



Intervention Proposal

Initiative: Nonsteroidal Anti-inflammatory Drugs:
Drug Usage Evaluation
Prepared for: Kansas Medicaid
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Initial Study **Follow-up/Restudy**

Executive Summary

Purpose: To promote safe, cost-effective use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Why was this Issue Selected: NSAIDs are one of the most commonly prescribed classes of drugs. Gastrointestinal (GI) problems are the most common side effects associated with NSAID use. NSAID-induced GI toxicities are a significant cause of morbidity and mortality in the U.S. and have a significant economic impact. Several risk factors have been identified that place patients at increased risk for adverse GI events. High risk patients may be targeted for preventive GI co-therapy or use of COX-2 inhibitors. Patients without risk factors, who are receiving a COX-2 inhibitor, may be identified for re-evaluation and potential use of lower costing non-selective NSAIDs.

Program-Specific Information:	<u>Performance Indicators</u>	<u>Exceptions</u>
• Increased risk of ADE: NSAID-induced GI toxicity		426
• Use of COX-2 inhibitors in the absence of risk factors for GI toxicity		154
• Increased risk of ADE: NSAID use with H ₂ receptor antagonist or sucralfate therapy		207
• Increased risk of ADE: NSAID use in geriatric patients		461
• Therapeutic Duplication: Concurrent use of >1 NSAID		22
• Drug-drug interactions with NSAID use		3,975

Setting & Population: All adult patients currently receiving NSAIDs; all available lines of business.

Type of Intervention: Letter + **High risk chart** + Individual patient profiles

Main Outcomes Measures: The performance indicators will be remeasured.

Anticipated Results: Safe, cost-effective use of NSAIDs will be achieved by limiting duration of therapy when appropriate, reducing duplicate therapy, decreasing the risk of NSAID-induced GI adverse events by treating appropriate patients with preventive co-therapy or COX-2 inhibitors, and minimizing drug-drug interactions. Physicians will be more aware of the costs of various NSAIDs, as well as the costs of preventive GI co-therapies and COX-2 inhibitors.

Purpose Of Initiative

The purpose of this initiative is to promote safe, cost-effective use of nonsteroidal anti-inflammatory drugs (NSAIDs). Reducing the risks for NSAID-induced adverse effects, especially GI side effects, as well as making prescribers more aware of the wide range of costs for various NSAIDs, COX-2 inhibitors, and preventive co-therapies, will lead to safer, more cost-effective treatment.

Why has this clinical issue been selected for review?

NSAIDs are one of the most commonly prescribed classes of drugs.¹ Gastrointestinal (GI) problems are the most common side effects associated with NSAID use. NSAID use has been shown to increase the risk of peptic ulcer disease by 3-5 fold. Approximately 15% of NSAID users will have dyspepsia and 1-4% will have significant GI complications each year (e.g., perforated ulcers or GI bleeding requiring hospitalization).² Serious NSAID-related GI complications lead to an estimated **107,000 hospitalizations and 16,500 deaths each year** (similar to the number of deaths due to AIDS) in arthritis patients alone,² and have been estimated to cost **\$4 billion annually in the US**.¹ The majority of patients who develop serious GI complications have no warning signs or symptoms. Several risk factors have been identified that place patients at increased risk for adverse GI events. High-risk patients may be targeted for preventive therapy.

Risk Factors for NSAID-Induced GI Adverse Events

The following factors have been identified as placing NSAID-using patients at greater risk for GI adverse events:²⁻⁴

- Advanced age (defined as >60-65 years old by most studies)
- High dose NSAID use
- Concurrent use of NSAIDs and corticosteroids
- Concurrent use of NSAIDs and oral anticoagulants
- Prior history of GI events (e.g., GI hemorrhage or ulcer)

Smoking and alcohol use have been reported to increase the risk of NSAID-induced ulcers, but the reported relationships between these factors are inconsistent. With regard to duration of therapy, cumulative risk tends to increase over time, but serious NSAID-induced GI events can occur at any time during NSAID therapy, and NSAID use for the shortest appropriate time and lowest effective dose is recommended.² Use of multiple NSAIDs has also been reported to increase the risk of adverse GI events.

GI Toxicity Among NSAIDs

A number of studies have attempted to rank NSAIDs based on GI toxicity. The roles of the cyclooxygenase isoenzymes (COX-1 and COX-2) are important to this discussion. Traditional NSAIDs inhibit both isoforms of cyclooxygenase, however the degree and ratio of inhibition varies between NSAIDs. Those that are more selective for COX-2 are proposed to have less associated GI toxicity as compared to those with higher COX-1 inhibition.⁵

The Role of Selective COX-2 Inhibitors

In clinical trials, celecoxib and rofecoxib have demonstrated similar pain relief efficacy as compared to traditional NSAIDs with a significantly lower incidence of ulcers confirmed by endoscopy. However, because of the lack of long-term data regarding gastrointestinal complication rates, the FDA required product labeling for celecoxib and rofecoxib to contain the same warnings about adverse GI events as the labeling of non-selective NSAIDs.

The health and cost impact of switching higher-risk patients from non-selective NSAIDs to selective COX-2 inhibitors has not been established. COX-2 inhibitors are reported to have equivalent efficacy to non-selective NSAIDs, but are more expensive than generic non-selective NSAIDs. COX-2 inhibitors may have the potential to decrease total treatment costs since patients may be able to discontinue GI protective co-therapy such as acid-reducing agents or misoprostol. Further studies are required to confirm these purported cost savings and the appropriate time frame and safety of discontinuing GI protective co-therapy. Use of selective COX-2 inhibitors in the absence of risk factors may not be cost-effective.

Prevention of NSAID-Induced GI Adverse Events

The safest method for reducing NSAID-induced adverse GI events is to limit the use of NSAIDs. For non-inflammatory conditions such as osteoarthritis, acetaminophen is recommended as first-line drug therapy. Use of concomitant prophylactic GI therapies in asymptomatic NSAID-users is discouraged due to the potential for masking of GI symptoms without reducing the risk of serious GI complications.⁶

In one examination of the ARAMIS database, approximately one-third of patients were receiving concomitant GI medications, mostly antacids or H2 receptor antagonists, 75% being used for prophylaxis rather than treatment.² Neither sucralfate nor traditional doses of H2 receptor antagonists have been shown to prevent gastric ulcers, the most common type of NSAID-induced ulcer.⁷ Several recent trials have demonstrated the efficacy of the proton pump inhibitor (PPI), omeprazole, in the treatment and prophylaxis of NSAID-induced ulcers. Omeprazole has been shown to have similar efficacy compared to misoprostol for gastric ulcer prevention, and is more efficacious for duodenal ulcer prevention. PPIs may be better tolerated than misoprostol, and so may be more attractive prophylactic treatment options for some high-risk patients.⁸

There are no data directly comparing the rates of adverse GI events in patients receiving a COX-2 inhibitor versus patients receiving non-selective NSAIDs + prophylactic co-therapy (misoprostol or a proton pump inhibitor). Until this data becomes available, prescribers will need to consider individual patient risk factors and characteristics, and relative costs of NSAIDs, COX-2 inhibitors, and prophylactic GI co-therapies when deciding which method will best protect their high-risk patients.

Specific Concerns for NSAID Use in the Elderly

Older patients are at higher risk of adverse effects from NSAIDs than younger patients. Aside from the well known GI side effects, the elderly may be at risk for other NSAID-associated adverse effects including renal and hepatic toxicities, and cognitive dysfunction.² Factors influencing NSAID-induced toxicities in the elderly include physiologic changes related to age (e.g. changes in hepatic metabolism or protein binding), concurrent medical problems, and polypharmacy, which may place elderly patients at higher risk for drug-drug interactions.⁹ Before prescribing NSAIDs to a patient over age 70, clinicians should consider the appropriateness of other analgesics such as acetaminophen, the minimum effective dosage, and the need to periodically review the continued need for treatment.

NSAID Drug-Drug Interactions

Several drug-drug interactions have been reported for both non-selective NSAIDs as well as the newer COX-2 inhibitors (see appendix). It is sometimes necessary to use interacting drugs concomitantly. If the combination cannot be avoided for clinical reasons, patients should be regularly monitored for toxicity.

Setting & Population

Date Range of Analysis:

Performance Indicators

Indicator #1 :	Increased risk of adverse drug events: NSAID-induced GI toxicity
<ul style="list-style-type: none"> • Why has this indicator been selected? • How will the patients be selected? 	<p>NSAID discontinuation is the most effective method for reducing GI toxicity risk. Initiating prophylactic treatment in all patients requiring NSAIDs may be unnecessary and cost-prohibitive, but should be strongly considered for high risk patients due to the substantial morbidity and mortality associated with NSAID-induced GI complications.</p>
Candidates (denominator):	Patients receiving a NSAID in the past 90 days for at least 30 days duration

- Exception criteria (numerator): Candidates with any of the following risk factors:
- Concurrent warfarin use
 - Concurrent steroid use
 - High dose NSAID (>75% maximum recommended daily dose)
 - History of GI event (PUD or GI bleed diagnosis)
 - Age > 70 years

Indicator #2 : **Use of COX-2 inhibitors in the absence of risk factors for GI toxicity**

- Why has this indicator been selected?
Non-selective NSAIDs and selective COX-2 inhibitors are reported to have equal analgesic efficacy. Use of selective COX-2 inhibitors in the absence of risk factors may not be cost-effective since COX-2 inhibitors are more expensive than generic non-selective NSAIDs.
- How will the patients be selected?
Candidates (denominator): Patients receiving COX-2 inhibitors within the past 90 days
Exception criteria (numerator): Candidates without any of the risk factors listed in indicator #1

Indicator # 3 : **Increased risk of adverse events: NSAID use with H₂ receptor antagonist or sucralfate therapy**

- Why has this indicator been selected?
Use of prophylactic GI therapies in asymptomatic NSAID-users is discouraged due to the potential for masking GI symptoms without reducing the risk of serious GI complications. Prophylactic co-therapy may be needed for patients with risk factors for GI toxicity. Misoprostol has been approved by the FDA for prophylaxis against gastric and duodenal ulcers associated with NSAID use. Proton pump inhibitors may be an acceptable alternative. H₂ receptor antagonists, sucralfate and antacids have not been found to effectively prevent NSAID-induced ulcers.
- How will the patients be selected?
Candidates (denominator): Patients receiving NSAIDs concomitantly with an H₂ receptor antagonist or sucralfate within the past 90 days
Exception criteria (numerator): Candidates without a diagnosis of active peptic ulcer disease or gastroesophageal reflux disease

Indicator # 4 : **Increased risk of adverse drug events: NSAID use in geriatric patients**

- Why has this indicator been selected?
Older patients are at higher risk of adverse effects from NSAIDs than younger patients. Aside from the well known GI side effects, the elderly may be at risk for other NSAID-associated adverse effects including renal and hepatic toxicities, and cognitive dysfunction.
- How will the patients be selected?
Candidates (denominator): Patients receiving NSAIDs within the past 90 days
Exception criteria (numerator): Candidates over the age of 70

Indicator # 5 :

Therapeutic Duplication: Concurrent use of >1 NSAID

- Why has this indicator been selected? Multiple NSAIDs should not be used concurrently due to increased risk of GI adverse effects and lack of evidence of increased efficacy.
- How will the patients be selected? Patients receiving multiple NSAIDs or COX-2 inhibitors concurrently will be identified.

Indicator # 6 :

Drug-drug interactions with NSAID use

- Why has this indicator been selected? Patients with potential drug-drug interactions are at increased risk of having an adverse drug event involving NSAIDs. If the combination cannot be avoided for clinical reasons, patients should be regularly monitored for toxicity.
- How will the patients be selected?
 - Candidates (denominator): Patients receiving a NSAID or COX-2 inhibitor within the past 60 days
 - Exception criteria (numerator): Candidates receiving an interacting drug (see appendix)

Intervention Material

Cover letter:
 Clinical Summary:

Physician Profiling Report:
 Individual Patient Profiles:

Outcomes Measurement

The effects of this initiative will be measured when six months of data are available after the mailing. Indicators to be measured include: (1) prophylactic therapy or COX-2 inhibitor use in patients with risk factors for GI toxicities, (2) use of COX-2 inhibitors in the absence of risk factors for GI toxicities, (3) use of H₂ receptor antagonists or sucralfate co-therapy in the absence of PUD or GERD, (4) use of NSAIDs in elderly patients, (5) duplicate therapy with NSAIDs or COX-2 inhibitors, and (6) NSAID-related drug-drug interactions.

An overall program analysis along with evaluation of the following groups will be prepared:

Group	Providers	Patients
Plan-wide	All providers	All patients
Targeted physicians	Intervention only	All patients
Targeted patients	Intervention only	Intervention only (adjusted for active program enrollment)
New patients	Intervention only	Patients started on targeted therapy after the intervention. This group should reflect any changes in the provider's prescribing patterns for patients just started on the targeted therapy.

Anticipated Results

Physicians will safely and cost-effectively utilize NSAIDs by treating patients at high risk for NSAID-induced adverse GI effects with prophylactic therapy or a COX-2 inhibitor, avoiding duplicate therapy and drug-drug interactions involving NSAIDs, utilizing low dose, short duration regimens when possible (especially in high risk and elderly patients), and recognizing the costs of non-selective NSAIDs, COX-2 inhibitors and GI agents used for prophylactic therapy.

1. Goldstein JL, Larson LR, Yamashita BD. Prevention of nonsteroidal anti-inflammatory drug-induced gastropathy: clinical and economic implications of a single-tablet formulation of diclofenac/misoprostol. *Am J Man Care* 1998;4:687-697.
2. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med.* 1998;105(1B):31S-38S.
3. Lanza FL. A guideline for the treatment and prevention of NSAID-induced ulcers. *Am J Gastroenterol.* 1998;93:2037-2046.
4. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. *Ann Intern Med* 1991;115:787-796.
5. Fosslien E. Adverse effects of nonsteroidal anti-inflammatory drugs on the gastrointestinal system. *Ann Clin Labor.* 1998;28:67-89.
6. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999;340(24):1888-1899.
7. Lanza FL. Prophylaxis against nonsteroidal anti-inflammatory drug-associated ulcers and erosions: a commentary on the new data. *Am J Med* 1998;104(3A):75S-78S.
8. Hawkey CJ. Progress in prophylaxis against nonsteroidal anti-inflammatory drug-associated ulcers and erosions. *Am J Med* 1998;104(3A):67S-74S.
9. Todesco S. Special considerations in the use of NSAIDs in the elderly. *Eur J Rheum Inflamm* 1994;14:7-13.

APPENDIX

POTENTIALLY SIGNIFICANT NONSTEROIDAL ANTI-INFLAMMATORY DRUG INTERACTIONS	
Drug Category	Interacting Drugs
Non-selective NSAIDs	ACE inhibitors (HTN or CHF diagnosis) Beta blockers (HTN or CHF diagnosis) Cyclosporine (>1 MD only flagged) Digoxin (elderly or ↓ renal function) Diuretics (HTN or CHF diagnosis) Lithium Triamterene (indomethacin only) Warfarin
Selective COX-2 Inhibitors	ACE inhibitors (HTN or CHF diagnosis) Diuretics (HTN or CHF diagnosis) Lithium Rifampin (rofecoxib only) Warfarin