

Gastroprotective strategies among NSAID users

Guidelines for appropriate use in chronic illness

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ABSTRACT

OBJECTIVE To review proper use of gastroprotective strategies in family medicine for patients requiring chronic nonsteroidal anti-inflammatory drug (NSAID) therapy.

QUALITY OF EVIDENCE Evidence of the efficacy and safety of strategies currently in use (prostaglandin analogues, cyclooxygenase-2 inhibitors, proton pump inhibitors) is derived from randomized controlled trials (level I evidence). The simultaneous use of multiple medications for very high-risk NSAID users is supported only by expert opinion (level III evidence).

MAIN MESSAGE Gastroprotective strategies should be reserved for NSAID users at substantially increased risk of gastrointestinal complications; low-risk patients can safely use NSAIDs alone. Cyclooxygenase-2 inhibitors, prostaglandin analogues, and proton pump inhibitors reduce the risk of NSAID-related gastrointestinal complications by 40% to 90%. Cyclooxygenase-2 inhibitors should be avoided by patients who have or are at risk for cardiovascular disease.

CONCLUSION Chronic NSAID use has been implicated in the development of severe and potentially life-threatening gastrointestinal complications, though certain strategies are known to decrease the risk of these NSAID-related gastrointestinal complications. Prescribing physicians must know which of their patients should be prescribed medications and which strategies are appropriate for particular patients.

RÉSUMÉ

OBJECTIF Faire le point sur l'usage approprié des médicaments gastroprotecteurs en médecine familiale chez les patients qui doivent prendre des anti-inflammatoires non stéroïdiens (AINS).

QUALITÉ DES PREUVES Les preuves de l'efficacité et de l'innocuité des médicaments gastroprotecteurs présentement utilisés (analogues des prostaglandines, inhibiteurs de la cyclooxygénase-2, inhibiteurs de la pompe à proton) proviennent d'essais aléatoires avec témoins (preuves de niveau I). L'utilisation simultanée de plusieurs médicaments gastroprotecteurs chez les utilisateurs présentant un risque très élevé repose uniquement sur l'opinion d'experts (preuves de niveau III).

PRINCIPAL MESSAGE Les stratégies de gastroprotection devraient être réservées aux utilisateurs d'AINS qui présentent une augmentation appréciable du risque de complications gastro-intestinales; les patients à faible risque peuvent prendre des AINS seuls sans danger. Les inhibiteurs de la cyclooxygénase-2, les analogues des prostaglandines et les inhibiteurs de la pompe à proton réduisent de 40 à 90% le risque de complications gastro-intestinales dues aux AINS. Les inhibiteurs de la cyclooxygénase-2 devraient être évités chez ceux qui ont ou qui risquent d'avoir une maladie cardiovasculaire.

CONCLUSION L'utilisation chronique d'AINS est susceptible d'entraîner des complications gastro-intestinales sévères et potentiellement létales; on sait toutefois que certaines stratégies peuvent diminuer le risque de telles complications. Il incombe au médecin de savoir à quel patient prescrire des médicaments gastroprotecteurs et quel type de médicaments prescrire à chacun.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for relief of pain associated with arthritis, musculoskeletal injury, headache, and menstruation. In 2000, approximately 20% of Canadians older than 65 years were prescribed an NSAID¹ and many more used NSAIDs purchased over-the-counter.²

While NSAIDs are well tolerated by most patients, their use is associated with a substantial risk of gastrointestinal (GI) complications, including GI bleeding, ulcer perforation, gastric outlet obstruction, and symptomatic peptic ulcer disease. Approximately 1% to 2% of NSAID users will develop GI complications yearly, a rate 3 to 5 times higher than the rate among those who do not use NSAIDs.³⁻⁶

Though NSAID use is associated with serious side effects, many patients still require prolonged NSAID therapy for effective analgesia. Analgesics that do not contain NSAIDs, such as acetaminophen, might not provide sufficient pain relief,^{7,8} and the use of narcotic analgesics can be associated with substantial cognitive side effects.^{9,10} Fortunately, physicians can use several strategies to lower the risk of GI complications among NSAID users. These include prescription of a gastroprotective medication along with a traditional NSAID or substitution of a cyclooxygenase-2 (COX-2) inhibitor. Nearly all NSAID users, however, will never develop any serious GI complications, and the medications used in gastroprotective strategies (GPSs) are expensive and are associated with substantial side effects in some patients. Therefore, it is important that primary care physicians be familiar with the advantages and disadvantages of the various GPSs and be aware of which patients are at increased risk of developing NSAID-related GI complications, that will require treatment with gastroprotective medications.

Quality of evidence

Data on risk factors have been obtained from various epidemiological studies. As patients cannot be randomly assigned risk factors, level II evidence is the best that can be achieved. Evidence supporting the use of prostaglandin analogues, COX-2 inhibitors, and proton pump inhibitors (PPIs) is derived from multiple randomized controlled trials (level I evidence). To date, no experimental trials or observational data support the use of multiple gastroprotective medications in combination. Therefore, use of multiple medications in combination is advocated solely on the basis of expert opinion (level III evidence).

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What are the options?

The classes of medications currently available that have been demonstrated to decrease the risk of GI complications among long-term NSAID users include prostaglandin E₁ analogues (misoprostol), COX-2 inhibitors, and PPIs. While H₂ receptor antagonists and sucralfate have been used for gastroprotection in the past, there is insufficient evidence that these medications decrease the risk of serious GI complications in patients using NSAIDs regularly.^{11,12}

Misoprostol. Misoprostol is a synthetic analogue of prostaglandin E₁, a compound normally secreted by the gastric mucosa that is essential for protecting the gastric mucosa from chemical damage.¹³ Misoprostol has been shown to decrease the incidence of gastric erosions and ulcers among NSAID users undergoing endoscopy.¹⁴ More importantly, subjects given 200 µg of misoprostol 4 times daily along with traditional NSAIDs are 40% less likely to develop GI complications than those using NSAIDs alone.¹⁵ The absolute reduction in risk, however, is quite modest; 266 average-risk NSAID users would have to be provided with misoprostol to prevent 1 NSAID-related GI complication.¹⁶ The other drawback to misoprostol is dose-related diarrhea, which occurs in more than 20% of users and is often severe enough to lead to premature discontinuation of therapy.¹⁶ Misoprostol may be prescribed twice daily in order to ameliorate these troublesome GI side effects, though taking it twice daily provides substantially less protection against GI injury than taking it 3 or 4 times daily¹⁷ and thus cannot be recommended as a satisfactory gastroprotective regimen.

Cyclooxygenase-2 inhibitors. Cyclooxygenase-2 inhibitors are a subclass of NSAIDs which specifically inhibit the production of compounds that mediate pain and inflammation via COX-2, while not affecting the production of gastroprotective prostaglandins through the action of cyclooxygenase-1. Cyclooxygenase-2 inhibitors are thus purported to provide analgesia equivalent to that of traditional non-selective NSAIDs while being less likely to promote the development of GI complications. Several clinical trials have demonstrated that COX-2 inhibitors and traditional NSAIDs are equally effective in providing analgesia for patients with osteoarthritis and rheumatoid arthritis.¹⁸⁻²⁰

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis

Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study

Level III: Expert opinion or consensus statements

Cyclooxygenase-2 inhibitors are also more effective in decreasing the rate of severe GI complications than are non-selective NSAIDs. Both celecoxib and rofecoxib have been shown in randomized clinical trials to decrease the risk of serious GI complications by 50% to 60% compared with traditional NSAIDs.^{19,20} Patients using COX-2 inhibitors also have a substantially lower rate of discontinuation of medication due to side effects than patients using traditional NSAIDs.²¹

Recently, COX-2 inhibitors have come under fire because their use has been associated with development of severe cardiovascular complications, including myocardial infarction and stroke. In VIGOR, the large clinical trial supporting the GI safety of rofecoxib, 0.4% of patients using rofecoxib developed myocardial infarction at a mean follow-up of 13 months, compared with only 0.1% of subjects using naproxen.²⁰ It was uncertain, however, whether the increased risk of myocardial infarction was due to rofecoxib's promoting cardiac events or a cardioprotective effect of naproxen.

More recently, 2 clinical trials following users of COX-2 inhibitors for up to 3 years showed both celecoxib and rofecoxib increased the risk of cardiovascular complications more than placebo did, though celecoxib led to an increased risk of cardiovascular complications only at supratherapeutic doses for arthritis (800 mg daily).^{22,23} Epidemiologic reviews of large health care databases, however, suggest that patients given rofecoxib, especially at doses exceeding 25 mg daily, are more likely to experience adverse cardiovascular outcomes than subjects using celecoxib or traditional NSAIDs.²⁴⁻²⁷ Another COX-2 inhibitor, valdecoxib, was found to increase the risk of myocardial infarction over placebo when provided intravenously immediately after coronary artery bypass surgery.²⁸ There are also concerns about the cardiovascular safety of traditional NSAIDs, as 1 unpublished trial examining whether NSAIDs offered protection against the development of Alzheimer disease demonstrated a rate of cardiac events in patients taking naproxen double that among those using placebo.²⁹ This study has been roundly criticized, however, for faulty methodology that might have substantially biased the findings.³⁰ Moreover, while 1 recently published epidemiologic study suggested that ibuprofen and diclofenac users might be at increased risk of cardiovascular complications,³¹ most published observational studies suggest that NSAIDs do not significantly increase the risk of adverse cardiovascular outcomes, and might, in fact, be protective.²⁴⁻²⁷

In late 2004, Health Canada advised that rofecoxib and valdecoxib should no longer be marketed to Canadian consumers and that celecoxib use should be restricted to patients who are not at risk of cardiovascular disease and be used only at doses of 200 mg daily or less.³² In 2005, Pfizer, the pharmaceutical company marketing celecoxib in Canada, stated that celecoxib is contraindicated in patients with New York Heart Association

Class II to IV congestive heart failure, as well as in advanced coronary artery and cerebrovascular disease.³³ A Health Canada advisory board, however, recently recommended that rofecoxib again be made available to Canadians and that decisions about whether a patient should be prescribed celecoxib or rofecoxib should be left to the discretion of the treating physician.³⁴

Proton pump inhibitors. Proton pump inhibitors are the most effective drugs currently available for healing established gastric and duodenal erosions and ulcers.³⁵ By the same mechanism, PPIs would also be likely to prevent the development of peptic ulcer disease in patients using NSAIDs.

Chronic NSAID users taking the PPI omeprazole at 20 mg daily have a lower incidence of endoscopic gastric and duodenal ulcers than NSAID users given either misoprostol or ranitidine,³⁶⁻³⁸ and PPI therapy is better tolerated than misoprostol therapy.³⁸ Furthermore, coprescription of omeprazole at 20 mg daily with a traditional NSAID was found to be as effective as celecoxib in prevention of recurrent GI bleeding among patients with a recent history of GI bleeding.³⁹ Coprescription of PPIs at standard doses once daily has been shown to decrease the risk of recurrent GI hemorrhage by up to 90% in patients with a recent history of GI bleeding induced by acetylsalicylic acid administration who require either low-dose ASA or continued NSAID therapy.^{40,41} Though PPIs will likely also be effective in preventing GI complications in users of traditional NSAIDs, there are currently no published clinical trials comparing rates of GI complications among subjects using traditional NSAIDs alone with those taking traditional NSAIDs and PPIs.

New safety issues have also arisen, as observational studies have suggested that PPI users might be at higher risk of developing community-acquired pneumonia⁴² and *Clostridium difficile*-associated diarrhea.⁴³ The links between PPI use and these complications are still tenuous, however, and patients with respiratory disease or with a history of *C difficile*-associated diarrhea do not have to avoid PPI therapy.

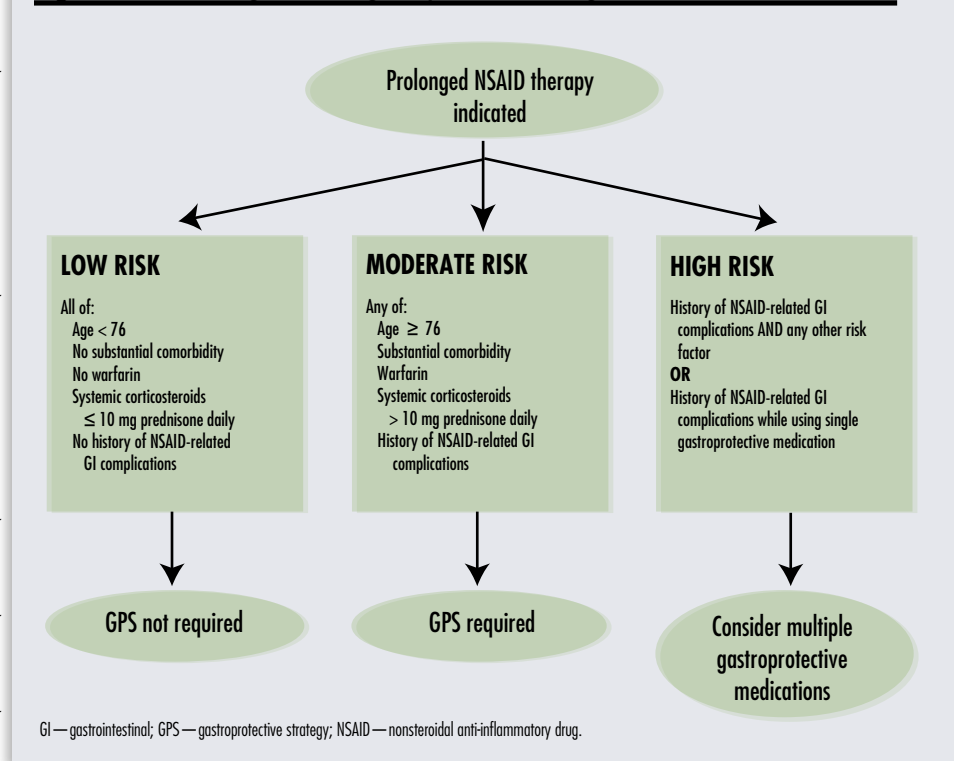
Who is at risk?

Although 1% to 2% of NSAID users yearly will develop serious GI complications,³⁻⁶ not every NSAID user is at equal risk of developing these complications. Several risk factors have been associated with an increased risk of serious GI events among NSAID users. These risk factors include increased age, concomitant use of systemic corticosteroids or warfarin, and a history of GI bleeding or peptic ulcer disease.^{3,44,45} Active infection with *Helicobacter pylori* and concomitant use of either low-dose ASA or selective serotonin reuptake inhibitors might also increase the risk of GI complications,⁴⁶⁻⁴⁹ though the evidence of increased complications is relatively weak. Not all risk factors for GI complications are of equal

magnitude. Whereas a person older than 60 years might have only 2 to 3 times the risk of GI complications of someone younger than 60 years, having a history of NSAID-related GI bleeding might increase the risk of recurrent bleeding up to 15 times over that of an NSAID user with no history of GI complications.⁴¹

Patients with severe concurrent medical illnesses are not necessarily at increased risk of developing NSAID-related GI complications, but are more likely to die either directly as a result of complications that do arise or due to decompensation of their other medical illnesses.⁵⁰ Therefore, GPSs should also be used for subjects with substantial medical comorbidities, as development of NSAID-induced GI complications can be devastating.

Figure 1. Decision algorithm for gastroprotective strategies for NSAID users



What should I do?

The Canadian Association of Gastroenterology recommends that any chronic NSAID user with 1 or more risk factors for NSAID-related GI complications should be considered for a GPS.⁵¹ These recommendations were published in 2002, however, before many of the concerns of adverse effects associated with GPSs came to light, particularly the increased risk of cardiovascular disease seen with COX-2 inhibitors. Furthermore, using a GPS might increase the cost of analgesic therapy by up to 10 times the cost of using NSAIDs alone. Two separate economic analyses have suggested that the use of GPSs is cost-effective only in subjects at exceptionally high risk of NSAID-related complications, including patients older than 76 years, patients with multiple risk factors, or patients with history of GI bleeding.^{52,53}

A suggested algorithm to aid in decisions regarding GPSs for patients requiring NSAIDs is provided in **Figure 1**. All patients requiring chronic analgesic therapy in whom therapy with acetaminophen is either ineffective or contraindicated should be assessed for the presence of risk factors for GI complications. Patients at low risk of NSAID-related GI complications can receive NSAIDs alone at the lowest dose and for the shortest duration that provides effective analgesia. Patients with a moderately increased risk of GI complications should be offered a GPS. Proton pump inhibitor therapy should be the first choice for patients who are already using a PPI chronically for symptoms of gastroesophageal reflux disease

and those with cardiovascular disease or who are at increased risk of cardiovascular disease. Cyclooxygenase-2 inhibitors can be used for patients who have no risk factors for cardiovascular disease or for patients who do not tolerate PPIs well, but should be used at the lowest dose that provides effective analgesia. Misoprostol should be reserved for patients who are unsuitable for COX-2 inhibitors and who cannot tolerate PPI therapy, but should be given at doses of more than 200 µg twice daily. Up to 60% of subjects developing complications of peptic ulcer disease do not have antecedent GI symptoms; thus physicians should not wait for GI symptoms to develop before prescribing a medication for appropriate patients.⁵⁴

Patients at very high risk, including those with multiple risk factors and those who develop NSAID-related GI complications despite use of a GPS, can be offered 2 simultaneous gastroprotective medications (eg, COX-2 inhibitor and PPI). There is, however, no clinical trial or observational evidence to support the use of gastroprotective drugs in combination. Physicians must also consider avoiding use of NSAIDs entirely by using non-NSAID therapy, including narcotics, to provide effective analgesia.

Conclusion

Strategies to reduce the risk of GI complications in chronic NSAID users are effective. Gastrointestinal benefits might be offset, however, by the high cost of implementing GPSs as well as the recent reports of increased cardiovascular risk associated with COX-2 inhibitors. Therefore,

physicians must be able to determine who should be prescribed gastroprotective medications and which GPSs are optimal for particular patients. Physicians should communicate the risks and benefits of instituting GPSs with any patients who require chronic NSAID therapy. ❁

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Competing interests

None declared

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EDITOR'S KEY POINTS

- Approximately 1% to 2% of people who use nonsteroidal anti-inflammatory drugs (NSAIDs) will develop gastrointestinal (GI) complications, an annual rate 3 to 5 times higher than that among those who do not use NSAIDs.
- Increased age, concomitant use of systemic corticosteroids or warfarin, and history of GI bleeding or peptic ulcer disease are clearly associated with an increased risk of serious GI events among NSAID users (level II evidence).
- Patients with a moderately increased risk of GI complications should be offered a gastroprotective strategy (level I evidence).
- Patients at very high risk, including those with multiple risk factors and those who develop NSAID-related GI complications despite use of a gastroprotective strategy, can be offered 2 simultaneous gastroprotective medications (level III evidence).

POINTS DE REPÈRE DU RÉDACTEUR

- Environ 1% à 2% de ceux qui prennent des anti-inflammatoires non stéroïdiens (AINS) développeront des complications gastro-intestinales (GI), un taux annuel de 3 à 5 fois supérieur à celui qu'on observe chez ceux qui n'en prennent pas.
- Les utilisateurs d'AINS plus âgés, ceux qui utilisent en même temps des corticostéroïdes systémiques ou de la warfarine et ceux qui ont une histoire de saignement GI ou de maladie ulcéreuse sont clairement plus à risque de présenter des complications GI sévères (preuves de niveau II).
- On devrait offrir une médication gastroprotectrice aux patients qui ont un risque modérément augmenté de complications GI (preuves de niveau I).
- À ceux qui présentent un risque très élevé, comme les patients qui ont plusieurs facteurs de risque ou chez qui les AINS déclenchent des complications GI en dépit d'une médication gastroprotectrice, on peut offrir simultanément 2 médicaments gastroprotecteurs (preuve de niveau III).

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