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Management of NSAID-Associated Upper GI Disorders Using *AMCP's Framework for Quality Drug Therapy*

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4. Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.

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Avey received his BS degree and MS degree in pharmacy administration from the University of Utah College of Pharmacy. He has more than 25 years experience in pharmacy, with a diverse background in retail, long-term care, and management; for the last 14 years, his focus has been on managed care pharmacy. One of his more notable achievements in this arena was to design and establish a pharmacy benefit management (PBM) division for Smith's Food & Drug Centers, a 150-store chain in the western United States. He worked directly with employers to design and implement their prescription drug programs.

Prior to his position at FMCP, Avey spent 4 years at Prospective Health Inc., serving as vice president of operations and building its PBM business from the ground floor. Under his direction, the operation grew from a start-up to an organization that processed 30 million pharmacy claims in 1999.

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Target Audience

Pharmacists working in all settings and other health care professionals

Learning Objectives

Upon completion of this program, participants will be better able to

1. identify risk factors for nonsteroidal anti-inflammatory drug-related gastrointestinal (GI) adverse events and describe their usual presentation and course,
2. list possible strategies to prevent NSAID-related GI events and discuss each strategy's merits and disadvantages,
3. describe the necessity of intermingling good leadership with good management to maximize an organization's potential for success,
4. define 4 types of change to improve drug therapy,
5. employ AMCP's *Framework* in his or her unique pharmacy practice to optimize patient outcomes.

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Management of NSAID-Associated Upper Gastrointestinal Problems

BYRON CRYER, MD

ABSTRACT

OBJECTIVE: To describe risk factors and review appropriate management strategies for patients who experience nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal (GI) adverse events.

SUMMARY: NSAIDs are the most heavily prescribed class of drugs. Their association with gastrointestinal events has been known for many years. Often presenting with little warning, serious GI events can be life-threatening. Primary care clinicians can and should prevent these events and manage symptoms before they progress to serious problems. Risk factors, including increasing age, presence or history of GI ulceration/bleed, and concomitant medications, are well known. Clinicians may be less familiar with the impact of multiple NSAID use (including low-dose aspirin), or *Helicobacter pylori* infection. Use of gastroprotective agents can prevent serious complications.

CONCLUSION: Familiarity with risk factors, use of appropriate interventions, and careful monitoring can prevent serious, life-threatening GI problems.

KEYWORDS: NSAID, COX-2 inhibitors, Gastrointestinal bleeding, Low-dose aspirin

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Management of nonsteroidal anti-inflammatory drug (NSAID)-induced gastrointestinal (GI) complications has been an issue of interest to clinicians in an almost universal way during the last several years. With the introduction of cyclooxygenase-2 (COX-2) inhibitors, the prevalence of NSAID use among the elderly in one Canadian province increased from 14% to nearly 20%; the increase has been correlated with an increase in the rate of hospitalizations for upper GI bleeding.[1] Similar increases probably occurred elsewhere. Our understanding of the subject matter continues to change over time as the data evolve. This article's goal is to review the most recent clinical and research observations related to management of this problem and provide an intervention framework for individual networks or practices.

NSAID-induced GI effects can be approached by examining 3 principal components—prevention, symptoms, and healing. Clinical approaches will vary with each component. When trying to manage symptoms, for example, various therapeutic strategies generally use acid-lowering mechanisms to reduce dyspepsia. This article focuses on symptom treatment and ulcer prevention since patients diagnosed with ulcers are generally managed by specialists rather than generalists. Generalists, including physicians, nurse practitioners, physician assistants, and pharmacists, are more likely to encounter the need to prevent ulcer formation when NSAIDs are prescribed or to manage symptom issues after initiation of NSAIDs.

Incidence of Endoscopic NSAID-Induced Gastric or Duodenal Ulcer

The precise incidence of NSAID-induced ulceration is dependent on the definition and monitoring methods used. If endoscopy is employed at baseline and then at regular intervals after NSAIDs are administered (e.g., 1, 2, 3 months), the incidence of NSAID-related ulceration approaches 40%. Specifically, gastric ulcers occur in 10% to 30% (mean=15%) of patients, and duodenal ulcers occur in 4% to 10% (mean=5%) of NSAID-treated patients. Thus, 4 of every 10 NSAID-treated patients develop an ulcer.[2] This data can be slightly misleading; nowhere near 40% of individuals who take NSAIDs experience perceptible GI problems. Generalists must remember this axiom: most NSAID-related ulceration is asymptomatic. Its corollary is that we must not use the presence of symptoms to predict which NSAID users will be at risk for complications.

Studies have assessed patients presenting with NSAID-related upper GI bleeds to determine how many of those patients experienced symptoms prior to presenting with a bleed on an NSAID. Armstrong and Blower, in an early study, examined 235 consecutive patients with life-threatening peptic ulceration complications over a 36-month period. Of the 235 patients, 141 (60%) were taking an NSAID, and mortality associated with a peptic ulcer complication in NSAID-treated patients was more

than double that of patients who did not report NSAID use. The first sign of ulceration was a life-threatening complication in 58.2% of NSAID-treated patients. Almost 80% of all ulcer-related deaths occurred in patients using NSAIDS. NSAID use was associated with older age, more preexisting medical conditions, and larger ulcers.[3]

Singh's later prospective observational study evaluated event rates for all NSAID-induced GI complications in 1,921 patients with rheumatoid arthritis (RA), with particular attention to the time course of events and prophylactic therapy's role. Using information from validated patient self-reports collected every 6 months and supplemented by review of hospital records for all hospitalizations, they found that approximately 15% of patients reported an NSAID-induced GI side effect during the 2.5-year observation period. Forty-two patients had a serious GI complication requiring hospitalization; 34 (81%) of these 42 patients did not have a preceding GI side effect. Asymptomatic patients taking antacids and H2 receptor antagonists were at significantly higher risk for GI complications compared with those who did not take these medications.[4] This underscores the point that NSAID-related symptoms are typically absent.

The incidence of complications is much lower when clinical symptoms are used to identify patients at risk of perforation. Clinically significant ulcers (ulcers that present with pain, perforation, or bleeding) occur in 1% to 4% of NSAID-treated patients, with an average of about 2%. Although a 2% incidence of adverse events for several classes of medicines causes little concern, because NSAIDs are the most commonly taken medications worldwide, the impact is significant—NSAID-associated mortality causes greater than 16,000 deaths in the United States annually.[1] Since symptomatic presentation cannot be used to risk-stratify, other characteristics must be considered prior to initiation of NSAID therapy to identify patients at risk.

Reducing Risk: Identify Risk Factors

It is possible to reduce the likelihood that an NSAID-related GI complication might occur. First, clinicians must identify risk factors in the at-risk population (Table 1). Risk factors are not quantitatively similar. Figure 1 describes how risk factors compare. Several risk factors significantly increase risk. Patients who have these risk factors are appropriate candidates for risk reduction using gastroprotective drugs or safer NSAIDs. Note also that patients having 4 risk factors (increasing age, history of peptic ulcer or bleeding, and cardiovascular disease) have a 9% risk for a major complication during 6 months of NSAID treatment.[5] Most clinicians are aware of and appreciate age, GI ulceration, and concomitant medications as risk factors; these are described briefly. Other risk factors are covered in greater depth because they are less well known.

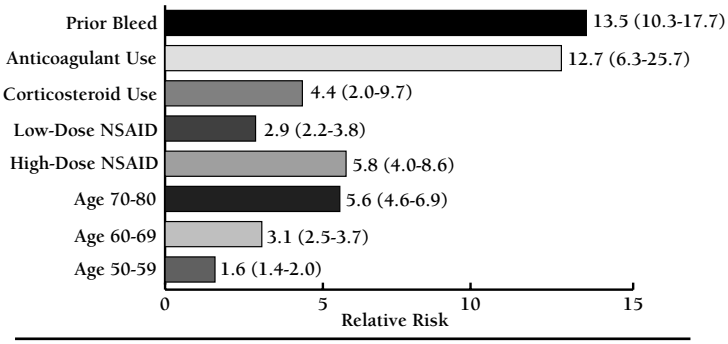
Age. Most risk assessment tools have included a threshold age above which or below which one either does or does not qualify for risk reduction. No magical age threshold exists that automatically places individuals at risk for having an NSAID-related event, however. Age-related risk increases incrementally, starting around age 50, increasing about 2 percentage points per decade to age 70 to 80. Patients in their eighth decade are at a 6-fold increased risk of having an NSAID-related GI complication.[5]

TABLE 1 Risk Factors for GI Complications With NSAIDs[6-10]

- Age (>65 years)
- GI ulceration
- A history of ulcer complications
- Concomitant wafarin or corticosteroids
- Multiple NSAID use, including low-dose aspirin use for cardioprophylaxis
- Cardiovascular disease
- *Helicobacter pylori* infection

GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

FIGURE 1 Risk Factor for Serious GI Adverse Events With NSAIDs: Relative Risks



Rodriguez L. Lancet. 1994; Guttham SP. Epidemology. 1997; Shorr RI. Arch Intern Med. 1993; Piper JM. Ann Intern Med. 1991.

GI ulceration or a history of ulcer complications. For patients with a history of a previous GI bleed, the risk is higher than 13 times the risk for those who have no history. It is essential that these patients have their risks reduced.[5]

Concommitant warfarin or corticosteroids. An NSAID user's risk for developing GI complications is 13 times greater when he or she is taking warfarin.[7-9]

Multiple NSAID use. Of these risk factors, "multiple NSAID use" has not been appreciated as well as it should be. Many clinicians wonder why someone would take multiple NSAIDs. After age, however, multiple NSAID use is the second most common risk factor. It frequently occurs when patients add over-the-counter (OTC) NSAIDs or low-dose aspirin to their prescribed COX-2 inhibitor or nonselective NSAID.[1] Data addressing the GI effects of low doses of aspirin or the GI effects of OTC NSAIDs, explain why addition of aspirin to an NSAID or a COX-2 inhibitor might exacerbate toxicities.

Wilcox's trial highlights the high prevalence of OTC use and OTC NSAID use in bleeders. A gastroenterology consultative service evaluated 421 consecutive patients with upper GI hemorrhage at a large inner-city hospital over 2 years. OTC

SIDEBAR The REDUCE Campaign

The American Gastroenterological Association (AGA) in association with the American Pharmacists Association has developed an educational effort called the REDUCE campaign. Its goal is to educate the public on the risk of analgesic-related events, especially in light of prevalent OTC and NSAID use and many of the misconceptions about these agents' safety. Their informative brochure, available from the AGA or on the Internet at http://www.2reduce.org/, prompts patients to self-assess for risk using a checklist. If patients determine they are at risk, the brochure encourages them to talk with their pharmacist or physician.

REDUCE = Risk Education to Decrease Ulcer Complications and Their Effects from NSAIDs; OTC = over-the-counter; NSAID = nonsteroidal anti-inflammatory drug.

aspirin or nonaspirin NSAID use during the week before admission was reported in 145 patients (35%) and 36 patients (9%), respectively. Fifty-six patients (14%) reported prescription nonaspirin NSAID use, and 27 patients (6%) reported prescription aspirin use. In other words, 21% of patients were taking nonaspirin NSAIDS and 44% were taking aspirin. Overall, 56% of patients had used an NSAID during the week before admission, and this was associated with ulcer-related bleeding and upper GI hemorrhage.[11]

In more recent trials, 80% of patients who present with upper GI bleeds have recently taken an NSAID.[12] NSAID use may represent a more important cause of peptic ulcer disease and ulcer-related hemorrhage than previously appreciated. It clearly surpasses *Helicobacter pylori (H. pylori)* as a cause of ulcer complication in patients.

Blot and Mclaughlin conducted independent analyses of data from an American College of Gastroenterology case-control study to evaluate and quantify potential GI bleeding risks associated with use of OTC analgesics. Information on use of multiple analgesics within the past week and data on other factors (e.g., alcohol and tobacco) were collected from 627 patients and 590 procedure-matched controls. GI bleeding risk was 2- to 3-fold greater among recent users of aspirin, ibuprofen, and other NSAIDs at OTC doses. Risk increased in a dose-related manner. Risk was unchanged among acetaminophen users. Alcohol consumption doubled risks of GI bleeding among drinkers.[13] Even with doses that are within the OTC's recommended label dosages, risk of GI bleeding increases.

The American Gastroenterology Association has tried to understand the patterns of OTC use (see Sidebar), and recently reported the results of 2 surveys separated by a 6-year interval. Daily use of OTC analgesics is fairly common, but of greater concern, 50% of OTC users report taking an amount of an OTC NSAID that falls within the prescription-dose range (that is, greater than the OTC dosage), thus increasing risk (see Sidebar).[14]

NSAID-related bleeding is also related to comorbidities or overall health status, and 15% to 20% of the patients in this study considered themselves in less than good health. Additionally, two thirds were unconcerned about the side effects, and one third of users who took OTC products believed combining OTC products with a prescribed NSAID was safe. About 50% of OTC NSAID use was ibuprofen, but the use of low-dose aspirin as an OTC product is increasing. Most studies indicate that about 20% of the population has indications for low-dose aspirin; in future years, aspirin use will increase.[14]

Low-dose aspirin. A study from the United Kingdom assessed dose-related differences associated with low-dose aspirin use. At 75 mg (comparable to a dose of 81 mg aspirin), risk of GI adverse events doubled, and risk was 3.9 times greater with 300 mg (comparable to 325 mg aspirin). They concluded, "No conventionally used prophylactic aspirin regimen seems free of the risk of peptic ulcer complications."[15]

A specific interest is whether a dose of aspirin exists that, if taken daily, would either have no GI risk or be associated with a lower risk of GI toxicity. When subjects were randomized to receive 10 mg (n = 8), 81 mg (n = 11), or 325 mg (n = 10) aspirin daily for 3 months, all doses significantly reduced gastric mucosal prostaglandin levels to approximately 40% of values measured at baseline. All doses induced significant gastric injury, and 325 mg caused duodenal injury. Aspirin at 325 daily significantly reduced rectal mucosal prostaglandin levels to approximately 60% of the baseline value. The findings indicate there is no dose of aspirin that will not induce GI events.[16]

Kelly and colleagues proved that enteric-coated aspirin does not provide a risk reduction benefit with non-enteric-coated or plain preparations of aspirin. They interviewed 550 patients (a cohort from the Framingham study) with upper GI bleeding after hospital admission and 1,202 controls identified from population census lists about use of aspirin and other NSAIDs during the 7 days before the onset of bleeding (cases) or interview (controls). The relative risks of upper GI bleeding for plain, enteric-coated, and buffered aspirin at average daily doses of 325 mg or less were 2.6, 2.7, and 3.1, respectively.[16]

Helicobacter pylori. Chan and colleagues addressed the uncertainty of whether infection with *H. pylori* is a risk factor for NSAID-induced upper GI bleeding. In a group of *H. pylori*-infected patients with bleeding upper GI ulcers, after subjects' ulcers were healed, half of the group received *H. pylori* eradication therapy for 1 week while the other half remained *H. pylori*-infected and took the proton pump inhibitor (PPI) omeprazole, 20 mg daily, for 6 months. Both groups were given 500 mg of naproxen twice daily for 6 months. Compared with the group that received *H. pylori* eradication, the omeprazole-treated group had an approximately 80% reduction in rates of recurrent upper GI bleeding, supporting the ability of PPI cotherapy to be very effective in the reduction of NSAID-associated upper GI bleeding.[17]

Reducing Risk

Researchers have studied several interventions to prevent serious GI events with nonselective NSAID use. An early strategy was to use a different NSAID formulation, specifically enteric-coating the

drug to reduce topical interaction of that NSAID with the stomach. However, after 4 weeks of administration, this strategy does not reduce risk compared with nonenteric formulations of NSAIDs.[1] The NSAID used most often as an enteric-coated formulation is aspirin. Enteric-coated aspirin will lessen dyspepsia, but the reduction in dyspepsia will not correlate with reduction in risk.

A second strategy was to use a different route of NSAID administration. Researchers suggested that bypassing the stomach (administering the NSAID parenterally) might be associated with a reduction in risk. The most familiar example is that of ketorolac. Rather than reducing risk, parenterally administered NSAIDs such as ketorolac are more ulcerogenic. Therefore, ketorolac's recommended duration of use is limited.[18]

With failure of these approaches, researchers moved toward 2 approaches currently considered acceptable strategies (assuming that prescribers are using the lowest effective dose of NSAID):

- cotherapy with misoprostol or a PPI or
- use of safer NSAIDs that specifically inhibit COX-2.

The Gold Standard: Coadministration of Misoprostol

The 6-month Misoprostol Ulcer Complication Outcomes Safety Assessment (MUCOSA) study was a randomized, double-blind, placebo-controlled trial to investigate whether concurrent administration of misoprostol reduces the occurrence of serious upper GI complications. This large trial enrolled 8,843 NSAID-treated patients receiving any of 10 specified NSAIDs for control of symptoms of RA. Patients were randomly assigned 200 micrograms of misoprostol or placebo 4 times a day. Serious upper GI complications were detected by clinical symptoms or signs (but not endoscopically). Misoprostol-treated patients had a 40% reduction in serious GI events compared with placebo-treated patients.[5]

H2 Receptor Antagonists

Many guidelines recommend H2 receptor antagonists to prevent NSAID-related GI events. Although each of the H2 blockers has been studied at usual ulcer-healing doses, none can adequately reduce the incidence of NSAID-related ulcerations.

In a double-bind, placebo-controlled trial, investigators studied the efficacy of 2 doses of famotidine (low-dose 20 mg and high-dose 40 mg, each given orally twice daily) compared with placebo in 285 patients without peptic ulcers who were receiving long-term NSAIDs. Clinical and endoscopic evaluation occurred at baseline and after 4, 12, and 24 weeks of treatment. The primary end point was the cumulative incidence of gastric or duodenal ulceration at 24 weeks. Placebo-treated patients had a cumulative incidence of gastric ulcers of 20%. Gastric ulcers occurred in 13% (a rate still unacceptably high) of the famotidine 20 mg twice-daily group, and 8% of the famotidine 40 mg twice-daily group. The reduction in occurrence of duodenal ulcers was similar (13% in the placebo group, 4% in the low-dose famotidine group, and 2% in the high-dose famotidine group). Famotidine was well tolerated.[19]

TABLE 2 GI Outcomes Trials: Design

	VIGOR (n = 8,076)	CLASS (n = 7,982)
Drug	Rofecoxib 50 mg QD (2x maximum chronic dose)	Celecoxib 400 mg BID (2x maximum chronic dose)
Patients	RA	OA (72%), RA (28%)
Comparator	Naproxen 500 mg BID	Ibuprofen 800 mg TID Diclofenac 75 mg BID
Low-dose ASA	No	Yes (21%)
Duration	Median 9 months Maximum 13 months	Median 9 months Maximum 13 months 6 months reported

ASA = aspirin; BID = twice daily; OA = osteoarthritis; QD = once daily; TID = thrice daily; RA = rheumatoid arthritis.

Researchers have examined higher doses of cimetidine, ranitidine, or nizatidine and for reasons that were initially unclear, only famotidine has demonstrated some benefit, albeit not as much as misoprostol or the PPIs. Thus, H2-blockers, in general, at usual ulcer-healing doses, should not be viewed as effective strategies for risk reduction for people who are taking NSAIDs.

COX-2 Specific Inhibitors

The list of 25 available NSAIDs in the United States includes 2 COX-2 inhibitors: celecoxib and valdecoxib. Prior to rofecoxib's withdrawal from the market, the 3 COX-2 inhibitors constituted about 50% of the prescribing for NSAIDs in the United States.

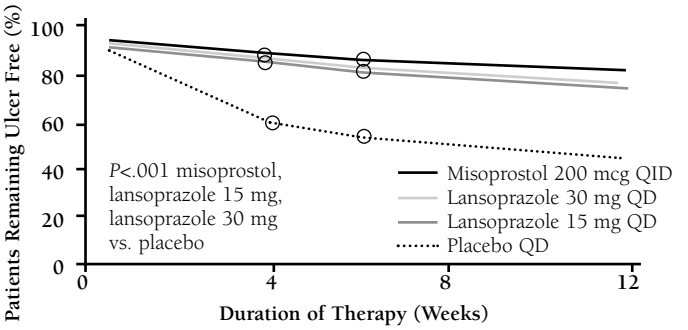
The cyclooxygenase (COX) isoform specific to the stomach is primarily COX-1. COX-1 is responsible for prostaglandin production, which protects against injury.

When COX-1 is inhibited by nonselective NSAIDs, prostaglandin production and GI protection are reduced. COX-2 selective inhibitors spare inhibition of GI COX-1 and confer a protective effect within the GI tract.[20,21] Several studies have been designed to examine this concept from the outcomes perspective, and the Vioxx Gastrointestinal Outcomes Resesarch (VIGOR)[22] and Celecoxib Long-term Arthritis Safety Study (CLASS)[23] trials are 2 of the most important. Each enrolled upwards of 8,000 patients. It is important to consider, however, whether the trials allowed use of low-dose aspirin or not.

Table 2 summarizes these trials' key points. In the CLASS (celecoxib) trial, 21% of patients took 81 mg or 325 mg aspirin daily, concomitant with either celecoxib, ibuprofen, or diclofenac.[23] In the VIGOR trial, low-dose aspirin use was not allowed.[22] Each of these studies was conducted for about 1 year. However, the CLASS trial, published in the *Journal of the American Medical Association,* reported data at 6 months.

The 6-month data from the CLASS trial indicate that ulcer complications or symptomatic ulcers were markedly reduced in the celecoxib group compared with the NSAID group, but the findings lacked statistical significance. However, 21% of patients were on low doses of aspirin that may have been responsible for

FIGURE 2 Efficacy of PPI in Recurrence of NSAID-Associated Ulcers



Note: *Lansoprazole and misoprostol are effective in preventing NSAID ulcer relapse. NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; QD = once daily; QID = 4 times daily.*
Graham et al. Arch Intern Med. 2002;162:169.

some of the ulcerations observed in the trial. To tease out celecoxib's effects on GI risk reduction with an NSAID, excluding patients taking aspirin is appropriate. In the subgroup of patients (79%) who were only taking celecoxib, ibuprofen, or diclofenac, a statistically significant reduction in risk was observed.[23] During the U.S. Food and Drug Administration (FDA) proceedings evaluating the CLASS and VIGOR trials, the 13-month trial dataset was assessed. There was no statistically significant difference between celecoxib versus ibuprofen, diclofenac, or the 2 NSAIDS combined.

The VIGOR trial data were more straightforward because the trial was conducted in the absence of aspirin use. During a median follow-up of 9 months, 2.1 confirmed GI events per 100 patient-years occurred with rofecoxib compared with 4.5 per 100 patient-years with naproxen. Rates of complicated confirmed events (perforation, obstruction, and severe upper GI bleeding) were 0.6 per 100 patient-years for rofecoxib and 1.4 per 100 patient-years for naproxen. The incidence of myocardial infarction was lower among naproxen-treated patients than among rofecoxib-treated patients. For each of its end points, either primary or secondary, there was a statistically significant reduction with rofecoxib compared with nonselective naproxen.[22]

Addition of PPI to Low-Dose Aspirin

What can be done to protect low-dose aspirin users? A Chinese study group studied 123 *H. pylori*-infected patients who had ulcer complications after using low-dose aspirin continuously for more than 1 month. Once ulcers were healed and *H. pylori* infection eradicated, patients were randomly assigned to lansoprazole 30 mg daily or placebo in addition to 100 mg of aspirin daily. During a median follow-up of 12 months, 14.8% of the 61 patients in the placebo group and 1.6% of the 62 patients in the lansoprazole group had ulcer recurrences. In the group of high risk (previously had a bleeding ulcer) aspirin users, 15%, or 1 of 6 participants, had a recurrent bleeding ulcer by the end of 1 year. Lansoprazole-treated patients were significantly less likely to have a recurrence of ulcer complications than placebo-treated patients. Mortality in the 2 groups was similar.[24]

Risk reduction was examined in a cohort study based on record linkage between a population-based prescription database and a hospital discharge registry in North Jutland County, Denmark, over 4 years. Occurrence of upper GI bleeding in 27,694 users of low-dose aspirin was compared with occurrence in the general population. Two hundred seven exclusive users of low-dose aspirin were admitted to the hospital with their first episode of upper GI bleeding. The standardized incidence rate ratio was 2.6. The standardized incidence rate ratio for combined use of low-dose aspirin and other NSAIDS increased to 5.6. Risk was similar among users of noncoated low-dose aspirin (2.6) and coated low-dose aspirin (2.6).[25]

Thus, multiple NSAID users who combine a traditional NSAID with low-dose aspirin, because their risks of upper GI bleeding are unacceptably high, need risk reduction strategies. Does the risk of combined use of low doses of aspirin plus a nonselective NSAID extend to the COX-2 specific inhibitors? Returning to the 6-month CLASS trial data, when aspirin was administered concurrently with celecoxib, the risk of having a GI event increased 4- to 6-fold.[23] Similar to the Danish study, rates of ulceration in the aspirin users, whether it be nonselective NSAID or COX-2 inhibitor, persist.

Average rates of clinically apparent ulceration for NSAID users range from 2% to 4%, but low-dose aspirin use increases the rate to 5% to 6%. Low-dose aspirin use confers sufficiently high risk that these individuals need an alternative approach. Even the safer NSAIDs (the coxibs) have limitations.

PPI Efficacy in Recurrent NSAID-Associated Ulcers

A prospective, double-blind, multicenter, active- and placebo-controlled study assessed 537 long-term NSAID users who were not infected with *H. pylori* and who had a history of endoscopically documented gastric ulcer. Patients were randomized to 1 of 3 groups: (1) placebo, (2) 200 micrograms of misoprostol 4 times a day, or (3) 15 or 30 mg of lansoprazole once daily for 12 weeks. Endoscopy was performed at 4, 8, and 12 weeks. Lansoprazole-treated patients receiving either dose remained free from gastric ulcer longer than placebo recipients. Figure 2 shows patients free of gastric ulcers at week 12. Misoprostol was associated with a significantly higher number of adverse events (diarrhea was seen in about approximately 20% of patients) and early withdrawal from the study. Factoring in withdrawals, therapy was successful for 69% in each of the active treatment groups, but only 35% of placebo-treated patients.

For the prevention of NSAID-induced gastric ulcers, PPIs and misoprostol are similarly effective and both are superior to placebo. If poor compliance and potential adverse effects are considered, the PPI approach becomes more attractive.[19] Subgroup analysis is

revealing. Ninety percent of patients taking naproxen in combination with low-dose aspirin with misoprostol or lansoprazole were ulcer-free at 2 weeks.

COX-2 Specific Inhibitor or Nonspecific NSAID + PPI

Two studies examined high-risk NSAID users in a head-to-head comparison of NSAID plus PPI versus a COX-2 inhibitor alone. One study assessed GI adverse events with celecoxib compared with diclofenac plus omeprazole in high-risk subjects. Patients with a past history of ulcers and who were negative for *H. pylori* were randomly assigned to either celecoxib 200 mg twice daily plus placebo daily or diclofenac 75 mg twice daily plus 20 mg of omeprazole daily for 6 months. Intention-to-treat analysis of 287 patients (144 receiving celecoxib and 143 receiving diclofenac plus omeprazole) revealed that the probability of recurrent bleeding during the 6-month period was 4.9% for celecoxib-treated patients and 6.4% for diclofenac plus omeprazole-treated patients. Approximately one quarter of celecoxib-treated patients experienced renal adverse events (hypertension, peripheral edema, and renal failure), as did 30.8% of those receiving diclofenac plus omeprazole.[26]

Lai's study of 115 *H-pylori*-negative patients with prior ulcer bleeding documented that recurrent ulcer complications with naproxen plus lansoprazole occurred with approximately the same frequency as recurrences with celecoxib alone.[24]

General Principles for NSAID-Associated Problem Management

Management of symptoms and management of risk are 2 different clinical considerations. Endoscopic evaluation of patients with dyspepsia typically reveals that few have ulcers on endoscopy. Conversely, few patients with bleeding ulcers have had symptoms prior to presentation. Thus, symptom management differs from management of upper GI risk. What do the data say about the management of symptoms?

A recent study that assessed dyspepsia in a group of NSAID-taking patients analyzed the ability of a PPI, in this instance esomeprazole, to reduce symptoms. In 2 identically conducted studies, the PPI either at 40 or 20 mg was able to significantly reduce more symptoms in these NSAID users than placebo.[27]

High-risk NSAID patients, defined as patients aged 60 years or older or with a history of ulcers within the last 5 years, were taking either a COX-2 inhibitor or an NSAID continuously at the time of study entry. These high-risk NSAID or COX-2 users were then randomized to placebo or the PPI, esomeprazole, 20 or 40 mg.

One very interesting observation was that high-GI-risk COX-2 users did not have a significant reduction in ulceration compared with nonselective NSAID users. But more importantly as it relates to the consideration of PPI plus NSAID, combining a PPI either with a nonselective NSAID or a COX-2 inhibitor markedly reduced ulcer rates. A question of great interest is whether use of a PPI plus COX-2 results in fewer ulcers than PPI plus NSAID.

TABLE 3 Comparison of FDA-Approved Proton Pump Inhibitors

Indications	Lansoprazole	Esomeprazole	Rabeprazole	Pantoprazole	Omeprazole
Heartburn and other GERD symptoms	✔	✔	✔		✔
Erosive esophagitis	✔	✔	✔	✔	✔
Maintenance of healed erosive esophagitis	✔	✔	✔	✔	✔
Helicobacter pylori eradication with antibiotics to reduce the risk of DU recurrence	✔	✔	✔	✔	
Active DU	✔		✔		✔
Maintenance of healed DU	✔				
Active benign GU	✔				✔
Healing of NSAID-associated GU recurrence	✔				
Risk reduction of NSAID-associated GU recurrence	✔	✔			
Hypersecretory conditions, including Zollinger-Ellison syndrome	✔		✔	✔	✔

DU = duodenal ulcer; FDA = U.S. Food and Drug Administration; GERD = gastroesophageal reflux disease; GU = gastric ulcer; NSAID = nonsteroidal anti-inflammatory drug.

TABLE 4 Management Guideline for NSAID Risk Reduction: Patient Profiles

	No/Low NSAID GI Risk	NSAID GI Risk
No aspirin	Traditional NSAID	COX-2 selective agent or, if on PPI, add traditional NSAID
Aspirin	Traditional NSAID or COX-2 selective + gastroprotective agents	A gastroprotective agent must be added irrespective of type of NSAID prescribed

COX-2 = cyclooxygenase-2; NSAID = nonsteroidal anti-inflammmatory drug; PPI = proton pump inhibitor.
Fendrick. Pharm Ther. 2002;27:579.

Unfortunately that was not answered by this study. The numerical difference between PPI plus COX-2 and PPI plus NSAID was not statistically different. This esomeprazole study has unfortunately not answered the question of whether ulcer rates differ with PPI plus COX-2 inhibitor compared with PPI plus traditional NSAID.

Another study assessed the PPI lansoprazole and showed that it was more effective than placebo or misoprostol in preventing symptoms of heartburn, abdominal pain or the composite of GI symptoms.[27] In summary, management of symptoms in patients who take NSAIDs can be easily managed with acid suppression. Currently 5 PPIs are available in the United States

(Table 3); there is a range of potential indications for which these agents might be used. Only 2 currently are FDA-approved for NSAID-related considerations: lansoprazole and esomeprazole.

A Clinicians' Guide to NSAID Therapy

Assimilating this information into a management strategy to reduce NSAID-induced ulceration or complications is not difficult. Older approaches asked clinicians to assign numerical values to risk factors and use a formula to calculate a likelihood index for NSAID-related bleed. Reasonable in concept, they were difficult to implement in practice because it took too long on any individual patient encounter to conduct the assessment.

A simpler approach (Table 4) requires us to ask 2 questions when determining patient risk:[28]

1. What is the patient's risk?
2. Is the patient taking aspirin?

Using the answers, clinicians can find the quadrant of the decision table in which the patient rests. Aspirin-free patients without GI risk have very low risk of developing an NSAID-related event and should be able to take a traditional NSAID. For patients who have GI risk and are not taking aspirin, data support using a COX-2-specific inhibitor or, alternatively, using a PPI plus traditional NSAID. This paper reviewed 2 studies to support that these approaches are comparable for GI risk reduction in patients who do not take aspirin.[28]

Low-dose aspirin users at low risk for NSAID-related GI events could be treated with a traditional or COX-2 selective NSAID plus aspirin with or without a gastroprotective agent. Use of a gastroprotective agent is debatable. Patients with GI risk who take low-dose aspirin (COX-2 inhibitor or a nonselective NSAID) are at high risk; a gastroprotective agent is indicated regardless of the type of NSAID used. Recent data support combining a PPI plus an NSAID or a PPI plus a COX-2 inhibitor.

Conclusion

Three major points summarize this review:

- For patients who take NSAIDS, management of upper GI symptoms and management of GI risks are separate therapeutic considerations;
- Patients who take multiple NSAIDS, commonly combining low-dose aspirin with a traditional NSAID or with a COX-2 selective NSAID, are an underappreciated group at high risk for NSAID-induced upper GI ulcer complications; and
- Treating NSAID users with a PPI is a strategy that successfully manages upper GI symptoms as well as reduces risks of upper GI ulcer complications.

DISCLOSURES

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Shortly after the program on which this supplement is based was presented, the entire American pain management landscape changed when rofecoxib's manufacturer announced that it was voluntarily withdrawing this COX-2 inhibitor from the market. Anticipating reader questions, the *Journal of Managed Care Pharmacy* asked Dr. Cryer to update his presentation by responding to several important questions.

APPENDIX NSAID Therapy—An Update

1. How do the recent concerns with COX-2s and naproxen affect the 4 quadrants of the decision table (A Clinicians' Guide to NSAID Therapy)? Are the COX-2 recommendations still valid? Should naproxen still be used?

Recommendations to confer gastrointestinal (GI) safety to patients who take nonsteroidal anti-inflammatory drugs (NSAIDs) need to be revised in light of new cardiovascular (CV) concerns with cyclooxygenase-2 (COX-2) inhibitors. With regard to the nonselective NSAID naproxen, the results from the one report suggesting that over-the-counter doses of naproxen might increase CV risks were not statistically significantly different from placebo and, therefore, could have entirely been attributed to chance. More importantly, that study's results are outliers from the well-established body of literature indicating that naproxen actually decreases CV risks.

In light of the above considerations, management recommendations for reducing GI risks with NSAIDs have been recently revised. Decisions for appropriate therapy for patients requiring NSAIDs should be primarily based on 2 considerations: (1) assessment of the patient's baseline GI risk (no/low NSAID-GI risk versus NSAID-GI risk) and (2) assessment of the patient's baseline CV risks (no CV risk versus CV risk). Based on the various combinations of GI and CV risks, evidence-based recommendations for 4 different patient scenarios are:

- **Patient with no CV and no NSAID-GI risk.** Patient's low CV risk assumes that low-dose aspirin is not taken. For patients at low NSAID-GI risk who are not taking aspirin, the likelihood of a GI event is very low. Therefore, these patients can be given a traditional NSAID without gastroprotective therapy. A very low number of these patients will develop GI complications. However, the low risk of GI events weighed against the high financial costs of GI risk-reduction favors a recommendation for traditional NSAIDs alone for the majority of these patients.
- **Patient with no CV risk but with NSAID-GI risk.** In patients with *modest* GI risk for NSAID-related complications, data indicate that use of a COX-2 specific inhibitor alone or use of a traditional NSAID + a proton pump inhibitor (PPI) are approaches that achieve comparable levels of GI risk reduction. Thus, either approach seems reasonable for patients with this combination of risk. There is, however, one important exception to this recommendation. Patients at highest risk for GI events—those with a previous history of GI bleeding—may not be sufficiently risk-reduced with either strategy. Therefore, patients with a previous history of GI bleeding should be given a COX-2 selective agent plus a PPI.* Since NSAID-GI risk reduction can be achieved at a much lower cost with etodolac when compared with labeled COX-2 inhibitors, etodolac should be the preferred COX-2 selective agent.
- **Patient with CV risk and no/low NSAID-GI risk.** Until long-term studies are available evaluating CV effects of the remaining COX-2 inhibitors, the most prudent approach for patients with CV risks is to use a traditional NSAID (± a PPI*). The degree of GI risk or the need for low-dose aspirin will direct whether the PPI* should be added or not.
- **Patient with CV risks and NSAID-GI risk.** These patients' baseline risk for NSAID-GI complications is high, and a major GI bleed could lead to significant CV complications. Thus, non-NSAID therapy should be considered. If a traditional NSAID is prescribed, a PPI* should be added.

** Misoprostol can be substituted for a PPI.*

A Clinicians' Guide to NSAID Therapy

	No/Low NSAID GI Risk	NSAID GI Risk
No CV risk (no aspirin)	Traditional NSAID	COX-2 specific NSAID *or* traditional NSAID + PPI
		Highest risk: COX-2 + PPI
CV risk (consider aspirin)	Traditional NSAID ± PPI* if the degree of GI risk warrants gastroprotection	Consider non-NSAID therapy A PPI* must be added if a traditional NSAID is prescribed

**Misoprostol can be substituted for a PPI.*
Adapted from Fendrick AM et al. Pharm Ther. 2002;27:579.

2. Should existing COX-2 patients be converted to a nonselective NSAID with gastroprotection?

As discussed above, this decision should be based on patients' baseline CV risks and GI risks. Based on the combination of those considerations, clinicians can use the above table to select the best form of NSAID therapy and GI protection for their patients.

3. What is the potential interaction between ibuprofen and aspirin?

The data suggesting a potential interaction between ibuprofen and aspirin are largely based on intermediate makers of platelet function (platelet aggregation and platelet thromboxane) rather than clinically significant end points such as CV thrombotic events. Furthermore, the data on a potential ibuprofen-aspirin interaction with intermediate markers of platelet function have been conflicting. Therefore, until the appropriate prospective, controlled studies have been conducted, there is currently not sufficiently compelling available information to change current prescribing recommendations for patients who concurrently take ibuprofen and aspirin.

Leadership Versus Management: Translating Pharmacists' Abilities Into Quality Performance

C.E. REEDER, PhD

ABSTRACT

OBJECTIVE: To describe the quality gap in health care as it was referred to in the Institute of Medicine's reports, to try to harness pharmacy's potential to improve the quality of drug therapy, and to provide insight into the elusive leadership, management, and dynamics of change.

SUMMARY: Current health care is nowhere near ideal. Successful quality initiatives have included establishing a "culture of quality" (promoting a learning organization), having good leadership, and developing strong management. Ideally, all of these concepts must be applied concurrently for the best results because using only one will not spirit medicine across the gap. To close the gap, pharmacists need to understand various types of change and select a change mechanism that will continuously improve care.

CONCLUSION: Optimizing drug therapy is both a great challenge and a great opportunity for pharmacy. *AMCP's Framework for Quality Drug Therapy* is a continuous quality improvement model that gives us the tools to plan, implement, and evaluate strategies to improve the quality of patient care and cross the "quality chasm."

KEYWORDS: Quality gap, Management, Leadership, Change

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This article bridges information about nonsteroidal anti-inflammatory drug (NSAID)-induced adverse events presented in the first article with information presented in the next article. The former represents a quality gap for health care. The latter describes *AMCP's Framework for Quality Drug Therapy (Framework),* developed by the Academy of Managed Care Pharmacy.[1] This article provides a primer on continuous quality improvement. The incidence of NSAID-related gastrointestinal adverse events is an ideal problem to be addressed. Using the *Framework,* leaders can step forward and promote good management and, most importantly, effect change. Three specific objectives are

- to describe the quality gap, as it was referred to in the Institute of Medicine's (IOM's) reports,
- to try to harness pharmacy's potential to improve the quality of drug therapy management, and
- to provide insight into the elusive leadership, management, and dynamics of change.

The initial IOM report, *To Err Is Human: Building a Safer Health System,* presented rather dramatic numbers.[2] The authors indicated that between 44,000 and 98,000 people die each year in hospitals due to medical errors. They also asserted that medications are responsible for about 7,000 deaths annually. Public and private policymakers saw these numbers and moved issues of patient safety and quality to the forefront of concerns. The statistics represent an opportunity for improvement.

Other figures are equally as appalling. Only 50% of Americans receive recommended preventive care. While 70% of patients with acute illnesses are treated with appropriate care, 30% receive treatments contraindicated for their conditions. For the 20% to 30% of patients with chronic conditions (a group that accounts for more than 70% of our health care expenditures), 60% appear to receive recommended treatments, but 40% receive treatments contraindicated for them, like NSAID therapy without gastroprotection.[3] Obviously, health care has room for improvement.

Errors are a fact of life. Thus, we need to identify an acceptable error rate. We can contemplate different error rates, using conservative goals that approach perfection. Yet translating an accuracy rate of 99.9% into every day life would mean approximately 84 unsafe airplane landings per day, 32,000 bank check errors per hour, or 16,000 pieces of lost mail per hour. It also means more than 9,000 prescription errors every day. Thus, even a 0.1% error rate has rather daunting consequences and is unacceptable in medicine. Contemplating an acceptable error rate is rhetorical in medicine—the only acceptable rate is zero errors.

The IOM's second report, *Crossing the Quality Chasm: A New Health System for the 21st Century,* makes an urgent call for fundamental change to close the quality gap, recommends a

redesign of the American health care system, and provides overarching principles for specific direction for policymakers, health care leaders, clinicians, regulators, purchasers, and others.[4]

> *"The current health care delivery system is not robust enough to apply medical knowledge and technology consistently in ways that are safe, effective, patient-centered, timely, efficient, and equitable…"*[4]

Current health care is nowhere near ideal. It is plagued by what the IOM refers to as a serious quality gap.

Management and Leadership

Other industries and companies have experienced quality chasms and successfully overcome their problems. Successful leaders and organization teams have described their efforts and interventions in the literature. Some of the most successful ideas have included establishing a "culture of quality," promoting a learning organization, having good leadership, and developing strong management. Ideally, all of these concepts must be applied concurrently for the best results because using only one will not spirit medicine across the gap.

Many organizations lack these 4 underpinnings of good quality and may be overwhelmed when they deliberate their implementation. Rather than thinking of these concepts as 4 more things to do, successful practitioners must incorporate them into their jobs so they become transparent and effortless. This makes quality a part of the organization's culture.

Organizational Culture and Learning Organizations

An organizational culture is a set of beliefs, values, customs, and norms that form the foundation of the organization and against which organizations and their members judge themselves. Organizational structure can be sketched or drawn, but organizational culture is less tangible. American automobile manufacturers embraced the idea of introducing the quality concept to their cultures some years ago when Japan's Toyota became a serious and devastating competitor. American automobile manufacturers restructured their businesses around quality, often incorporating quality into their mission statements. Although many manufacturers were concerned that better quality would be costly, they were mistaken. Quality-driven programs can deal with cost realistically. There is nothing wrong with doing the right thing for the right reason within limited budgets.

A learning organization is one in which individual members and groups at all levels continually increase their capacity to produce results they care about. The organization is aware of and monitors its own behavior. It makes achieving extraordinary performance and individual satisfaction and fulfillment surpass possibility and approach probability. Private business must promote a learning environment—a learning organization—to survive today. Health care is certainly no different.

The information needed for self-assessment and improvement is integral to any organization. One of the *Framework's* assumptions is that pharmacies have this information and will use it to learn about themselves. This requires a systematic process of measuring and evaluating, then soliciting feedback and changing. This is not unlike many theories of biology; corporations and businesses are living organisms. The most successful among them adapt, learn, and move forward.

Keeping It Continuous

Continuous Quality Improvement (CQI) is simply an organized way to do this. CQI mechanisms allow organizations to go through 3 types of change: incremental, transitional, and transformational.[5,6]

- *Incremental* change approaches problems in a step-wise fashion. In slow-moving business environments, stability is a goal, and the ruling motto is, "If it ain't broke, don't fix it."
- *Transitional* change acknowledges that the problem will be addressed gradually and continually, using a plan to move forward. The magnitude of the change is greater than just incremental over time because there are more external forces and greater risk in staying stable. There is also more opportunity. Consider, for example, the transitional change that took place as pharmacies incorporated computing technology. What began as primarily dispensing assistance has evolved into sophisticated electronic patient record and treatment management.
- *Transformational* change is rapid and can be likened to the change that occurs after a hurricane devastates an area and forces rebuilding. Transformational change is most necessary when risk is great (i.e., risk of bankruptcy or loss of market share to a rival). Transformational changes in pharmacy often occur in the form of legislative action or mandates, sometimes with little notice, which require us to do things quite differently. Two examples are the implementation of the privacy provisions of the Health Insurance Portability and Accountability Act of 1996 and the forthcoming medication therapy management provision of Medicare Part D. Transformational change occurs only rarely in health care. Incremental change is more common because it is the nature of medicine to test, retest, study, then proceed cautiously to change. American health care, due to external forces, is in a mode of transitional change.

CQI can be used to improve both clinical and organizational performance. The business literature describes organizations as evolving and improving. Clinical processes fit well into business models because both organizations and clinical processes involve many people working together in a structured way to accomplish a goal. CQI helps identify barriers within any organization or within structures with which we must work (but have no authority over) such as networks, contracts, or fee-for-service contracts. The latter types of organizations can be frustrating for management because of the lack of authority. If CQI becomes part of a culture, it makes transition a natural process.

TABLE 1 Differences Between Managers and Leaders[5,6]

Manager	Leader
Administers	Innovates
Replicates	Originates
Maintains	Develops
Focuses on systems and structures	Focuses on people
Relies on control	Inspires trust
Has a short-range view	Has a long-range perspective
Asks how and when	Asks what and why
Has an eye on bottom line	Has an eye on the horizon
Accepts the status quo	Challenges the status quo
Is a classic "good soldier"	Is one's "own person"
Does things right	Does the right thing

TABLE 2 Effecting Change

What do you want to accomplish?
- Begin with the end in mind

What needs to be changed to get there?
- Compare where you are with where you want to be - How wide is the gap?
- Do you need evolution or revolution?

Who are the leaders, where are they, and what are their capabilities?
- Top-down, bottom-up, or middle-out?

Mount J. AMCP Framework white paper, 2002.

Leading Versus Managing

The terms "leading" and "managing" are often used interchangeably; however, leadership has to do with vision, while management has to do with the mechanics of achieving the vision. Managers are frequently asked to maintain the status quo, adding stability and order to the organization's culture. They may be less skilled at instigating change and envisioning the future. On the other hand, leaders are able to raise people's expectations, involve them emotionally, and change the organization's direction. Management is a necessary but insufficient condition for moving organizations forward.

According to J.P. Kotter, leadership copes with internal and external change. Management copes with the complexity of using available resources to achieve the vision.[5] Successful organizational change is 70% to 90% leadership and less than 30% management.[6] Table 1 describes some specific ways that leaders and managers differ.

Any Path Suffices?

The Cheshire cat in Lewis Carroll's *Alice in Wonderland* offers a lesson for all organizations. The Cheshire cat was somewhat Socratic, never answering questions directly, rather answering a question with another question. Alice meets the Cheshire cat when she comes to a fork in a road. She says, "Cheshire cat, Cheshire cat, which path do I take?" And he looks down, smiles, and asks, "Well, where are you going?" She replies, "You know, I don't know." He says, "Then it doesn't really matter which path you take."

When organizations lack direction, it doesn't matter which path they take. The business environment is increasingly complex and competitive. Businesses, including health care, must have a sense of direction. Regardless, many companies, from small to large, do not. Most successful businesses use strategic planning to determine their sense of direction and communicate their direction using mission, vision, and values statements.

Steven Covey, a popular author on management and leadership, suggests that management is bottom-line focused, while leadership is top-line or vision-focused. His maxim, "begin with the end in mind," is simple, but remarkably insightful.[7] Leaders must inspire others to think about what they are producing or want to deliver, "beginning with the end in mind."

In understanding our current situation or dilemma, we must realize that we are either products of our own proactive design, of other people's agendas, of our own circumstances, or of poor habits. This begs the question, "Why are we doing things the way we are now?" Doing things one way because that's the way they've always been done is almost always a mistake.

Making Change

To bring about change, we must understand clearly and communicate effectively what we wish to accomplish (beginning with the end in mind). Table 2 lists questions that are useful in implementing the change process. The change process begins with identifying the magnitude of the gap between the status quo and the vision we wish to achieve. How the change will occur must also be decided. Will the process be *evolutionary* or *revolutionary*? Most changes in pharmacy practice occur in an evolutionary or incremental manner; revolutionary or transformational change is much less common and much more disruptive. Identifying organizational leaders, their positions in the company, and their capabilities are key to successful implementation. Always keep in mind that leaders in an organization do not always hold managerial titles or top positions in the company. In the case of an unacceptable dispensing error rate, a pharmacy technician may be the person with the knowledge and skills to articulate the best way to resolve the problem and to lead the effort.

Change may be planned or unplanned. Planned change follows specific, proactive efforts to create a new direction. When managed well, planned change can have positive effects on an organization. Unplanned change occurs randomly and can have negative effects on the organization. Good planning, a clearly articulated vision, and a sound strategy, however, can reduce the frequency of unplanned events.

Everett M. Rogers, in his 1995 book, *Diffusion of Innovations,* identifies the typical stages of change associated with the adoption of an innovation.[8] These stages of change apply to many of the issues we face in pharmacy and medicine whether it is a new medication, a new technology, or a new theory of disease. Rogers's

5 stages depict a cascade of events that will occur if change or innovation is to be adopted (Figure 1). Stakeholders involved with the innovation must first *understand* the proposed change and its reasons. Leaders have to be able to *persuade* people that the proposed change is a good idea and worth adopting. Stakeholders will *decide* whether or not to accept and support the change; once this occurs, the change must then be *implemented*. Last, there must be a *confirmation* that the change was appropriate and effective.

Rogers also describes 5 factors that may influence the rate of adoption of an innovation. These factors temper how rapidly the change or innovation is accepted by stakeholders. These factors are:

1. Relative advantage: Is it better than what we do now?
2. Compatibility: Is this change consistent with our mission, vision, and values?
3. Complexity: How difficult will the change be?
4. Try-ability: Can the innovation be tested or attempted on a small scale rather than by total adoption? Can we implement this gradually, incrementally, or transitionally?
5. Observability: Can we see this working?

Change that is incongruent with our mission will not work, not because it is a bad idea, but because it will not fit the organizational values. When implementing change in an organization, immediate feedback helps people see that change is making a difference and allows mid-course corrections.

Types of Change Adopters

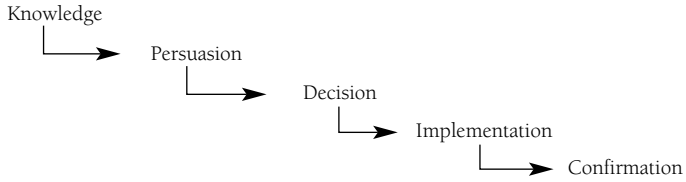
Different people will be more or less inclined to accept and support change. Rogers identifies these 5 distinct groups of adopters and their frequency[8]:

1. innovators (2.5%),
2. early adopters (13.5%),
3. early majority (34%),
4. late majority (34%), and, finally,
5. laggards (16%).

His definitions were based on research conducted in the 1940s by sociologists Bryce Ryan and Neal Gross, who published a study of the diffusion of hybrid seed among Iowa farmers. Now, as then, most people (68%) are members of either the early majority or late majority group of adopters. The personality types of these 5 groups vary significantly[8]:

1. Innovators actively seek change and innovation. They cope well with uncertainty and are assertive in their desire for changes.
2. Early adopters are not quite as aggressive in adopting new technology and ideas but are opinion leaders. The early adopters and innovators are small in numbers, but they are the organization's change brokers and true leaders.
3. Early majority adopters think about proposed change, only adopting it after deliberation and considerable interaction with peers.
4. Late majority adopters may decide to adopt the change under the force of economic necessity or peer pressure.
5. Laggards are fortunately one of the smaller groups; they are the last people to change, hold tenaciously to a point of reference in the past, are suspicious of innovations, and have lengthy decision processes.

FIGURE 1 Rogers' Stages of Change



Rogers EM. Diffusion of Innovation, chapter 5.[8]

Leaders and managers must identify each type of person and use tailored communication approaches to ensure his or her participation in the change process. Introducing a quality improvement model to the organization's culture is a key strategy to implementing and evaluating change that will require your leadership abilities at every level.

Summary and Conclusion

That our health care system has problems is obvious, and the quality gap is real. Optimizing drug therapy management is both a great challenge and a great opportunity for pharmacy. The *Framework* is a continuous quality improvement model that gives us the tools to plan, implement, and evaluate strategies to improve the quality of patient care and cross the "quality chasm."

DISCLOSURES

This article is based on the proceedings of a Foundation for Managed Care Pharmacy symposium held on July 17, 2004, in Napa Valley, California, and supported by an educational grant from TAP Pharmaceutical Products, Inc. The author did not receive an honorarium for participation in the symposium upon which this article is based; he discloses no potential bias or conflict of interest relating to this article.

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AMCP's Framework for Quality Drug Therapy

STEVEN G. AVEY, MS, RPh

ABSTRACT

OBJECTIVE: To describe *AMCP's Framework for Quality Drug Therapy.*

SUMMARY: *AMCP's Framework for Quality Drug Therapy* was designed by a consortium of pharmacists and pharmacy organizations. It was built on customer assumptions and expectations, and it defined "customer" broadly. The document includes background information, a description of the process used, a list of customers' expectations, and a self-assessment grid. It can be applied in part or in its entirety in a wide variety of pharmacy settings.

CONCLUSION: The scope of *AMCP's Framework* is unprecedented—it can help bridge the gap between the status quo and the ideal in drug therapy. The *Framework* is available at no charge from AMCP.

KEYWORDS: Medication management, Quality, Expectation

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The level of effort involved in creating *AMCP's Framework for Quality Drug Therapy (Framework)* lends credibility to the tool that emerged from the process. The process was multidisciplinary and involved the Academy of Managed Care Pharmacy and the other major pharmacy associations, including the American Society of Health-System Pharmacists, American Pharmacists Association, and American Society of Consultant Pharmacists. More than 100 pharmacists participated in its development, and consensus conferences entertained thought leaders from around the United States. The final document, *AMCP's Framework for Quality Drug Therapy* was published in June 2002.[1,2]

Pharmacy customers were considered from a broader perspective than just the patient. While a patient is generally concerned with such issues as prescription-filling speed at the pharmacy, dignified treatment, and convenience, the *Framework* also addresses other critical areas where well-managed drug therapy could help improve the overall health of patients and possibly lower other health care expenditures. AMCP amplified the typical interview question like "What would be important to you?" with an assumption-based question like "Would receiving the right drug be important to you?" Most patients trust their pharmacist implicitly and assume that they always get the right drug. This is true even when refilled medications look different from what a patient has received for years (see assumptions below), causing many patients to take the new and different pills without checking with the pharmacist to verify accuracy.

The diverse nature of pharmacy customers was important to AMCP's analysis for *Framework* development. The Academy interviewed patients as well as physicians, pharmacists, pharmaceutical industry representatives, academics, health plan representatives, payers, and nurses (referred to as health care practitioners throughout the document), and government representatives to learn their expectations and concerns about drug therapy. In doing so, we began with certain assumptions (Table 1).

TABLE 1 Assumptions on Which the AMCP *Framework* Is Based

- People want to be healthy
- People want to receive the "right" drug
- The health care system should maintain and improve health and prevent and treat disease
- The patient's doctor and pharmacist should work together to ensure good health care
- Payers for health care have finite resources
- Drug therapy demands attention, and pharmacists are uniquely trained and positioned to provide it
- Pharmacists should be accountable for the drug therapy process, but it is dependent upon a lot of other health care providers

The assumption that reads "People want to be healthy" is accurate; however, that is not the same as "People are willing to live healthy lifestyles." There is a rather substantial difference between these 2 assumptions. Latest reports show that obesity and type 2 diabetes are on the rise, mainly from poor diet and lack of exercise. Regardless of how Americans actually live (smoking, overeating, or excessive drinking), they want and expect to be healthy. Surveys have shown that patients believe physicians and pharmacists routinely collaborate in their care. It is also evident that pharmacists frequently do not have the amount of information they need and that information sharing is a problem. All of the people interviewed, except for most of the physicians, thought that pharmacists should have more information. Additionally, all groups except physicians supported pharmacists' unfettered access to medical records. Physicians wanted to work closely with pharmacists but were somewhat reluctant to share medical records.

Expectations

Expectations were developed from customers' remarks (Table 2). While the customers who were interviewed did not specifically state that they expect to achieve appropriate therapy outcomes, the message was consistent. When people take medications, they expect to get better. Reports produced by the Institute of Medicine (IOM) demonstrate that, in many cases, this expectation is not met. The surveys indicated that most people do not think about medication errors when it comes to expectations about prescription drugs. When errors do occur, however, patients want the pharmacist's undivided attention and assurances that the error will be corrected immediately, with no recurrence.

Customers expect coordinated, competent care. It would be surprising to most customers how little coordination of care actually takes place. Customers also expect that care will be affordable and that the health care system constantly looks out for the patient's best interest. AMCP broadened the definition of "provider" to include the physician, the pharmacist, the nurse, and others. In the past decade, as our health care system has tried to balance health care costs with clinical outcomes, concerns have arisen about access to and quality of health care. The expectations that the system should be accessible and that patients' interests should be paramount reflect these concerns.

The *Framework's* Purpose

The *Framework* was created to improve the quality of drug therapy through incremental change in all pharmacy settings. From a practical perspective, the *Framework* should allow health systems to reduce adverse drug events, improve the likelihood that a positive outcome will occur when drug therapy is initiated, and ensure that the benefits of therapy exceed the possibility of harm. Another expected consequence of using the *Framework* is the reduction of medication errors. Goals associated with using the *Framework* will vary by organization. Achieving these goals will depend on how effective the organization is at developing good action plans.

TABLE 2 Expectations

- Patients achieve appropriate drug therapy outcomes
- Drug-related problems will be identified, resolved, and prevented
- Care is coordinated and providers are competent
- There is value in the care that patients receive, and it is affordable
- The system is accessible and is looking out for the patient's best interest
- There will be a professional covenant between the patient and the provider
- The system provides adequate and appropriate information and education regarding appropriate drug use

An important goal for many organizations should be proper formulary management. Building formularies based on cost or rebate may not serve patients' best interests or meet overall health system goals. Formularies that are based on finding the most valuable medications are more appropriate and more consistent with *Framework* best practices.

Providing the most appropriate medication and continuously monitoring for reduction of adverse drug events are also important. This list is not exhaustive, but an example of things the *Framework* can assist with includes reducing medication errors, reducing adverse drug events, improving compliance, and doing a better job of educating people on the importance of dosage schedules.

Important *Framework* Perspectives

The *Framework* focuses on system changes. Often, systems allow practitioners to follow less than the safest of procedures. When medication errors occur, often the first question asked is, "Who did it?" Blaming an individual may not get to the root of the problem. A better question to ask might be "How could the system allow an error to occur?" It is much more difficult to resolve a system flaw than it is to blame the problem on an individual practitioner and simply demand that he or she show more caution in the future.

Pharmacy practice, in general, is a good example of a system problem. Pharmacy students are educated at an advanced clinical level. They have extensive expertise and are generally enthusiastic about sharing information with patients. When students become pharmacists and enter practice, the system usually doesn't support the kind of clinical services they were prepared to give. Early enthusiasm regarding the provision of excellent clinical services turns to frustration, and, over time, the system assimilates these energetic and enthusiastic practitioners into the existing suboptimal system.

The *Framework* is independent of practice setting. It is a Continuous Quality Improvement (CQI) tool that is patient-focused and patient-driven, meaning it was developed based on what patients need rather than on what pharmacists have to offer. The *Framework* is a process for quality improvement; it is

TABLE 3 The *Framework* Core Focus Areas

1. Employ fundamental skills, tasks, and functions for effective drug therapy management.
2. Health management, health promotion, and disease prevention programs and services are offered.
3. The patient is effectively assessed, accurately diagnosed, and appropriate drug therapy is selected.
4. The patient is served by a distribution system that provides accurate drug therapy and understandable health information in a timely manner.
5. Patient response to drug therapy is monitored for effectiveness, adherence, and avoidance of adverse effects, and drug therapy is adjusted to achieve optimal outcomes.
6. Medical benefits are provided through a system that has an appropriate drug-use policy and benefit design.
7. The health system performs ongoing assessment to ensure that the results of drug therapy lead to healthy individuals and populations.

incremental or *transitional,* not *transformational.* It advocates taking systems as they exist and slowly improving them over time.

The Hepler Strand Pharmaceutical Care Model was developed by Linda Strand and Doug Hepler in 1989 and 1990[3]; health care practitioners viewed the model as a *transformational*, even *revolutionary,* change. Their model suggested a completely different environment, where patients engage in substantial discussions with their pharmacists. Although the model had a positive impact on the practice of pharmacy, it did not revolutionize the profession, and it never fostered the development of the kind of care and services Hepler and Strand envisioned the pharmacist would provide. Patients did not expect or want to sit down for lengthy discussions with a pharmacist, and payers were unwilling to reimburse pharmacists for these extensive services. Patients tend to trust their physicians and expect their pharmacists simply to augment the information already provided by their medical practitioners.

As indicated, the Hepler Strand Pharmaceutical Care Model has had a substantial impact on the practice of pharmacy, but it required extensive and costly philosophical, organizational, and functional changes. From an implementation perspective, it has simply not achieved what the authors had hoped. The concept, however, represents ideal health care from pharmacists, and that goal is achievable. Through a CQI process, practice settings can slowly develop into sites that deliver much more effective therapy management. Many organizations, including the Veterans Administration, Department of Defense, and Indian Health Service, have recognized the *Framework's* vision-based potential.

Key Elements

The *Framework* has several key elements:

- A white paper entitled "Making It Easy to Do It Right," written by Brent James, MD, an IOM Chasm Team member. The paper closely examines how pharmacy should bridge the gap of quality.[1]
- "Organization Culture and Effecting Change in Pharmacy in the 21st Century," by Jeanine K. Mount, PhD, RPh, of the College of Pharmacy at the University of Wisconsin at Madison. This document covers many of the points presented in the previous article in this supplement.[1]
- A description of customer expectations and how they were derived, in their entirety.
- The Grid and Self-Assessment Tool, which is meant to help pharmacists identify the areas that need the most improvement.

To develop the *Framework,* AMCP asked pharmacists and other health care professionals to identify components that describe optimal drug therapy management. They identified components necessary for prevention of disease, such as screening for hypertension, hyperlipidemia, diabetes, or asthma. They identified components of acute and chronic care, bringing the total number of components to more than 250.

The hundreds of tasks or components of good drug therapy management were then sorted into 7 "core focus areas" (Table 3). The core focus areas are not meant to relate to each other in any sequential way; patients would not be exposed to them in any specific order. Nor do all the core focus areas apply to every pharmacy practice. Only one or two core focus areas might apply to any individual pharmacy setting or organization. The rest might not be applicable. Each organization will need to review each focus area and determine if the components relate to its practice. If the focus area does not relate, the organization simply moves on to the next one to determine its suitability for analysis.

Each core focus area has several functional areas; these are subsets that group similar components together. Drug therapy management is so much more than just distribution of medication. Pharmacists need to be involved in patients' care management plans. Coordinated care among health care practitioners will ensure that accessible and appropriate medication will match with diagnosis. Benefit designs must usher patients through the system. Once thorough assessment of these core focus areas is complete, pharmacists are ready to build an action plan.

The Action Plan

The *Framework* includes templates to develop action plans. The first template, *Framework* Data Collection and Analysis and Gap Analysis Worksheet, consolidates information assessed in the core focus areas. It guides participants through the planning process.

The second template is designed to be copied for each component that needs improvement. It, too, is an easy-to-follow tool that guides participants to think about all aspects of the problem, including the resources needed to improve care. Health care practitioners who find that osteoporosis care is less than ideal

in their system may be guided through gathering data to establishing screening programs to setting targets. It is critical that the results of interventions and actions must be measurable so that improvements are obvious. Assigning responsibilities to individuals or teams and tracking progress will prepare an organization for success.

Staff Development

Initially, organizations can expect staff to be somewhat skeptical of any improvement process like the *Framework*. Since more than 60% of employees are early majority or late majority adoptors, specific interventions suggested in Dr. Reeder's article will be essential. Making all employees part of the solution is critical. Educating individuals about quality improvement and possibly offering professional skill development for team members are worthy considerations. CQI is a circular process of assessment, evaluation, planning, implementation, and feedback (Figure 1). The process is never complete, as organizations continue the process working on other components that apply to their setting.

Quality improvement is not discussed at most colleges of pharmacy in the United States. New pharmacists are usually unfamiliar with this approach. If the *Framework* is a benchmark for best practices, and AMCP believes it is, this tool should be included in pharmacy curricula.

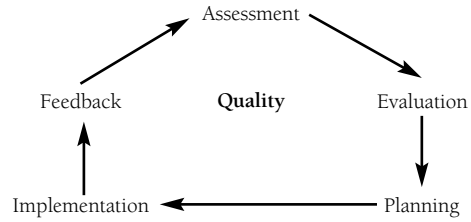
Self Assessment: NSAID-Induced GI Events

This section is best executed with the *Framework* documents in hand. The process starts when organizations identify areas about which they are concerned; the example here is medications that cause gastrointestinal (GI) bleeding. Other areas of concern might include medication error reduction, patient education, compliance, or patient assessment. To start, team participants scroll through the grid and find components related to the area of concern.

Core Focus Area #1 is for an organization to employ fundamental skills, tasks, and functions for effective therapy management. Many organizations find that functional area 1.3, patient education, is a problem. Many patients who take over-the-counter or prescription nonsteroidal anti-inflammatory drugs (NSAIDs) are unaware that they may be at risk for GI bleeding. Component 1.3.3 addresses another common deficit: "Sufficient resources are available to answer all patient questions regarding their disease states, treatment plan, drug therapy, health management, or disease prevention." Keeping specific concerns in mind, an organization's staff members read each component and answer the question, "Does this apply?" If it does, they complete the columns describing the problem's frequency and level of importance.

From there, the action plan can be developed. In the clinical example presented, organizations might assemble an information packet for physicians who treat osteoarthritis and rheumatoid arthritis with NSAIDs. These packets might contain guidelines from nationally recognized organizations. Organizations might examine their databases to determine which physicians are frequent or heavy prescribers of cyclooxygenase-2 drugs and NSAIDs and document the number of patients who experience GI bleeding for 6 months prior to implementing the action plan. Six months after the implementation date, organizations would reexamine the data to determine if fewer patients have experienced GI bleeding.

FIGURE 1 Value to Practice



Conclusion

At a time when so few things in life are free, a tool like the AMCP *Framework* is unprecedented. It can help bridge the gap between the status quo and the ideal. Using it to identify two or three components is a clever way to galvanize transitional change and improve care for our primary customers: patients.

DISCLOSURES

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Management of NSAID-Associated Upper GI Disorders Using *AMCP's Framework for Quality Drug Therapy*

The Academy of Managed Care Pharmacy is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. A total of 0.10 CEU (1.0 contact hour) will be awarded and a continuing education statement will be sent to pharmacists for successful completion of this continuing education program, which is defined as receiving a minimum score of 70% on the posttest and completion of the Program Evaluation form. ACPE Universal Program No. 233-999-05-002-H01. (Release date: 3/1/05; Expiration date: 3/1/08)

Continuing Education for this program is processed solely through the AMCP.org CE Learning Center site at www.amcp.org (CE Center/Online CE). No mailed forms will be accepted.

The posttest worksheet (below) is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

In order to receive CE credit for this program, you must complete the following forms online:

1. Posttest form for this program, "Management of NSAID-Associated Upper GI Disorders Using *AMCP's Framework for Quality Drug Therapy,"* on the AMCP.org CE Learning Center site—to receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.
2. Program Evaluation form

Upon successful completion of this program, you will automatically receive your CE statement. Your CE credits will be automatically archived and tracked for you on the AMCP.org CE Learning Center site. All information is kept confidential.

Note: There will be a $10 processing fee for nonmembers. (See payment instructions on site.)

Posttest Worksheet: Management of NSAID-Associated Upper GI Disorders Using *AMCP's Framework for Quality Drug Therapy*

1. Which of the following is not true?
   a. NSAID-induced GI effects can be approached by examining 3 principal components—prevention, symptoms, and healing.
   b. When trying to manage symptoms, various therapeutic strategies generally use acid-lowering mechanisms to reduce dyspepsia.
   c. Generalists, including physicians, nurse practitioners, physician assistants and pharmacists, are more likely to encounter the need to prevent ulcer formation when NSAIDs are prescribed or to manage symptom issues after initiation of NSAIDs.
   d. A specialist should be consulted before symptoms of NSAID-induced GI effects occur.

2. When patients experience NSAID-related GI effects,
   a. the first sign of ulceration is rarely a life-threatening complication.
   b. clinical symptoms are closely correlated with endoscopic findings.
   c. ulcers that present with pain, perforation, or bleeding occur in 1% to 4% of NSAID-treated patients, with an average of about 2%.
   d. NSAIDs must be discontinued and are no longer a treatment option.

3. Which of the following strategies is best to reduce risk of NSAID-related GI events?
   a. Use enteric-coated formulations whenever possible
   b. Use a parenterally administered NSAID
   c. Add an H2-receptor antagonist to the drug regimen
   d. Add misoprostol to the drug regimen

4. Select the sentence that is true.
   a. Concurrent low-dose aspirin therapy increases the risk of NSAID-induced GI effects.
   b. Low-dose aspirin therapy has little to no effect on gastrointestinal prostaglandin levels
   c. People taking low-dose aspirin and other NSAIDs are 30 times more likely to experience an upper GI bleed than people taking NSAIDs alone.
   d. Most clinical trials of NSAIDs exclude people who take low-dose aspirin.

5. Which of the following statements represents a quality gap in our health care system?
   - Only 50% of Americans receive recommended preventive care.
   - While 70% of patients with acute illnesses are treated with appropriate care, 30% receive treatments contra-indicated for their conditions.
   - For the 20% to 30% of patients with chronic conditions (a group that accounts for more than 70% of our health care expenditures), 60% appear to receive recommended treatment, but 40% receive treatments contraindicated for them, like NSAID therapy without gastroprotection.
   - Smallpox has been eradicated in the United States.

   a. All of the statements
   b. Statements a, b, and c
   c. Statement d
   d. None of the statements

6. In a learning organization,
   a. individual members and groups at all levels continually increase their capacity to produce results they care about.
   b. the organization is aware of and monitors its competitors' behavior.
   c. management stresses downplaying extraordinary performance and individual satisfaction and fulfillment in favor of the group norm.
   d. quality circles make most of the decisions.

7. Identify the 3 types of change:
   a. Instrumental, transitional, and transformational
   b. Incremental, transitional, and transformational
   c. Incremental, transitional, and transductional
   d. Inductional, transitional, and transformational

8. A legislative mandate that forces an immediate and profound change is what kind of change?
   a. Incremental
   b. Transitional
   c. Transformational
   d. Sequential

9. *AMCP's Framework for Quality Drug Therapy*
   a. is an evidence-based research document.
   b. describes specific steps that must be followed in precise order.
   c. is an industry-driven quality guide that tells patients what they need.
   d. is a flexible consensus document that can be used in several pharmacy settings.

10. *AMCP's Framework for Quality Drug Therapy*
    a. advocates incremental change.
    b. promotes formularies that are based on finding the most valuable medications.
    c. includes a self-assessment grid.
    d. All of the above.

NOTES

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