

# The Demise of the Super-aspirins: An Opportunity for Integrative Medicine?

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The recent findings of significant cardiac risks with long-term use of the selective COX-2 inhibitors and naproxen leave many patients without access to drugs they may depend on for sustained management of pain. These cardiac risks can arise from disturbances in the ratio of prostacyclin and thromboxane A<sub>2</sub>. Integrative medicine offers a variety of interventions that do not disrupt this ratio, including herbs, nutraceuticals, mind-body strategies, and physical care. Clinical studies for evaluating these interventions, and research on sustainable production of those that are natural substances, should be given greater funding priority at this time.

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The possible loss, or restriction of use, of the new selective COX-2 inhibitors—popularly dubbed “super-aspirins”—both for patients experiencing chronic pain from a variety of conditions including osteoarthritis and for cancer patients who have tumors that may overexpress cyclooxygenase-2 (COX-2), has serious implications. More than 80 million people are estimated to take prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) daily, of which approximately 30% are COX-2 inhibitors.<sup>1</sup> Many patients have been frantically calling their doctors for suggestions of alternative medication strategies for their pain, but physicians have had little to offer. For cancer patients with COX-2-expressing tumors or with precancerous colon polyps, the diminished availability of these drugs as possible chemoprevention or cancer treatment agents is also of understandable concern.

Although earlier work had raised some concerns of cardiac risks with the selective COX-2 inhibitors, awareness of the risks of COX-2 inhibitors increased sharply with the September 2004 decision of Merck to withdraw rofecoxib from the market following the results of a clinical trial that showed a doubling of heart attack and stroke risks relative to the placebo condition after 18 months of use. How do the COX-2

inhibitors increase cardiac risk? While the mechanisms of this activity are not yet entirely clear, some preliminary assessments point to the impact of selective COX-2 inhibition on the production of prostacyclin. Prostacyclin (PGI-2) and thromboxane A<sub>2</sub> (TXA-2) interact in a dynamic fashion in the body to prevent thrombus formation: PGI-2 decreases clotting, while TXA-2 increases it. Both PGI-2 and TXA-2 are produced in the arachidonic acid cascade from the same prostaglandin precursor, PGH-2. PGI-2 results from the activity of COX-2 on PGH-2, while TXA-2 results from the activity of COX-1 on PGH-2.<sup>2</sup> Selective COX-2 inhibition by the super-aspirins reduces PGI-2 production without affecting TXA-2. The end result is a dominance of the prothrombic TXA-2 and the potential for higher rates of heart attacks and other thrombus-linked cardiac risks. Of course, there are likely to be other mechanisms that may have a simultaneous impact. However, this specific mechanism was suggested as early as 2002<sup>2</sup> but was apparently disregarded until the outcome of the recent trials indicated the clinical significance of the resulting increases in cardiac risk. While it has long been thought that naproxen had a cardioprotective effect, recent data show that naproxen, unlike aspirin, actually inhibits systemic PGI-2 synthesis in monocytes by 77%, which is consistent with a COX-2 inhibitory effect (both drugs showed evidence of COX-1 inhibition as well).<sup>3</sup>

For years, many cancer patients have been using NSAIDs for long-term pain management and more recently to combat malignancy. So I will raise an obvious question: Does an integrative medicine model have anything to offer the patients who have now lost access to or confidence in these medications? Even a cursory look at the literature on integrative medicine indicates that there are numerous nutraceutical COX-2 inhibitor options for pain relief. And while the

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evidence is mostly regarding osteoarthritis, the application for cancer is clear. Natural agents and dietary strategies that inhibit COX-2 without the concern found with the drugs that abolish prostacyclin production provide potential value for cancer patients with COX-2-expressing tumors. Let me present a few of the relevant findings for consideration.

A recent summary of systematic reviews of complementary and alternative medicine therapies for arthritis-related pain pointed out several therapies with reasonable evidence of efficacy in osteoarthritis and rheumatoid arthritis.<sup>4</sup> Avocado/soybean unsaponifiables (a specific extract of the oil of avocado and soybeans) were found to provide long-term relief of osteoarthritis of the hip. Promising data were found for the herb devil's claw (*Harpagophytum procumbens*) and moderate support for topical capsaicin and Phytodolor, an extract of *Populus tremula* (poplar), *Fraxinus excelsior* (ash), and *Solidago virgaurea* (goldenrod). Glucosamine was found to have moderate to large treatment effects, while a related product, chondroitin, was also found to have significant treatment effects. SAME (S-adenosylmethionine) was found to be as effective as NSAIDs in osteoarthritis. Gamma-linolenic acid, found in borage, evening primrose, and black currant seed oils, was effective in rheumatoid arthritis. Various homeopathic treatments were found to have some general effectiveness in arthritis and related diseases, although pain was not specifically examined in the trials assessed. Convincing data have not been found for acupuncture in osteoarthritis or rheumatoid arthritis, although there appear to have been difficulties with trial design and the use of sham needling.

Another author has examined reviews of the use of chiropractic and massage therapy in pain conditions, including back pain, for which COX-2 inhibitors have been used.<sup>5</sup> For neither condition could high-quality evidence of efficacy on back pain be found; there are, however, problems with design of the trials that were included in the reviews, and the possible effectiveness of these therapies cannot be ruled out. Other natural therapies with some potential in pain relief include soybeans, tart cherries,<sup>6</sup> boswellia,<sup>7</sup> and a variety of mind-body interventions.<sup>8</sup> Soybeans, it is interesting to note, diminished some pain variables in a mouse mode of bone cancer pain, suggesting that dietary soy may contribute to the management of this significant drain on the quality of life of advanced cancer patients.<sup>9</sup>

Curcumin, a traditional anti-inflammatory food and herbal medicine that also reduces platelet aggregation, has been found to slightly increase PGI-2 production, in contrast to the PGI-2-inhibiting effect possessed by other anti-inflammatories. While there is a

good deal more that needs to be investigated about the role of the curcuminoids as clinically relevant anti-inflammatories, it could certainly be said that the biochemistry of these compounds ought to be investigated, as they may demonstrate a biosynthetic pathway that circumvents the prostacyclin problem of the selective COX-2 inhibitors. Of course, exercise, physical therapy, and weight loss also have important roles to play in the management of osteoarthritis.

It seems, then, that a variety of integrative approaches, which do not rely directly on selective COX-2 inhibition, may be able to offer relief to patients suffering from pain conditions. What about the problem of patients with cancers that commonly overexpress COX-2? An integrative approach to the management of COX-2-expressing cancers was, in fact, the first topic that was presented in the very first issue of *Integrative Cancer Therapies*, in a review by Jeanne Wallace.<sup>10</sup> Wallace's review outlined the basics of the anti-inflammatory diet and reviewed a number of supplements that decrease the production of inflammatory and tumor-promoting eicosanoids, including supplements such as bromelain, boswellia, and fish oil. Boswellia was observed to decrease cerebral edema associated with radiochemotherapy treatment of brain tumor, an example of useful control of treatment side effects by this leukotriene inhibitor.<sup>11</sup> Fish oil, which we use very commonly in our clinical work at the Block Center for Integrative Cancer Care, is of particular interest in connection with COX-2 inhibition and cardiac issues. Fish oil, discussed in a recent review in this journal (volume 3, number 2), has a variety of anticancer and anticachectic effects relevant to treatment of malignancy.<sup>12</sup> Its major mechanism of action is the replacement of arachidonic acid in the arachidonic acid cascade with molecules that possess the omega-3 linkage, resulting in the synthesis of 3-series prostaglandins, rather than 2-series prostaglandins such as PGE-2, a known tumor promoter. Because it circumvents the production of PGH-2, levels of PGI-2 tend to decline.<sup>13</sup> However, accompanying this decline is a similar decline in the levels of TXA-2. These 2 compounds are replaced by PGI-3 and TXA-3, a thromboxane that lacks platelet-aggregating effects.<sup>14</sup> The effects of this replacement are 2-fold. First, because both PGI-2 and TXA-2 decline, there is no relative increase in the levels of the thrombogenic TXA-2. Second, PGI-3 itself inhibits platelet aggregation (though perhaps not as strongly as PGI-2).<sup>15</sup>

What are the clinical results of this alternative biochemistry? Omega-3 fats in fish oils reduce sudden cardiac death in patients with coronary heart disease.<sup>16</sup> As shown in a meta-analysis of fish oil trials that included more than 14,000 patients, daily omega-3 intake reduced all-cause mortality by 16% and death

by myocardial infarction by 24%.<sup>17</sup> Fish oil also appears to have antiarrhythmic effects, which may help explain the first 2 results.<sup>18</sup> Related products such as extract of New Zealand green-lipped mussel and krill oil, which contain omega-3 fatty acids, may have similar effects. Thus, using omega-3 fatty acids as anti-inflammatories would avoid the cardiac risks of the selective COX-2 inhibitors. Further exploration of the use of omega-3 fatty acids in inflammatory conditions related to cancer (including cancer prevention, COX-2-expressing cancers, and conditions such as cachexia) can thus be undertaken without concerns of elevated cardiac risks. In fact, omega-3 fats may alleviate thrombogenic states associated with cancer, including the well-known elevated risk of blood clots during cancer chemotherapy.

Integrative medicine, then, may have much to offer both pain management and cancer management. While new second-generation COX-2 inhibitors are under development, perhaps an alternative stream of research into the mechanisms of the herbal and supplemental therapies for pain syndromes and cancer, and the use of fish oil and related products, should receive strong consideration in allocation of research funds. While mechanistic and clinical studies should obviously be funded, research also needs to be directed to quality control and sustainable supplies of these natural substances. Devil's claw, for instance, is still wild-harvested in the Kalahari desert, and while current harvest levels appear to be sustainable, any major increase in demand could rapidly result in depletion of the resource (or use of adulterants in commercial products). Whether various marine resources such as cod (the source of much fish oil) and krill can be harvested sustainably at levels high enough to supply a burgeoning demand is uncertain. There are even doubts being raised about the sustainability of fish oils and fish meal used as food supplements in aquaculture, the growing of fish for the commercial market.<sup>19</sup> Development of natural products takes an interdisciplinary approach that is rare in the pharmaceutical industry, but the herb and supplement industry and governmental agencies involved in natural product development do have the experience needed for successful research in this area.

The crisis and challenge we face due to the risks that have come to light with the use of COX-2-inhibiting drugs provides us with a unique opportunity. This is an optimal time for integrative medicine to step up and offer meaningful options in both pain management and cancer management. Such a move may be able to address the needs of the millions of patients who are

now being left in the lurch after the demise of the super-aspirins, with the contribution of the significantly innovative measures discussed here.

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