoprostol (800 mcg/day) and the COX-2 inhibitors (without concurrent aspirin use) are the only agents that have been shown to reduce the incidence of NSAID-associated ulcer complications in randomized studies. Furthermore, evidence from endoscopic studies supports the use of PPIs (omeprazole and lansoprazole) and high-dose H2R blockers (famotidine 40 mg bid-*not on VA National Formulary*) for the prevention of gastric and duodenal ulcers in patients receiving NSAIDs. Based on the available evidence, the PBM/MAP make the following recommendations:

1. **INDIVIDUALS WHO ARE AT HIGH RISK FOR NSAID-INDUCED ULCERS BUT WHO REQUIRE NSAIDS.**

   For preventing complications in patients who are at high-risk for NSAID-induced ulcers but who require NSAIDs, salsalate (which does not inhibit COX-1) is preferred as first-line therapy. Second line alternatives include combining a nonselective NSAID (e.g. ibuprofen, naproxen, etc) with appropriate gastric cytoprotection (e.g. PPI, misoprostol, famotidine-*see number 3 below)* or using a COX-2 inhibitor (celecoxib or rofecoxib).

2. **INDIVIDUALS AT HIGH RISK FOR NSAID-INDUCED ULCERS, REQUIRE NSAIDS, BUT ARE RECEIVING CARDIOVASCULAR PROPHYLAXIS WITH LOW DOSE ASPIRIN.**

   Based on data from the CLASS study (page 4), adding usual cardioprotective doses of aspirin (e.g., 81 mg or 325 mg daily) to a COX-2 inhibitor (or, presumably, salsalate) reduces or eliminates the GI safety benefit. More specifically, the celecoxib/aspirin combination appeared to increase the risk of GI injury to the same level (about 2%) as the nonselective NSAID group with or without aspirin. Therefore, patients at high risk for NSAID-induced ulceration should not be considered to be at a lower risk when a COX-2 specific agent is combined with aspirin. As a result of this data, although limited, the PBM/MAP do not recommend the combination of a COX-2 inhibitor plus aspirin in high-risk patients because the safety benefit may be reduced or lost.

3. **INDIVIDUALS AT HIGH RISK FOR NSAID-INDUCED ULCERS, REQUIRE NSAIDS, BUT ARE RECEIVING CARDIOVASCULAR PROPHYLAXIS WITH LOW DOSE ASPIRIN.**

   In patients who are at high-risk for NSAID-induced gastropathy, receiving low dose aspirin and requiring NSAIDs, a nonselective NSAID should be combined with gastroprotective therapy. Based upon the available evidence, dosing complexity, potential side effects and cost, a PPI

(lansoprazole 15 to 30 mg daily) is the preferred means of prophylaxis. Misoprostol (at least 200 mcg tid) and high-dose famotidine (40 mg bid-*not on VA National Formulary)* are alternatives for those patients who require prophylaxis but cannot tolerate a PPI.

DOSAGE AND ADMINISTRATION

Celecoxib (Celebrex)
Osteoarthritis: 100 mg bid or **200 mg qd** (Preferred dose is 200 mg qd since the doses were equally beneficial). Rheumatoid Arthritis: 100 mg to 200 mg bid (The doses were equal in their effectiveness, however some patients derived additional benefit from the 200 mg bid).

Rofecoxib (Vioxx)
Osteoarthritis: **12.5 mg** qd. Some patients may receive additional benefit from 25 mg qd.

CONCLUSIONS
Because published data are lacking and cost is significantly greater than formulary NSAIDs, celecoxib and rofecoxib should be considered second-line NSAIDs for the treatment of RA and OA, reserved for patients at high risk for adverse outcomes from traditional NSAIDs. In patients with osteoarthritis, felt to be at high risk for NSAID-induced GI toxicity, consideration should be given to using acetaminophen or other therapeutic options prior to an NSAID. In patients requiring treatment with a NSAID, at low risk for GI toxicity, a non-COX-2 selective formulary NSAID (e.g. ibuprofen, naproxen salsalate, sulindac, piroxicam, tolmetin) is recommended. In patients requiring treatment with a NSAID, at moderate risk for NSAID GI injury, a trial of salsalate or etodolac should be attempted as first line therapy. In those patients requiring NSAID therapy, at highest risk of GI toxicity, treatment options include salsalate, a non-COX-2 selective formulary NSAID with cytoprotection (e.g., PPI, misoprostol, famotidine-*not on VA National Formulary)* or a COX-2 inhibitor. Data from the CLASS trial suggests, that in those individuals receiving prophylaxis with low dose aspirin (less than or equal to 325 mg qd), any GI protective benefit of the COX-2 inhibitors over NSAIDs may be reduced or eliminated. The use of low dose aspirin in combination with nonselective NSAIDs (ibuprofen or diclofenac) did not appear to significantly increase the risk for GI toxicity. As a result of this data, although limited, the PBM/MAP do not recommend the combination of a COX-2 inhibitor plus aspirin in high-risk patients because the safety benefit may be reduced or lost. In those high-risk patients receiving cardiovascular prophylaxis with low dose aspirin and requiring NSAIDs, nonselective NSAIDs should be combined with lansoprazole because of the available evidence, ease of administration, low occurrence of side effects and cost of therapy compared to misoprostol or famotidine. However, misoprostol and famotidine 40 mg bid (not on VA national formulary) can be considered as alternatives to lansoprazole in these high-risk individuals. As with other NSAIDs, extreme caution should be used when prescribing a COX-2 inhibitor in high-risk patients since no published information exists in these individuals.

Table 1. Salsalate and Etodolac Endoscopic Trials

Clinical Trial	Treatment	Results	Comments
Lanza, et al [17] Healthy subjects Salsalate n=20 Naproxen n=20 (14 days) SB endoscopist, PG	Salsalate 3.5 g qd (divided bid) Naproxen 375 mg bid Normal baseline endoscopy	Gastroduodenal lesions 10% Salsalate group and 55% naproxen group (p=0.002)	A larger number of patients in the salsalate group reported an ADE compared to the naproxen group. The difference was due to reversible tinnitus/hearing loss. No patients withdrew.
Roth, et al [18] Rheumatoid arthritis Salsalate n=18 Naproxen n=21 (3 months) SB endoscopist and rheumatologist, R, PG	Salsalate 1.5 g bid (doses Titrated 2 to 4 g qd) Naproxen 375 mg bid (doses titrated to 500 to 1000 mg qd) Eligible pts if no history of major GI bleed, ulcer >2 cm or diffuse erosions on baseline endoscopy	38% of naproxen treated pts had gastroduodenal lesions compared to none on salsalate. (p=0.003 Wilcoxon signed rank test)	28-29% of patients had a history of gastroduodenal ulcer prior to study entry (no difference between groups). In the naproxen group, only 2/11 patients with prior ulcer developed ulcer/erosion. Median doses: salsalate 1.5 g bid, naproxen 375 mg bid. No difference in ADEs except for reversible tinnitus or hearing loss with salsalate.
Scheiman, et al [19] Healthy subjects Salsalate n=10 Enteric-coated ASA n=10 (6 days for each treatment) SB (endoscopist), R, crossover	Salsalate 1.5 g bid EC ASA 650 mg qid Baseline endoscopy; reendoscopy after 6th day of 1st drug; then 7 day washout period; reendoscopy prior to crossover to 2nd agent, then final endoscopy after 6th day of 2nd drug.	1 patient (10%) receiving salsalate had a grade 1 lesion. 6 patients (60%) receiving EC ASA developed grade 2 or 3 lesions. (p=0.01 Wilcoxon signed rank test)	3 patients receiving salsalate and 2 receiving EC ASA reported tinnitus. Tinnitus was not associated with serum salicylate level. In addition, there was no correlation between salicylate levels and gastroduodenal ulcers.
Cryer, et al [20] Healthy Volunteers Salsalate n=7 ASA n=7 Placebo n=6 (7.5 days) DB, PC, R	Salsalate 1.5 mg bid ASA 975 mg qid Placebo qid Baseline and end of study endoscopy	Endoscopy was scored by region (fundus, antrum, bulb, postbulbar) and the sum of scores were compared (0-4 for each region): 11.6 for ASA vs 4.6 for salsalate and 3.9 for placebo. Significant differences were noted for salsalate or placebo compared to ASA (p<0.001 paired t-test). No difference was noted between salsalate and placebo.	
Taha, et al [21] Rheumatoid arthritis Etodolac n=15 Naproxen n=15 (4 weeks) DB, R, PG	Etodolac 300 mg bid Naproxen 500 mg bid Baseline and end of study endoscopy	Mucosal lesions developed in 3 (20%) of etodolac pts vs 8 (53%) of naproxen treated pts (p<0.05 Wilcoxon signed rank test)	Patients receiving etodolac required less rescue paracetamol. However the only significant difference between etodolac and naproxen in terms of efficacy was right hand grip strength which was better in the naproxen group.
Lanza, et al [22] Healthy volunteers Etodolac 600 mg qd n=12 Etodolac 1000 mg qd n=12 Indomethacin n=12 Ibuprofen n=12 Naproxen n=12 Placebo n=12 (7 days) SB (endoscopist), R, PG	Etodolac 300 mg bid Etodolac 500 mg bid Indomethacin 200 mg qd (divided tid) Ibuprofen 600 mg qid Naproxen 500 mg bid Placebo bid Baseline and end of study endoscopy.	In terms of comparison of indomethacin, ibuprofen and naproxen to etodolac, the incidence of gastric lesions was significantly less with etodolac (p<0.05). When etodolac was compared to placebo, there was no significant difference in ulcer formation.	The endoscopist and an independent gastroenterologist reviewed endoscopic photographs in a random sequence for reproducibility of scoring.

ADE=adverse effect; DB=double-blind; bid=twice daily; PC=placebo-controlled; PG=parallel group; pts=patients; qd=daily; R=randomized; SB=single-blind; tid= three times daily

Table 2. Salsalate Efficacy Trials

Clinical Trial (ref)	Treatment	Results (statistical test)	Comments
Montrone, et al. [31] Rheumatoid arthritis: Salsalate n=23 Piroxicam n=20 (4 weeks) DB, R	Salsalate 1.5 g bid Piroxicam 20 mg qd	Ritchie index, morning stiffness, grip strength, VAS, patient assessment of efficacy. (Wilcoxon's signed-rank and Kruskal-Wallis) Both groups improved significantly from baseline for all measures ($p<0.05$). It was noted that there were no between-drug differences (no p value was provided)	Treatment effectiveness was reported to be fair to good in 75% of piroxicam versus 58% of salsalate treated pts. Four pts in the salsalate group withdrew from treatment (2 tinnitus) and none in the piroxicam group.
Deodhar, et al [32] Rheumatoid arthrits: Placebo n=18 Salsalate n=18 Indomethacin n=18 (1 week on each treatment) DB, R, PC, crossover study	Each patient was assigned to a random treatment sequence of placebo, salsalate and indomethacin given tid for 1 week (Total number of patients=18)	Duration of morning stiffness, VAS, articular index, grip strength, patient and physician assessments, patient's preference, and ESR. (Student's t-test for paired values). In all above measures, salsalate and indomethacin were significantly better than placebo ($p<0.05$) except grip strength and ESR. Although no p value is provided, it is noted that there was no difference between indomethacin and salsalate except duration of morning stiffness was less with salsalate.	15 patients completed the study. 2 pts on placebo withdrew due to severe pain, and 1 on salsalate withdrew due to tinnitus.
Bombardier, et al. [33] Rheumatoid arthritis: Salsalate n=143 Diclofenac n=151 (8 weeks) DB, R, PC	Salsalate 2-4.5 g qd (divided bid) Diclofenac 50-150 mg qd (divided tid)	Primary multivariate analysis: p=0.29 (MANOVA) Total painful joint Pain VAS score Physician's global score 38% of salsalate and 31% of diclofenac pts withdrew due to lack of efficacy, ADE, Lab abnormality, protocol violation, intercurrent illness (see comments).	Mean daily dose: Salsalate 3.55 g, Diclofenac 112 mg Greater percent of pts were on a higher dose of diclofenac compared to salsalate. A greater number of patients reported ADE with salsalate (tinnitus/hearing loss).
Atkinson, et al. [34] Salsalate 771 patients 90% Osteoarthritis 9.7% Rheumatoid arthritis 0.3% Both OA and RA (25 day duration) OL, MC, prospective	Salsalate 1.5 g bid If effective, continue dose. If effective, but ADE limits use, decrease by 1 tablet (750 mg). If not effective and no ADE, increase by 1 tablet (750 mg). If not effective and ADE, D/C salsalate. Max. dose 4.5 g qd	Physician assessment of patient improvement and patient satisfaction with therapy were recorded on a clinical evaluation card. All ADE were recorded and graded by the physician in terms of relationship to salsalate admin. (Descriptive statistics were used to analyze data from the clinical evaluation cards. ADE associations were evaluated by chi-square tests and trends by use of rank scores). Patient satisfaction was rated as excellent or good in 67.2-80.7 % of individuals. Mean salsalate dose at 1st and 3rd weeks were approximately 2.9 g for OA and RA.	The objectives of this trial were to prospectively evaluate the use of tinnitus as a method of establishing the best dose of salsalate in routine practice settings. However, there was minimal dose adjustment over the study period. Patient satisfaction increased over the study duration for OA and RA. 6.7% of patients withdrew due to tinnitus (their doses weren't adjusted downward prior to d/c).
McPherson, TC [35] Salsalate 182 patients Inflammatory polyarthritis, Osteoarthritis or nonarticular rheumatism (15 day duration) OL, MC	Salsalate 1.5 g bid	To evaluate current status of disease, investigator rated five indices of arthritis: pain, stiffness, joint swelling, limitation of motion, and disability as mild, moderate or severe. Changes from baseline were assessed. At baseline and study completion, both physician and patient independently estimated the global degree of rheumatic disease as mild, moderate or severe. ADEs were recorded. Median improvement of 47% was noted in 79% of patients measured on a summary index.	

ADE=adverse effect; DB=double-blind; bid=twice daily; d/c=discontinuation; ESR=erythrocyte sedimentation rate; MC=multicenter; OA=osteoarthritis; OL=open-label; ; PC=placebo controlled; PG=parallel group; pts=patients; qd=daily; RA=rheumatoid arthritis; R=randomized; SB=single-blind; tid= three times daily; VAS=visual analogue scale

Appendix 1:

Gastrointestinal Risk Assessment Tool (GI Score): This scoring tool was developed by Dr G. Singh and Colleagues at Stanford University and is based upon hospitalization data (566 hospitalizations from serious GI injury) from 6,386 patients with rheumatoid or osteoarthritis followed prospectively. The authors used Cox proportional hazard models to determine risk factors. The GI Score is calculated from individual patient responses to 6 questions. Each question is assigned a certain number of points. Once the points have been added up, a GI risk score from 1 to 4 is assigned (1 lowest risk, 4 highest risk). The 6 questions are as follows:

1. How old are you?

Age	Points	Age	Points	Age	Points
<20 years	0	41-45	6	66-70	13
21-25	1	46-50	8	71-75	14
26-30	3	51-55	9	76-80	16
31-35	4	56-60	10	81-85	17
36-40	5	61-65	12	>85 years	18

Points:_____

2. How do you rate your current health status on the following scale?

Health Status	Points
Very Poor	4
Poor	3
Fair	2
Well	1
Very Well	0

Points:_____

3. Has a physician ever told you that you have rheumatoid arthritis (not osteoarthritis or other forms of arthritis)?

No: 0 points Yes: 2 points **Points_____**

4. If you are taking prednisone or other corticosteroid, for how many months have you taken them in the past year?

Months	Points
0	0
1-3	1
4-6	3
7-10	4
11-12	5

Points:_____

5. Have you ever been hospitalized for a stomach or intestinal problem such as bleeding or an ulcer? (If the answer is yes, skip the next question).

No 0 points Yes: 8 points **Points:_____**

6. If no, have you ever had gastrointestinal side effects (heartburn, stomach pain, nausea, vomiting) when taking NSAID pain relievers?

No 0 points Yes: 2 points **Points:_____**

Total Points:_____

Evaluation of Patients Risk for serious NSAID-Induced Gastrointestinal event within the next year:

Risk Level	Points	Recommendations
1-No risk	0-10	Patients may use a non-selective formulary NSAID
2-Moderate risk	11-15	Patients may use a non-selective formulary NSAID
3-Significant risk	16-20	<30 days or intermittent use- standard NSAID;>30 days use- salsalate or etodolac*, if failure or intolerant, then COX-2 inhibitor
4-Substantial risk	>20	Use salsalate or COX-2 inhibitor

*Although limited, data does exist supporting etodolac to be a safer alternative to traditional NSAIDs.
Patients with osteoarthritis must fail treatment with acetaminophen 4000 mg daily and/or salsalate prior to initiating a COX-2 inhibitor.
Patients with an allergy to sulfonamides should **not** receive celecoxib.
Dyspepsia is **not** a reason to use a COX-2 inhibitor since COX-2 inhibitors may also lead to dyspeptic symptoms.
Lack of response to NSAIDs is **not** a reason to use a COX-2 inhibitor. COX-2 inhibitors are not more effective than other NSAIDs
The use of low dose aspirin (325 mg qd or less) may reduce or eliminate any GI protective benefit of the COX-2 inhibitors, but did not appear to significantly increase the GI toxicity of NSAIDs (ibuprofen or diclofenac) in the CLASS trial.

Table 3. Monthly Cost of Therapy

Drug	Dose	VA National Formulary (Y/N)	Cost per Month ($)
Acetaminophen	1000 mg qid	Yes	2.40 (500 mg tablet)
Piroxicam	20 mg qd	Yes	1.20
Ibuprofen	800 mg tid	Yes	1.87
Sulindac	200 mg bid	Yes	2.39
Indomethacin	25 mg tid	Yes	2.70
Salsalate	**1500 mg bid**	**Yes**	**2.83**
Naproxen	500 mg bid	Yes	4.23
Diclofenac	75 mg bid	No	5.04-13.20*
Etodolac	300-400 mg bid	Yes	6.90
Tolmetin	400 mg tid	Yes	13.50
Rofecoxib	**12.5**-25 mg qd 50 mg qd†	No	39.00 66.00
Celecoxib	**200 mg qd** 100 mg bid 200mg bid	No	39.00 39.00 78.00
Nabumetone	750 mg bid or 1500 mg qd	No	48.60
Misoprostol	200 mcg tid-qid	Yes	41.40-55.20
Misoprostol+Naproxen	200 mcg tid-qid+ 500 mg bid	Yes	45.63-59.43
Lansoprazole+Naproxen	15 or 30 mg qd +500 mg bid	Yes	33.93
Famotidine+Naproxen	40 mg bid+500 mg bid	Famotidine-No Naproxen-Yes	77.43

*Generic manufacturer price variation† Dose approved only for acute pain. The PBM/MAP criteria for nonformulary use of the COX-2 inhibitors does not permit the use of COX-2 agents for acute pain.

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Annotated References: (randomized trials listed in tables 1 and 2)

Fries JF, Spitz PW, Williams CA, et al. A Toxicity Index For Comparison of Side Effects among Different Drugs. Arthritis Rheum 1990;33(1):121-130.

Fries and colleagues developed a morbidity and mortality toxicity index for comparing overall toxicity of groups of drugs. The process of developing this index included identifying techniques for valid assessment of the number of specific toxic events occurring with a drug (numerator) and a valid estimation of the number of years exposed to the drug (denominator). Next, the authors established weights for various adverse effects; determined index structure utilizing weights and severity; and finally, used statistical methodology for fine-tuning and comparison among drugs.

Fries JF, Williams CA, Bloch, DA. The Relative Toxicity of Non-Steroidal Anti-Inflammatory Drugs. Arthritis Rheum 1991;34(11):1353-1360.

The authors discuss a toxicity index (above) that they used to compare 11 different NSAIDs. The toxicity index took into account symptoms, laboratory abnormalities and hospitalizations and weighted them for severity. The most toxic agents were indomethacin, tolmetin, and meclofenamate. The least toxic were coated or buffered aspirin, salsalate, and ibuprofen.

Hawkey CJ. COX-2 Inhibitors. Lancet 1999;353:307-314.

The authors of this review discuss the discovery of the 2 isoforms of COX and screening of drugs for COX-1 versus COX-2 selectivity. All of the COX-2 specific or selective drugs, currently available and in development, are listed.

Lanza FL. A Guideline for the Treatment and Prevention of NSAID-Induced Ulcers. Am J Gastro 1998;93:2037-2046

This review discusses the identification of patients at high risk for NSAID-related GI complications. In addition, the authors talk about strategies for prevention and treatment of NSAID-induced ulcers.

Rothstein R. Safety Profiles of Leading Nonsteroidal Anti-Inflammatory Drugs. Am J Med 1998;105(5A):39S-43S.

The author of this article talks about how newly marketed NSAIDs have tried to utilize special physical or pharmacologic properties to reduce the GI toxicity of NSAIDs. He also discusses how the use of injectable, enteric coating and pro-drug formulations has not provided the desired safety. However, other factors may be involved in decreasing the GI toxicity from NSAIDs including selective COX-2 inhibition, shortened half-life, low or absent enterohepatic recirculation, and nonacidic pro-drug formation.

Singh G, Ramey DR. NSAID Induced Gastrointestinal Complications: The ARAMIS Perspective-1997. J Rheumatol 1998;25 Suppl 51:8-16.

This report is based upon data from the ARAMIS PMS database. This program prospectively follows outcomes, adverse effects, and economic impact of illness in patients with OA and RA. Individuals in this cohort answer questions from the Stanford Health Assessment Questionnaire (HAQ) every 6 months. The questionnaire includes inquiries about medications, side effects, severity of side effects, hospitalizations, emergency department visits, outpatient surgery, and other medical procedures. Patients are contacted until they complete the questionnaire. Questions that are answered in this yearly report are as follows: What are the GI side effects of NSAID use; What is the magnitude of this problem; Are there warning signs for serious GI complications; Who is at greatest risk; Do some NSAIDs cause more GI toxicity than others; and finally, Do H2-receptor antagonists and antacids help prevent serious GI complications?

Wallace JL. Nonsteroidal Ant-Inflammatory Drugs and Gastroenteropathy: The Second Hundred Years. Gastro 1997;112:1000-1016.

This review focuses on both the mechanisms and prevention of NSAID-induced gastrointestinal tract (stomach, small intestine and colon) injury. The authors also discuss new approaches for developing NSAIDs that are safer for the GI tract (zwitterionic phospholipids, pure enantiomers of chiral NSAIDs, NO-releasing NSAIDs, and specific COX-2 selective agents).

Wolfe MM. Future Trends in the Development of Safer Nonsteroidal Anti-Inflammatory Drugs. Am J Med 1998;105(5A):44S-52S.

This review also focuses on the mechanisms and prevention of gastrointestinal injury. The authors also talk about future development of GI-safer NSAIDs (same as above).