

Quantifying the Impact of NSAID-Associated Adverse Events

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are the cornerstone of pain management in patients who have inflammatory, acute pain (eg, headache, postoperative pain, and orthopedic fractures), and chronic pain (eg, rheumatoid arthritis, osteoarthritis, and gout).^{1,2} Approximately 70% of people 65 years or older use NSAIDs at least once per week, with half of them taking at least 7 doses per week. In 2000, more than 111 million prescriptions were written for NSAIDs in the United States, at an approximate cost of \$4.8 billion.³ The use of NSAIDs is likely to increase even more as the US population continues to age and experience painful conditions that are more common among older adults.⁴

Both traditional NSAIDs and the second generation cyclooxygenase-2 (COX-2) inhibitors offer superior efficacy compared with acetaminophen, but also carry significant risk for serious gastrointestinal (GI), cardiovascular (CV), and renal adverse events.^{1,5-7} A systematic review of 17 prospective observational studies found that 11% of preventable drug-related hospital admissions could be attributed to NSAIDs.⁸ Studies have documented that the risk of adverse events associated with NSAIDs are both dose-dependent and duration dependent.^{1,7,9}

In 2005, the US Food and Drug Administration (FDA) issued a public health advisory warning of an increased risk for serious CV events with NSAID use.¹⁰ In 2007, the FDA published a medication guide for NSAIDs that recommended using the lowest dose possible for treatment. The guide listed myocardial infarction (MI), stroke, kidney problems, and GI bleeding as some of the serious potential side effects. Despite the emerging evidence, few studies have been conducted to help quantify the true burden of these side effects, especially when NSAIDs are used for acute pain.

The Impact of Pain Management

Acute pain is typically associated with an event, such as an injury or surgery, and usually resolves when the underlying event is treated or healed. Examples include headache, postoperative pain, fractures, low back pain, and neck pain.^{11,12} Approximately 40% of patient visits to primary care providers are due to mild to moderate acute pain.² More than 70% of emergency department (ED) visits are for acute pain, making it the most common reason

Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used among patients experiencing many different types of pain, including inflammatory, acute pain (eg, injury, low back pain, headache, postoperative pain), and chronic pain (eg, rheumatoid arthritis, osteoarthritis). However, both traditional NSAIDs and second-generation NSAIDs (cyclooxygenase-2 inhibitors) can lead to very expensive and serious adverse events. Gastrointestinal, cardiovascular, and renal complications associated with NSAIDs have been shown to be dose-dependent. In 2005, to help minimize these risks, the US Food and Drug Administration issued a public health advisory stating that “NSAIDs should be administered at the lowest effective dose for the shortest duration consistent with individual patient treatment goals.” This article reviews the undue clinical and economic burden associated with NSAID-related serious adverse events.

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why patients seek treatment. Among the over 115 million ED visits annually in the United States, headache alone accounts for 2.1 million.^{11,13} Considering that the average cost of a visit to the ED is \$1349, the costs associated with acute pain are substantial.¹⁴

Acute pain can also occur in the presence of chronic pain conditions such as osteoarthritis and low back pain; this type of pain is referred to as breakthrough pain. Both osteoarthritis and low back pain have placed significant economic burden on the US healthcare system.^{12,15} Data from the National Health Interview Survey show that in 2011, 28.4% of American adults reported experiencing low back pain within the previous 3 months.¹⁶ Buurma et al (2012) estimated that in 2011, there were 116.5 million cases of acute low back and neck pain in the United States. By 2021, the number is expected to reach 128.5 million cases (or, a 10% growth over the next decade).¹⁷

Similarly, the number of Americans with osteoarthritis is rising. Researchers estimate that the prevalence of arthritis in the United States among patients over 40 years of age grew from 10.1% in 1999 to 12.8% in 2008 ($P = .011$).¹⁸ Data from the Medical Expenditure Panel Survey (MEPS) showed that osteoarthritis was among the 5 most commonly treated conditions in 2009, totaling \$29.5 billion. MEPS data showed that 17.4 million adults between the ages of 40 and 64 years were treated for osteoarthritis in 2009.¹⁹

NSAIDs: The Hidden Costs

The cost of treating acute and chronic pain conditions is well documented. What is less well understood is the price tag attached to the side effects associated with their treatment. Some estimates suggest that each year more than 100,000 patients are hospitalized for NSAID-related GI complications alone, with direct costs ranging from \$1800 to \$8500 per patient per hospitalization. Moreover, it has been reported that 16,500 persons die annually from these complications. In the elderly, the medical costs of adverse GI events associated with NSAID use likely exceed \$4 billion per year.²⁰

NSAID use is also associated with costly adverse events impacting the CV and renal systems. For example, NSAID use has been associated with increased risk for hospitalization due to MI as well as for heart failure (HF). According to recent data from the Agency for Healthcare Research and Quality, the average hospitalizations for acute MI and congestive HF cost \$18,500 and \$10,500, respectively. Likewise, acute renal failure, which is also associated with NSAID use, can ultimately lead to expensive dialysis treatment.

Although direct cost data specific to NSAID adverse events are limited, several studies have examined healthcare

utilization that results from the morbidity and mortality associated with these adverse events.

Gastrointestinal Adverse Events

A meta-analysis published in 2012 examined the relative risk (RR) of upper GI complications (upper GI bleeding and/or perforation, or peptic ulcer) for both traditional NSAIDs and COX-2 inhibitors using pooled data from 28 observational studies published between 1980 and May 2011. Researchers found an increased risk for upper GI complications across all 16 of the NSAIDs studied. Data showed that the risk was lowest for aceclofenac and celecoxib (RR, 1.4 and 1.5, respectively) and highest for ketorolac and azapropazone (RR, 11.5 and 18.5, respectively). Most of the NSAIDs were associated with an RR for upper GI complications between approximately 2 and 4. Researchers also found that the risk was dose-dependent. The use of high daily doses was associated with an approximately 2- to 3-fold increase in RR compared with low to medium doses for all NSAIDs except celecoxib, for which the effect was not dose-dependent.¹

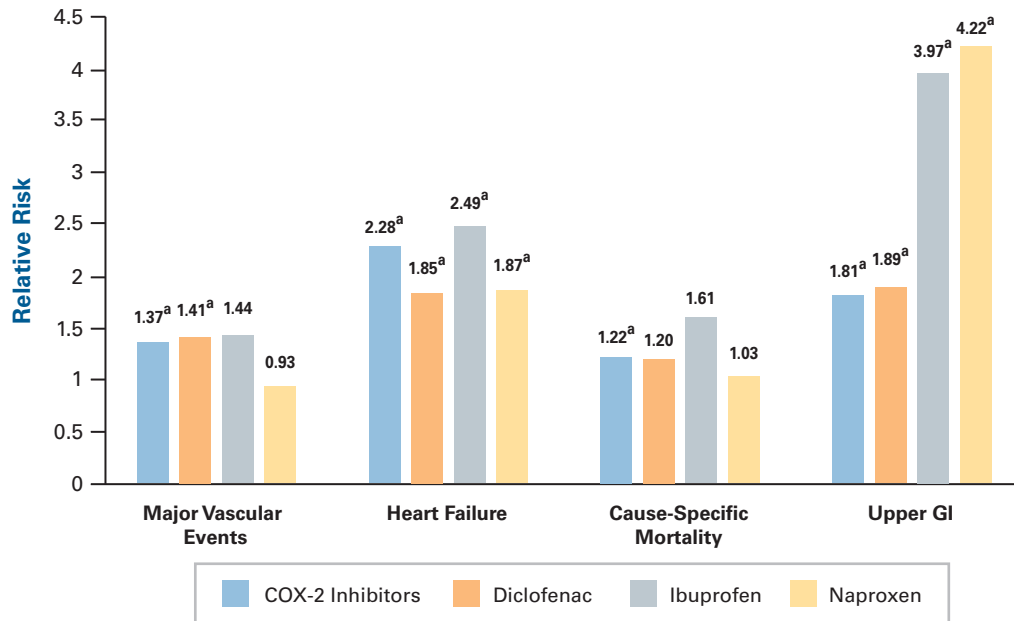
One of the more recent studies conducted regarding the GI side effects associated with NSAIDs was a 2013 meta-analysis by the Coxib and traditional NSAID Trialists' (CNT) Collaboration of 280 studies (124,514 participants). The study examined the relationship between the use of NSAIDs and upper GI complications, such as peptic ulcer perforations, obstructions, and bleeding. Data for naproxen, ibuprofen, and diclofenac, as well as for the COX-2 inhibitors rofecoxib, etoricoxib, lumiracoxib, valdecoxib, and GW403681, were analyzed. CNT researchers found an elevated risk for upper GI complications across all of the medications studied. The RR was nearly twice as high for ibuprofen and naproxen compared with diclofenac and COX-2 inhibitors (**Figure 1**).⁶

A similar increased risk was found in a study among Quebec residents. Patients using NSAIDs had a risk of developing GI adverse events that was 2.5 times (95% confidence interval [CI], 2.04-3.00) that of patients not taking NSAIDs. In addition, researchers estimated that the average cost for GI adverse events added an average of 66% to the cost of care. In patients over the age of 85 years with more than 5 physician claims, the costs of management of adverse events associated with NSAIDs increased the cost of each prescription by a factor of 7.5.²¹

Cardiovascular Risks

The CNT study described above also examined the vascular risk associated with NSAIDs. The primary outcome was major vascular events, defined as nonfatal MI, nonfatal

■ **Figure 1.** Relative Risk of Vascular and Upper GI Events by Drug Type: Results From the CNT Collaboration⁶



CNT indicates Coxib and traditional NSAID Trialists; COX-2, cyclooxygenase-2; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.
^a $P \leq .05$.

stroke, or death from a vascular cause. The study also measured the risk for major coronary events, stroke, hospitalization for HF, and death.

As shown in Figure 1, there was an elevated risk for major vascular events, HF, and cause-specific mortality for the COX-2 inhibitors. Diclofenac use at higher doses was associated with an increased risk for major vascular events and HF. Ibuprofen and naproxen use carried an increased risk for HF.⁶

A separate prospective study following 7636 individuals without a previous history of stroke examined the risk of stroke associated with traditional NSAIDs and COX-2 inhibitors. After adjusting for baseline body mass index, blood pressure, cholesterol level, and smoking status, researchers found that the risk of stroke increased by 1.58 for nonselective NSAID use and 2.40 for COX-2 selective NSAID use.²²

A study among patients 30 years or older with a history of HF from the Danish National Patient Registry examined the link between NSAID prescription claims after hospital discharge and subsequent death, hospitalization due to HF, and hospitalization due to MI. Researchers included data for rofecoxib, celecoxib, ibuprofen, diclofenac, naproxen, and other NSAIDs. Data showed an increase in risk of death, hospitalization due to HF, and hospitalization due to MI across all NSAIDs. Researchers also found that for most of

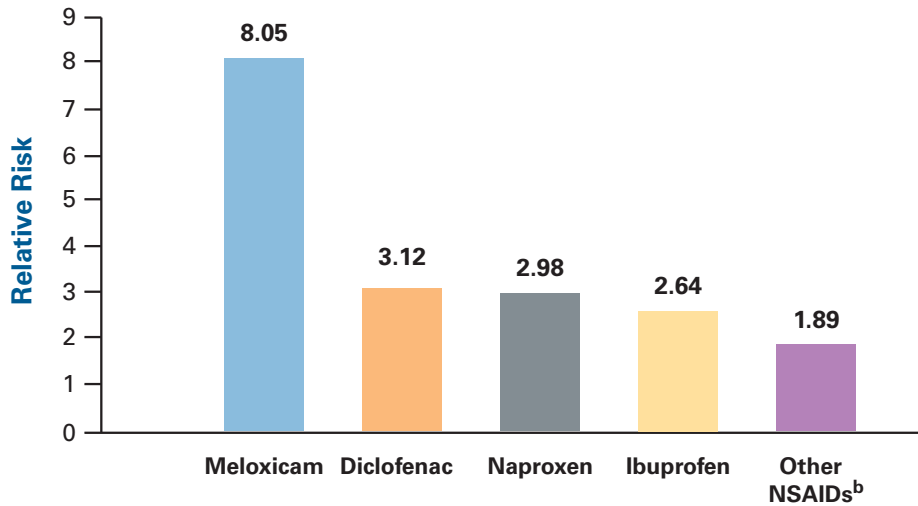
the NSAIDs studied, there was a clear, dose-dependent risk across all 3 end points. For example, high-dose diclofenac was associated with an increased risk for hospitalization due to MI at 100 mg per day (hazard ratio [HR], 2.43; $P < .001$), but had a nonsignificant increase at daily doses below 100 mg (HR, 1.14; $P = .26$).²³

Renal Adverse Events

A few studies have examined the renal complications associated with NSAID use. A 2005 nested-case control study among 386,916 individuals aged 50 to 84 years from the General Practice Research Database in the United Kingdom examined data for common NSAIDs, including diclofenac, ibuprofen, meloxicam, and naproxen (Figure 2).⁷ Researchers found that NSAID use was associated with a 3-fold greater risk for acute renal failure compared with non-NSAID use (95% CI, 1.8-5.8) after adjusting for age, sex, body mass index, and several comorbidities. Also, data showed that this risk was dose-dependent and increased with long-term use.⁷

A separate nested case-control study using administrative health databases in Quebec examined data for 121,722 new NSAID users older than 65 years to determine the factors associated with acute renal failure in this population. They found an increase in RR of 2.3 for traditional NSAIDs

■ **Figure 2.** Relative Risk of Renal Failure Among NSAID Users by Drug Type^{7a}



NSAID indicates nonsteroidal anti-inflammatory drug.

^aAdjusted for age, sex, calendar year, body mass index, heart failure, hypertension, diabetes, antihypertensive use, oral steroid use, NSAID use, and consultant visits and hospitalizations in the previous year.

^bOther NSAIDs include aceclofenac, acemetacin, azapropazone, etodolac, fenbufen, fenoprofen, flurbiprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, piroxicam, tenoxicam, tiaprofenic acid, and sulindac.

■ **Table 1.** Risk of Serious Events Based on Duration of NSAID Therapy^{7,24,25}

Days	1-14	15-30	31-60	181-240	241-365
RR of upper GI events	3.0	2.7	2.1	3.8	5.4
Days	1-14	15-30	31-90	91-180	
RR of first MI	1.39	1.22	1.25	1.54	
Days	1-30	31-365	366-730	>730	
RR of ARF	2.65	2.42	4.33	3.71	

ARF indicates acute renal failure; GI, gastrointestinal; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk.

and a similar increase for users of rofecoxib (RR, 2.31) or naproxen (RR, 2.42). This study also found the risk was dose-dependent.⁹

Duration, Dose, and Adverse Events

Although the FDA warns against long-term use of NSAIDs, several studies have found that the increased risk for GI-, CV-, and renal-related complications is present even when NSAID use is relatively short in duration.^{7,24,25} As shown in **Table 1**,^{7,24,25} the risk increases within the first few weeks of treatment and persists during the course of NSAID therapy. These data suggest that safety and tolerability risks of short-term NSAID therapy should not be overlooked by clinicians.

In addition, as outlined above, studies illustrate that GI, CV, and renal adverse events associated with NSAID use are dose-dependent. It also important to note that dosing used in many of these trials reflect NSAID use that is common

to clinical practice; in other words, everyday use of NSAIDs carries notable risk.

Strategies for Reducing the NSAID-Related Burden

Various strategies have been employed to help mitigate the risk for adverse events (**Table 2**).^{1,7,26-28} COX-2 inhibitors were initially developed as a safer alternative to traditional NSAIDs. However, data soon emerged that linked their use to an elevated risk for CV-related adverse events. Another strategy involves the addition of an enteric coating, which is often used on aspirin and ibuprofen to help alleviate stomach irritation.

Another option used by some clinicians is to add a gastroprotective agent to the NSAID regimen. This approach has shown some reduction in GI events. However, a pharmacoeconomic study comparing the cost of GI adverse events in patients taking NSAIDs (n = 10,540) with those taking NSAIDs plus the gastroprotective agent misoprostol (n =

Table 2. The Impact of Various Strategies on Serious Adverse Events^{1,7,26-28}

	Serious GI Events	Serious CV Events	Serious Renal Events
Lower dose	↓	↓	↓
COX-2 selective inhibition	↓	↑	↑
NSAID + gastroprotective agents	↓	—	—

COX-2 indicates cyclooxygenase-2; CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

1533) found that the groups had statistically similar rates of GI-related hospitalizations, GI-related healthcare resource utilization, and costs associated with these resources over the 2-year period.²⁹ Additionally, none of these strategies address the risk for CV or renal complications.

Over the past decade, data have shown that the risk for adverse events is strongly associated with baseline risk, NSAID dosage, and duration of use. It is up to the clinician to carefully weigh the risk and benefits for each patient based on his or her pain symptoms and baseline risk for GI, CV, or renal complications. While individual risk factors are an important consideration, another key strategy to reduce risk for all patients is for clinicians to prescribe the lowest effective dose for the shortest possible duration, as recommended by the FDA and numerous other regulatory bodies and medical organizations.³⁰

Conclusion

NSAIDs remain a viable choice among clinicians and patients for the treatment of a variety of painful conditions. Efforts to mitigate the common GI-related adverse events have had mixed results, and have failed to address the added risk for serious CV and renal complications. Moreover, several studies comparing the safety of traditional NSAIDs with the newer COX-2 inhibitors on the market have shown that the RR varies, and that neither drug class has a clear safety advantage. The available data suggest that NSAID-related adverse events place a substantial clinical and economic burden on the healthcare system. Finding the lowest effective dose and shortest duration of treatment that still provides sufficient clinical efficacy should be the goal for physicians who are managing their patients' pain with NSAIDs.

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REFERENCES

- Castellsague J, Riera-Guardia N, Calingaert B, et al. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). *Drug Saf.* 2012;35(12):1127-1146.
- McCarberg B, Gibofsky A. Need to develop new nonsteroidal anti-inflammatory drug formulations. *Clin Ther.* 2012;34(9):1954-1963.
- Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology.* 2001;120(3):594-606.
- The State of Aging and Health in America 2013.* Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2013.
- Lee C, Straus WL, Balshaw R, et al. A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analysis. *Arthritis Rheum.* 2004;51(5):746-754.
- Coxib and traditional NSAID Trialists' Collaboration. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet.* 2013;382(9894):769-779.
- Huerta C, Castellsague J, Varas-Lorenzo C, García Rodríguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *Am J Kidney Dis.* 2005;45(3):531-539.
- Howard RL, Avery AJ, Slavenburg S, et al. Which drugs cause preventable admissions to hospital? a systematic review. *Br J Clin Pharmacol.* 2007;63(2):136-147.
- Schneider V, Lévesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: a population-based, nested case-control analysis. *Am J Epidemiol.* 2006;164(9):881-889.
- Public health advisory: FDA announces important changes and additional warnings for COX-2 selective and non-selective nonsteroidal anti-inflammatory drugs (NSAIDs). US Food and Drug Administration website. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm150314.htm>. Published April 7, 2005. Accessed September 20, 2013.
- International Association for the Study of Pain. What is the problem? http://www.iasp-pain.org/AM/Template.cfm?Section=Fact_Sheets3&Template=/CM/ContentDisplay.cfm&ContentID=11783. Published 2010. Accessed October 1, 2013.
- Institute of Medicine. *Relieving pain in America: a blueprint for transforming prevention, care, education, and research.* Washington, DC: The National Academies Press; 2011.
- Coda BA, Bonica JJ. General considerations of acute pain. In: Loeser JD, Butler SH, Chapman CR, Turk DC, eds. *Bonica's Management of Pain.* 3rd ed. Hagerstown, MD: Lippincott Williams & Wilkins; 2001:222-240.
- Agency for Healthcare Research and Quality. Medical expenditure panel survey. <http://meps.ahrq.gov/mepsweb/index.jsp>. Accessed October 1, 2013.

Reports

15. Jacobson L, Mariano AJ. General considerations of chronic pain. In: Loeser JD, Butler SH, Chapman CR, Turk DC, eds. *Bonica's Management of Pain*. 3rd ed. Hagerstown, MD: Lippincott Williams & Wilkins; 2001:241-254.
16. *Health, United States, 2012: with special feature on emergency care*. Hyattsville, MD: National Center for Health Statistics; 2013.
17. Decision Resources, LLC. Pain management study: acute pain. Burlington, MA. 2012.
18. Ong KL, Wu BJ, Cheung BM, Barter PJ, Rye KA. Arthritis: its prevalence, risk factors, and association with cardiovascular diseases in the United States, 1999 to 2008. *Ann Epidemiol*. 2013; 23(2):80-86.
19. Roemer M. Health care expenditures for the five most common conditions of adults ages 40 to 64, 2009. http://meps.ahrq.gov/mepsweb/data_files/publications/st382/stat382.pdf. Accessed September 2013.
20. Bidaut-Russell M, Gabriel SE. Adverse gastrointestinal effects of NSAIDs: consequences and costs. *Best Pract Res Clin Gastroenterol*. 2001;15(5):739-753.
21. Rahme E, Joseph L, Kong SX, Watson DJ, LeLorier J. Gastrointestinal health care resource use and costs associated with nonsteroidal antiinflammatory drugs versus acetaminophen: retrospective cohort study of an elderly population. *Arthritis Rheum*. 2000;43(4):917-924.
22. Haag MD, Bos MJ, Hofman A, et al. Cyclooxygenase selectivity of nonsteroidal anti-inflammatory drugs and risk of stroke. *Arch Intern Med*. 2008;168(11):1219-1224.
23. Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. *Arch Intern Med*. 2009;169(2):141-149.
24. Helin-Salmivaara A, Virtanen A, Vesalainen R, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. *Eur Heart J*. 2006;27(14):1657-1663.
25. Helin-Salmivaara A, Saarelainen S, Grönroos JM, et al. Risk of upper gastrointestinal events with the use of various NSAIDs: a case-control study in a general population. *Scand J Gastroenterol*. 2007;42(8):923-932.
26. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med*. 2011;8(9):e1001098.
27. Spiegel BM, Chiou CF, Ofman JJ. Minimizing complications from nonsteroidal antiinflammatory drugs: cost-effectiveness of competing strategies in varying risk groups. *Arthritis Rheum*. 2005;53(2):185-197.
28. Rossat J, Maillard M, Nussberger J, Brunner HR, Burnier M. Renal effects of selective cyclooxygenase-2 inhibition in normotensive salt-depleted subjects. *Clin Pharmacol Ther*. 1999;66(1): 76-84.
29. Rahme E, Joseph L, Kong SX, Watson DJ, Pellissier JM, LeLorier J. Gastrointestinal-related healthcare resource usage associated with a fixed combination of diclofenac and misoprostol versus other NSAIDs. *Pharmacoeconomics*. 2001;19(5, pt 2): 577-588.
30. Medication guide for non-steroidal anti-inflammatory drugs (NSAIDs). US Food and Drug Administration website. <http://www.fda.gov/downloads/drugs/drugsafety/ucm089162.pdf>. Accessed September 20, 2013.