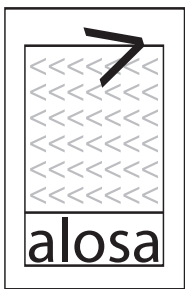




# Life after Vioxx...

**T**he unexpected withdrawal of Vioxx in September 2004, followed by Bextra in April 2005, has led many physicians to reassess the place of selective cox-2 inhibitors in pain management. These concerns were heightened last spring when the FDA applied the same “black box warning” to all NSAIDs as well, cautioning that they each can increase the risk of cardiovascular events. What is really known about the comparative efficacy and safety of these drugs?



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*Balanced data about medications*



## Clearing the air about efficacy.

The overwhelming evidence from clinical trials shows that selective cox-2 inhibitors do **not** have any stronger analgesic efficacy than conventional NSAIDs such as naproxen (e.g., Aleve) or ibuprofen (e.g., Motrin).<sup>1</sup> Different patients may respond differently to different analgesics, but there's virtually no evidence that the cox-2 drugs relieve pain any better than their older counterparts. Elaborate media campaigns directed at patients created an aura of superiority that was not backed up by clinical trial data.

## A word on gastroprotection.

The main advantage of drugs like Vioxx (rofecoxib) or Celebrex (celecoxib) was the expectation that they would lower the risk of gastrointestinal bleeding compared to older NSAIDs. **However...**

- this protection was relative, not absolute;<sup>2,3</sup>
- concurrent use of low-dose aspirin for cardioprotection can sharply reduce the g.i. protection offered by these drugs;<sup>2</sup>
- only a small proportion of patients who will need chronic analgesics are at high risk of NSAID-induced g.i. bleeding in the first place;<sup>4</sup> [see box]
- there are other effective ways of protecting patients from analgesic-induced g.i. side effects, such as adding a proton pump inhibitor to a conventional NSAID.<sup>5</sup>

### Which patients are at most risk for g.i. side effects?

- older age

- history of peptic ulcer disease

- using oral steroids

- taking warfarin (Coumadin) or another anticoagulant

## The tipping point for cardiovascular risk.

There has long been concern about whether selectively inhibiting the cox-2 enzyme might increase the risk of cardiovascular events through a variety of thrombogenic effects as well as other mechanisms. A key randomized trial of rofecoxib (Vioxx) published in 2000 unexpectedly demonstrated a 5-fold increase in the rate of myocardial infarction in patients randomized to that drug.<sup>3</sup> Several large observational studies since then have also found higher rates of MI in patients taking Vioxx.<sup>6,7</sup> In September 2004, a Merck-sponsored randomized clinical trial found that patients given Vioxx had twice the number of MIs or strokes that controls did.<sup>8</sup> The company withdrew the drug from the market. Bextra (valdecoxib) was withdrawn seven months later.

## What about the benefits and risks of the drugs that remain?

Confusion increased when FDA warned in April 2005 that *all* NSAIDs and the remaining selective cox-2 inhibitor, Celebrex (celecoxib), would be required to carry the same black-box warning that they can increase the risk of cardiovascular events.<sup>9</sup> This created concerns for physicians and patients over the whole class of agents, but provided little guidance on what to do or whether the risk is the same for all of these drugs. The evidence suggests that it is not.<sup>10</sup> We have reviewed the data from all available randomized controlled trials (RCTs) and epidemiological (epi) studies and summarize it here:



<b>Vioxx</b> (rofecoxib)	Considerable evidence of increased risk of MI, stroke, and other cardiovascular complications seen in RCTs and epi studies, especially at higher doses. [withdrawn from market]
<b>Bextra</b> (valdecoxib)	Doubling or tripling of cardiovascular events compared to placebo in two RCTs of patients undergoing cardiac surgery. Also causes potentially fatal dermatologic side effect of Stevens-Johnson syndrome. [withdrawn from market]
<b>Celebrex</b> (celecoxib)	At high doses (200-400 mg b.i.d.), dose-related doubling or tripling of myocardial infarction in one RCT compared to placebo, but no increase in risk found in another RCT with a single daily dose of 400 mg/d. Several epi studies have found no elevated risk signal compared to Vioxx or other NSAIDs.
<b>Motrin, etc.</b> (ibuprofen)	Conflicting evidence of risk, much less clear than with previous three drugs. However, little information is available on cardiac risk from randomized placebo-controlled trials.
<b>naproxen:</b>	Evidence of slightly <i>reduced</i> risk of MI in many but not all RCT and epi studies.
<b>aspirin:</b>	Clear evidence of reduction in risk of MI based on large RCTs in men; less evidence of benefit in women.

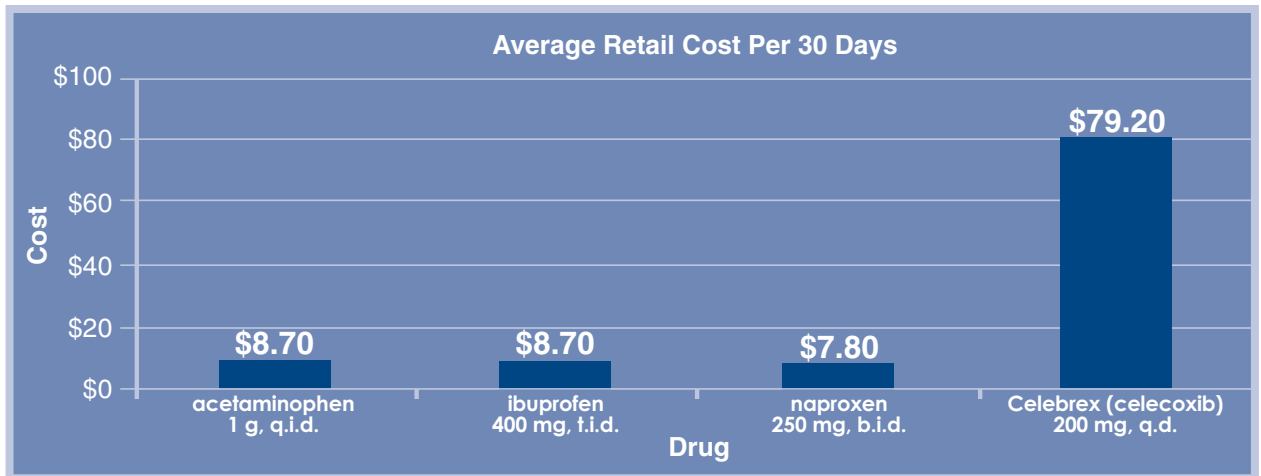
References are provided in the evidence document accompanying this material.

## Back to basics.

One good outcome of the current resurgence of interest in the risks and benefits of the coxibs and NSAIDs is that many prescribers have begun to re-think their management of acute and chronic pain.<sup>11</sup> Pain specialists and rheumatologists recommend this approach:<sup>12</sup>

- 1. Start with acetaminophen (Tylenol, etc.).** Because it is sold over-the-counter and has been available for decades, many clinicians underestimate the utility of this drug. Unless a patient has contraindications such as liver disease, alcoholism, or poorly controlled hypertension, consider 1 g t.i.d.-q.i.d. as an initial pain medication. This may well be adequate for a significant number of patients and can form the foundation of further treatment for others.
- 2. Naproxen is probably the safest NSAID in terms of cardiac risk.** If a non-aspirin NSAID is needed, the bulk of evidence indicates that naproxen carries the lowest cardiac risk, and may even be cardioprotective to a small degree. (But it should *not* be used to replace low-dose aspirin for this purpose.) Naproxen is also available at low cost from multiple generic manufacturers [see cost comparison chart]. It should be taken with meals or milk. If g.i. symptoms develop, or a patient is at high g.i. risk [see box], consider adding an H<sub>2</sub> blocker or a proton pump inhibitor. There is evidence that taking omeprazole along with a conventional NSAID can provide gastroprotection comparable to that provided by Celebrex.<sup>5</sup>
- 3. All patients who require cardioprotective use of low-dose aspirin should receive it regardless of their NSAID regimen.** Unfortunately, the available evidence suggests that (a) low-dose aspirin reduces the modest gastroprotective benefit of the cox-2 inhibitors, and (b) this does not seem to protect against the elevated risk of MI caused by the coxibs.
- 4. Whatever regimen is chosen, prescribe the lowest dose that will control pain, and the shortest duration of therapy. Monitor patients** for side effects including fluid retention, hypertension, reduction in renal function, and evidence of gastrointestinal toxicity (abdominal pain, black stools, fecal occult blood, anemia).

**Who really needs a cox-2 inhibitor?** The recommended approach will work best for most patients. The available data indicate that the one cox-2 inhibitor remaining on the market, Celebrex, appears to pose less cardiac risk than did Vioxx and Bextra, and little is known about its safety compared to older non-selective NSAIDs. However, the greater rate of cardiac events seen at high doses in placebo-controlled trials is worrisome. Taken together, the data suggest that Celebrex be reserved for patients who require an NSAID, are at increased risk of the gastrointestinal complications from which it provides modest protection, and cannot tolerate the suggested regimens.<sup>7</sup>



**For patients with chronic arthritis pain,** rheumatologists advocate several additional strategies to avoid having to commit a patient to years of high-dose NSAID therapy:<sup>12</sup>

- 1. Protect the affected joints** with a cane, brace, weight loss, and lower extremity exercise programs.
- 2. Evaluate the need for controlled opioid analgesics.** For carefully selected patients, measured use of codeine, tramadol, hydrocodone, or oxycodone may be a safe and appropriate choice.
- 3. Don't wait too long before surgery.** For some patients with severe osteoarthritis, the most effective treatment is joint replacement, which will usually improve function and will lessen the need for pain medication in many cases.

## In summary...

The renewed concern about the safety and efficacy of old and new NSAIDs can provide a fresh opportunity to reassess the approach to pain management. In many instances, such reassessment will enable patients to experience better analgesic results with lower risk of cardiovascular as well as gastrointestinal side effects.

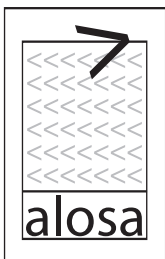
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Additional references documenting these recommendations are provided in the evidence document accompanying this material.

This material was produced for the Independent Drug Information Service (iDiS) by Dan Solomon, M.D., M.P.H., Assistant Professor of Medicine at Harvard Medical School, and Jerry Avorn, M.D., Professor of Medicine at Harvard Medical School.

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