Cyclooxygenase Inhibition: Pain, Inflammation, and the Cardiovascular System

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Inhibitors of the cyclooxygenases (COXs), the nonsteroidal antiinflammatory drugs (NSAIDs), relieve inflammatory pain, but are associated with gastrointestinal and cardiovascular complications. Given the widespread use of NSAIDs, there has been a longstanding interest in optimizing their risk–benefit ratio, for example by reducing their gastrointestinal risk. More recently, the focus has shifted toward the cardiovascular complications of NSAIDs and very large prospective studies have been performed to compare cardiovascular risk across distinct NSAIDs. Surprisingly, much less attention has been paid to the efficacy side of the risk–benefit ratio. There is marked variability in the degree of pain relief by NSAIDs due to the complex interplay of molecular mechanisms contributing to the pain sensation, variability in the disposition of NSAIDs, and imprecision in the quantification of human pain. Here we discuss how NSAIDs relieve pain, how molecular mechanisms relate to clinical efficacy, and how this may inform our interpretation of clinical trials.

Pain is a multidimensional experience involving nociceptive, affective, and cognitive networks that serve a protective role against tissue damage. However, chronic pain that persists beyond the "normal" time of wound healing severely impacts psychosocial and physical health. Approximately 20–30% of the adult population in the United States and Europe suffer from chronic pain, predominantly back pain, joint pain, and headache.1,2 The economic burden of pain resulting from healthcare utilization and lost productivity has been estimated at $560 to $635 billion annually in the United States, exceeding the costs associated with heart disease, diabetes, or cancer.3 Nonsteroidal antiinflammatory drugs (NSAIDs), inhibitors of the cyclooxygenases (COXs), are among the most commonly used analgesics due to their lack of addictive potential and ready availability over the counter. Short-term use of NSAIDs is particularly prevalent (perhaps 50–80% per year) in individuals at risk for acute and chronic musculoskeletal injuries such as athletes and soldiers.4–6 Extended periods of NSAID treatment (e.g., more than 3 times per week for more than 3 months per year) have been reported by 10% of adults in the United States,7 a rate that can be expected to increase steeply with age. However, NSAIDs are not without risk. They can damage the gastrointestinal mucosa, raise blood pressure, and cause adverse cardiovascular events, including myocardial infarction, stroke, and heart failure, and perhaps arrhythmias and sudden cardiac death. Given the widespread consumption of NSAIDs, even small risks associated with these drugs have substantial public health impact. Therefore, research, drug development, and regulatory actions during the past decade have focused primarily on the safety of analgesics in the NSAID class.

Gastrointestinal safety was the initial impetus for the development of COX-2 selective NSAIDs.8 Following the mechanistic prediction9–11 and detection of cardiovascular adverse effects of these drugs, the focus shifted towards the cardiovascular complications of NSAIDs (reviewed in Refs.12–14). This has recently been highlighted by two large clinical trials designed specifically to address the comparative cardiovascular safety of NSAIDs, the Standard Care vs. Celecoxib Outcome Trial (SCOT)15,16 and the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION) trial.17,18 In contrast, less attention has been paid to the comparative efficacy of NSAIDs. Indeed, careful reading of the SCOT and PRECISION trials suggest that the doses of celecoxib and the comparator NSAIDs used in these studies were not equally efficacious and underdosing of celecoxib may have led to an underestimation of its cardiovascular risk.14,19–23 In this article we take a closer look at the analgesic efficacy of COX inhibition. We discuss how NSAIDs relieve pain, how molecular mechanisms relate to clinical efficacy, and how this may inform our interpretation of clinical trials—in particular SCOT and PRECISION.

Cyclooxygenases and Prostanoids

The pharmacologic targets of NSAIDs, COX-1 and COX-2, are key enzymes in the formation of a class of lipid mediators known...
as prostanoids. The COX biosynthetic-response network constitutes a cell-to-cell communication system that regulates, modulates, or fine-tunes cellular signaling processes in essentially all tissues. Thus, in most biological processes, prostanoids act in the context of multiple other pathways resulting in both functional synergies and redundancies.

Prostanoid synthesis is predominantly initiated by phospholipases A2, which release arachidonic acid from membrane phospholipids. The COXs are integrated into the membrane lipid bilayer and form a labile intermediate, prostaglandin (PG) H2, from arachidonic acid. At least eight prostanoid isomerases, encoded by distinct genes, transform PGH2 to five distinct prostanoids, which act on G-protein-coupled receptors. Together, these molecules form a pyramid-like core topology within the ~300 molecule arachidonic acid biosynthetic-response network (Figure 1). Consequently, COX inhibition results in manifold biochemical effects which may translate into both benefits—by suppressing prostanoids regulating pathological processes—and adverse reactions—by suppressing prostanoids with cytoprotective or homeostatic roles.

The two COX isoforms are encoded by separate genes. COX-1 is constitutively expressed in most tissues and generally controls basal production of prostanoids with physiological functions, such as gastric epithelial cytoprotection or platelet activation. Thus, one of the major complications of NSAIDs is damage to the gastrointestinal mucosa, which is protected primarily by COX-1, but also COX-2-derived prostanoids. The bleeding phenotype induced by aspirin and other NSAIDs by coincident inhibition of platelet COX-1 and consequent suppression of platelet thromboxane (Tx) A2 formation is another example of an adverse effect caused by depressing prostanoids with a fundamental homeostatic role, in this case hemostasis. Indeed, this property has been exploited as the therapeutic mechanism underlying cardiovascular prevention with low-dose aspirin. Unsurprisingly, low-dose aspirin’s most frequent complication is gastrointestinal bleeding.

Most tissues do not express COX-2 under basal conditions but upregulate this immediate early gene in response to inflammatory stimuli. Resulting COX-2 products, particularly prostaglandin (PG) E2, act to potentiate the acute inflammatory response. This involves the vascular processes underlying some of the cardinal signs of inflammation, such as vasodilation, capillary permeability, plasma leakage, chemoattraction of leukocytes, and differentiation and expansion of immune cells. PGE2 and prostacyclin (PGI2), produced during local inflammation, augment pain signaling by peripheral and central neurons (see below). PGE2
formed in brain venules during systemic inflammation passes the blood–brain barrier and disinhibits neurons in the median preoptic nucleus to generate fever. COX-2-derived prostanoiads also play a role in other central responses to systemic inflammation, such as sleepiness and anorexia, and COX-2 expressed in the brain may modulate the affective component of pain. Indeed, as a growing body of evidence suggests that inflammatory processes play a role in affective disorders, COX-2 products have also been implicated in anxiety and major depression. Inhibition of COX-2 in cells involved in inflammation, fever, and pain explains the therapeutic activity of NSAIDs.

In addition to the inhibition of prostaglandins, the clinical activity of NSAIDs may also involve a modulation of endocannabinoid metabolism. COX-2 has the capacity to oxygenate the endocannabinoids N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), which exert analgesic, antiinflammatory, and possibly anxiolytic effects through ligation of the cannabinoid receptors or through direct interactions with ion channels involved in pain sensing. Oxygenation by COX-2 is one of the metabolic processes that terminates the biological activity of AEA and 2-AG and some of their degradation products, the prostamides, may act as proinflammatory mediators. Thus, inhibition of COX-2 may prolong the analgesic activity of endocannabinoids by retarding their degradation and reducing the concentration of proinflammatory prostamides.

While COX-2 has initially been viewed in light of its key role in inflammation, it is also involved in the production of prostanooids with homeostatic functions. Some tissues, including the vasculature, renal medulla, and brain, express COX-2 basally in the absence of inflammation. While COX-1 and COX-2 catalyze the same enzymatic reaction, COX-2 has a lower activation threshold and requires considerably lower arachidonic acid concentrations to initiate the reaction. Thus, even low basal expression levels of COX-2, as are detectable in the vasculature, can effectively produce prostanooids. Indeed, the importance of COX-2-derived PGI2 in the antithrombotic mechanisms of the vessel wall and the regulation of renal perfusion and blood pressure by COX-2-derived PGI2 and PGE2 is well established, explaining mechanistically the cardiovascular adverse events observed with COX-2-competitive NSAIDs. Evidence also suggests that COX-2 plays a physiological role in learning-dependent synaptic plasticity in the brain; however, the consequences of COX-2 inhibition on these aspects of brain function have not been explored.

Given the complex topology of the COX network, NSAIDs administered to ameliorate pain and inflammation can be expected to inhibit coincidentally multiple network nodes that have regulatory functions in physiological processes. Whether this translates into adverse drug effects depends on the ability of non-COX pathways to compensate for perturbed prostanooid function. Thus, situations in which such other buffering pathways are simultaneously challenged through disease (e.g., preexisting hypertension), environmental factors (e.g., dehydration, salt loading), or perhaps genetics may result in the manifestation of complications, such as a rise in blood pressure.

INFLAMMATORY PAIN
NSAIDs are effective in the treatment of inflammatory pain, which is initiated via detection of noxious stimuli (nociception) and augmented by processes which render the nociceptive system more excitable (peripheral and central sensitization). Unlike opioids, NSAIDs do not block central paths in the nociceptive system, but rather inhibit the formation of prostanooids involved in the sensitization of the nociceptive system. Thus, the analgesic efficacy of NSAIDs is moderate on average and highly dependent on the molecular mechanisms evoking the pain sensation.

Nociception
Pain induced by an acute injury is initially localized, relatively proportional to the degree of tissue damage, and typically increases with movement. This type of pain is referred to as “nociceptive pain.” Noxious signals associated with the injury are detected by peripheral nociceptor terminals of primary afferent neurons, transmitted via the spinal cord to the brain, processed and interpreted as highly unpleasant. Nociceptor terminals express molecules, such as transient receptor potential ion channels (TRP), voltage-gated sodium channels (Na+), voltage-gated calcium channels (VGCC), or acid-sensing ion channels (ASICs), which respond to heat, cold, acids, or mechanical stress and transduce them into action potentials. The signal is then transmitted through peripheral axons to the cell bodies of the primary neurors, located in the dorsal root ganglia. Unmyelinated C-fibers and myelinated Aδ-fibers transmit noxious stimuli, whereas thinly myelinated Aβ-fibers transmit innocuous, mechanical stimuli such as touch. The central axons of the primary neurons enter the spinal cord through the dorsal horn and synapse with secondary somatosensory neurons and, to some extent, with motor neurons to form withdrawal reflex circuits. Signal propagation to the secondary neurons is subject to modulation by descending tracts from the brainstem and by interneurons in the dorsal horn. The signal is then transmitted to the thalamus, from where tertiary afferent neurons project to multiple areas of the cortex involved in pain processing.

Peripheral sensitization
As immune surveillance cells recognize the danger signals unmasked by tissue injury, the innate immune system initiates an inflammatory response to remove cell debris and begin the healing process. Activated endothelial cells, stromal cells, and infiltrating immune cells release vasoactive and inflammatory mediators, including histamine, bradykinin, substance P, serotonin, nitric oxide, cytokines, chemokines, and prostaglandins, which amplify signal transduction in the peripheral terminals of nociceptors. These inflammatory mediators augment the responsiveness of nociceptors by increasing expression of pain-sensing ion channels and promoting release of pronociceptive mediators (“autosensitization”), as well as lowering the activation threshold of pain-sensing ion channels (i.e., via phosphorylation of TRP or Na+ channels, “heterosensitization”). This process, termed peripheral sensitization, is one of the mechanisms underlying pain hypersensitivity (“primary hyperalgesia”). Thus, peripheral inflammation renders normally nonpainful or mildly
Central sensitization

Peripheral inflammation and continuous inputs from sensitized nociceptors promote central sensitization, a process that alters pain processing in the spinal dorsal horn, and in subcortical and cortical regions of the brain.49,50 Thus, in addition to enhanced perception of pain (“primary hyperalgesia”), innocuous stimulation such as touch or warmth is now processed to cause a painful sensation (“allodynia”). The receptive fields of the dorsal horn neurons are expanded and the pain spreads to regions beyond the site of tissue damage (“secondary hyperalgesia”).43 Exposure of nociceptors to inflammatory mediators stimulates primary afferent neurons to release pro-nociceptive transmitters, including substance P, calcitonin gene-related peptide, dynorphin, neurokinin A, neurotrophins, brain-derived neurotropic factor, glutamate, adenosine triphosphate, nitric oxide, and prostaglandins.42 Diffusion of such mediators, including prostaglandins, in the spinal cord contributes to the widening arc of the pain receptive field. The activation thresholds of dorsal horn and neighboring neurons are lowered and the activity of pain facilitatory pathways increased. Descending anti-nociceptive trajectories are disinhibited and sensory processing altered in their originating brain regions (i.e., the anterior cingulate cortex, hypothalamus, and amygdala) and in regions through which they travel (i.e., the periaqueductal gray and rostral ventromedial medulla).51 Sensory processing is also altered in other subcortical and cortical regions.52,53

Central sensitization is usually reversible within hours to days following an adequate response of the nociceptive system, such as in postoperative pain. However, chronic inflammatory diseases may result in persistent modification of the architecture of the nociceptive system, which may lead to long-lasting changes in its responsiveness, independent of the original pain stimulus.54,55 Such persistent modifications include the formation of synaptic connections between pain sensing primary neurons and mecha-nosensory Aδ fibers in the dorsal horn, which results in functional recruitment of harmless tactile inputs into the pain pathway.49 These mechanisms contribute to the transition from acute to chronic pain. Pain becomes the dominant syndrome irrespective of its original cause.

The involvement of COX products in central sensitization has been illustrated in various experimental models. Expression of COX-1 and COX-2 in the spinal cord is altered in models of central sensitization.56–59 Inflammatory and nociceptive stimulation,60 intrathecal administration of substance P and N-methyl-d-aspartic acid (NMDA),61 and systemic administration of cytokines increase spinal PGE2 formation.58 Presynaptically, PGE2 facilitates spinal release of the excitatory neurotransmitter glutamate and neuropeptides, including substance-P and calcitonin gene-related peptide (CGRP).63 Postsynaptically, PGE2 activates directly or sensitizes dorsal horn neurons.64 These events

Figure 2  Nociception, peripheral, and central sensitization. Inflammation, such as arthritis of the knee, induces peripheral and central sensitization of the nociceptive system. These processes involve upregulation of COX-2 and production of PGE2 in inflamed tissue and the spinal cord. PGE2 signaling through EP receptors lowers the activation threshold of pain sensing ion channels on nociceptors and facilitates signal transduction to the brain (primary hyperalgesia). PGE2 diffusing within the spinal cord contributes to the widening of the pain receptive field (secondary hyperalgesia). At the presynaptic level, PGE2 facilitates the spinal release of the excitatory neurotransmitter glutamate (Glu), substance-P (SP), or calcitonin gene-related peptide (CGRP), resulting in enhanced nociceptive processing. At the postsynaptic level, PGE2 directs dorsal horn neurons, enhances AMPAR and NMDAR activity, or blocks inhibitory glycnergic neurotransmission (F, a pressure stimulus; TRPV1, a transient receptor potential cation channel; Cav3.2, a voltage-dependent calcium channel; Nav1.8, a voltage-gated sodium channel; NMDAR, N-methyl-d-aspartic acid receptor; AMPAR, quisqualate receptor).

Painful stimuli more painful. Pain is now more intense and sustained; for example, it may persist at rest (Figure 2).

COX-1 derived prostanooids are thought to contribute to peripheral sensitization in the early phase of inflammation.45 As inflammation progresses, COX-2 derived prostanooids predominate. COX-2 is induced in cytokine-activated cells such as endothelial cells,46 and, to a greater extent, in tissue resident and infiltrating immune cells, including macrophages, neutrophils, and mast cells.47 Prostaglandins, most notably PGE2 through ligation of E prostanoid (EP), receptors, stimulate protein kinase (PK) C- and PKA-dependent phosphorylation of ion channels involved in sensing pain, including TRPV1 and Nav1.8, thereby lowering their activation threshold and increasing the gain of the signaling system.40 PGE2 may also enhance the sensitivity of peripheral neurons to other excitatory mediators such as bradykinin.48

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facilitate the ascending transmission of nociceptive responses and reduce descending inhibitory neurotransmission. In addition, evidence suggests that prostacyclin and PGD2 also contribute to central sensitization; however, the mechanisms underlying these effects require additional study.

**ANALGESIC ACTIVITY OF NSAIDS**

**Determinants of efficacy**

Multiple pain mechanisms can contribute to clinical symptoms. For example, inflammatory processes can play a role in a nerve response to mechanical damage, as in the case of root compression from a herniated disc. In this case, pain induced by nerve compression, often described as “neuropathic pain,” which is not effectively treated with NSAIDs, coexists with pain induced or amplified by the accompanying inflammatory response, which does respond to NSAIDs. This may explain why decompression interventions may fail to alleviate pain, and why antiinflammatory therapy can successfully relieve pain in some patients even if root compression persists. Pain associated with chronic inflammatory diseases such as arthritis can also have multiple coinciding mechanisms.

Thus, pain driven by mechanical stress on joints, inflammation, or persistent central sensitization mechanisms may occur simultaneously or vary in their contributions over time. Similarly, circuitry changes associated with chronic pain and acute inflammatory flare-ups may coincide. NSAIDs act primarily by reversing inflammation-driven peripheral sensitization. Thus, NSAIDs can be expected to be efficacious in situations in which this is a dominant mechanism (e.g., acute injuries, sports injuries, dental pain, gouty arthritis, arthritis flare-ups). NSAIDs are less effective in treating pain due to structural nerve damage (“neuropathic pain”) or in tempering the persistent circuitry changes during the transition to chronic pain. An unanswered question is to what degree NSAIDs alleviate symptoms associated with central sensitization. One of the conditions where multiple pain mechanisms, including central sensitization, can variably coincide is osteoarthritis. Approximately 30% of osteoarthritis patients exhibit symptoms consistent with central sensitization, as indicated by the use of central sensitization-associated pain descriptors or detected objectively via quantitative sensory testing analysis. Central sensitization is especially apparent among osteoarthritis patients who experience a high level of pain that is not proportional to radiographic evidence of pathologic changes of the joint, and may contribute more to the pain phenotype in women with symptomatic osteoarthritis compared to men. Generally, a higher degree of central sensitization is associated with high intensities of pain, poorer quality of life, and a higher likelihood of developing chronic pain after joint replacement. Central sensitization also plays a role in pain associated with rheumatoid arthritis and lower back pain.

Given the involvement of COX products in central sensitization (see above), it has long been hypothesized that NSAIDs may also have a centrally acting component in humans. Inhibition or deletion of neuronal COX-2 in mice reduces centrally generated, secondary inflammatory pain hypersensitivity. Dissecting central from peripheral actions of NSAIDs in humans is more difficult, as systemically administered compounds may reduce central sensitization 1) indirectly by reducing the peripheral inflammatory processes that drive central sensitization and/or 2) directly by inhibiting COX driven mechanisms of central sensitization in the spinal cord or brain. A study comparing an NSAID that does not cross the blood–brain barrier with one that does might shed light on this question, but all approved NSAIDs cross the blood–brain barrier—albeit to variable degrees.

The impact of COX-2 inhibition on central sensitization (whether directly or indirectly) was recently illustrated by a mechanistic study in patients with painful osteoarthritis of the knee. Patients received either placebo or etoricoxib, a COX-2 selective NSAID (which is not approved in the US), in a crossover design for 4 weeks. Pain and functional parameters were assessed and quantitative biomarkers of peripheral and central sensitization measured before and after the treatment periods. Pressure algometry on the arthritic knee—which identifies the threshold at which increasing pointed pressure becomes painful—was used as a measure of primary hyperalgesia. COX-2 inhibition raised this threshold, indicating primarily alleviation of peripheral sensitization. Secondary hyperalgesia, the spreading of the pain field beyond the site of injury, as quantitated by pressure algometry on the lower leg (distal to the affected knee), was also reduced by etoricoxib in comparison to placebo, suggesting that COX-2 inhibition can also decrease central sensitization. “Temporal summation,” a feature of the transmission of signals from the primary sensory neurons to the dorsal horn neurons, was assessed as another proxy of the spinal processes involved in central sensitization. Such processes at the interface between primary and secondary sensory neurons facilitate the integration of fast, repetitive stimuli such as heat or mechanical force, resulting in a pronounced pain sensation in response to repetitive nonpainful stimuli. In the osteoarthritis study, COX-2 inhibition reduced temporal summation evoked by repetitive subthreshold pressure stimuli both over the painful arthritic knee and on a more distal location compared to placebo. Again, this supports the notion that NSAIDs can ameliorate pain associated with central sensitization processes, although it does not prove that the site of action is the spinal cord (see above).

Interestingly, patients who experienced only limited pain relief from COX-2 inhibition experienced a more pronounced analgesic response to the NSAID if they had a higher degree of central sensitization, as indicated by temporal summation. While the ultimate question as to how much the degree of central sensitization affects or predicts the response to NSAIDs requires further investigation, these results support the concept that the mechanistic factors contributing to an individual patient’s pain phenotype may explain some of the interindividual variability in the response to NSAIDs.

**VARIABILITY IN THE RESPONSE TO NSAIDS**

It has long been appreciated that the response to any NSAID may vary substantially from patient to patient. Heterogeneous mechanisms underlying the pain sensation, clinical presentation, comorbidities, and concomitant medications, prior pain experience and expectation all contribute to interindividual variability.
among those with the same diagnosis. Similarly, the comparative analgesic efficacy of distinct NSAIDs in an individual can be expected to relate to multiple factors, including the biology of the inflammatory/painful process, the disposition of the drug (e.g., half-life, plasma concentration, concentration in the inflamed tissue, central nervous system penetration), the duration of drug action, and perhaps the degree of selectivity for inhibition of COX-2.12–14 In addition to such potentially identifiable sources of variation, there is considerable variability in the actual quantitation of pain and of pain relief, which relies widely on self-reported pain levels in clinical outcome trials.

**Interindividual variability**

During and following the development of COX-2-selective NSAIDs, very large phase III and IV clinical outcome trials have assessed the safety of these compounds in comparison with traditional NSAIDs in osteoarthritis and rheumatoid arthritis patients. The primary focus was initially the gastrointestinal and later cardiovascular safety of COX-2 inhibition. The common assumption across studies was that COX-2 selective NSAIDs would provide a degree pain relief that was similar or “noninferior” to that provided by traditional comparator NSAIDs. As efficacy was a secondary endpoint in the majority of NSAID safety studies and tens of thousands of patients were enrolled, larger datasets on efficacy exist than with most other analgesics. However, very few details regarding the efficacy outcomes were reported and deeper analyses into the variability of pain relief and potential underlying factors (e.g., subgroup analyses by demographic factors) were generally not performed. Often the only efficacy outcomes reported were changes in pain intensity from baseline, measured by asking patients to quantify pain levels on a visual analog scale (VAS) from 0–100 mm (where 0 mm equals no pain and 100 mm represents maximal imaginable pain).

Based on self-reported levels, pain relief from NSAIDs is highly variable. The PRECISION trial ("Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen") was one of the largest prospective NSAID trials (~24,000 patients) that reported analgesic efficacy, measured as the change from baseline in patient’s assessment of arthritis pain on a VAS, as a secondary endpoint.17,18 Its primary aim was to compare the cardiovascular risk of celecoxib, naproxen, and ibuprofen in osteoarthritis and rheumatoid arthritis patients with concomitant cardiovascular disease or elevated risk for cardiovascular disease.17,18 Figure 3 illustrates the interindividual variability in the response to celecoxib detected in PRECISION. It shows the distribution of the change of pain intensity from baseline after the 1st month of treatment (in mm on a 100-mm VAS) among patients allocated to celecoxib (average dose ± standard deviation (SD), n = 7,974) at baseline was ~8.2 mm, the distribution was wide (±25 mm SD, n = 7,372), revealing that a large fraction of patients reported no improvement or even an increase in pain levels.

Attempts have been made to elucidate which reduction in an individual patient’s pain level measured on a 100-mm VAS or 100-point numerical scale would translate into an improvement of well-being. This has been termed a “minimally clinically important difference.” For example, a reduction in pain level by 8 to 10 mm discriminates between knee osteoarthritis patients...
who report “no change” vs. feeling “slightly better” after 6 months of treatment.\(^{83–85}\) However, the sensitivity and specificity of this metric in discriminating between “responders” or “nonresponders” are less than optimal, in the range of 70–86% and 60–80%, respectively.\(^{83–85}\) Additionally, the “minimally clinically important difference” is not uniform across the scale; it is larger among patients with higher baseline pain levels.\(^{85}\) Despite these limitations a “minimally clinically important difference” is often used to interpret efficacy data in clinical trials.

In PRECISION the “minimally clinically important difference” was arbitrarily set at 13.7 mm (VAS),\(^{86}\) although this threshold was originally determined in patients with rotator cuff disease and not specifically in arthritis patients.\(^{87,88}\) Based on this threshold, only \(\approx41\%\) of the patients in PRECISION allocated to celecoxib responded to the treatment; thus, the majority of patients free of established cardiovascular disease.\(^{15,16}\) In SCOT, the reduction in variability was small, perhaps because even high doses of celecoxib may have been, on average, less effective than the comparator NSAIDs, resulting in a higher than expected dropout during the run-in phase.

**Variability between distinct NSAIDs**

The question whether differences exist in the efficacy of chemically distinct NSAIDs is important for clinical care and in the design and interpretation of clinical trials. Pain management in arthritis patients continues to follow a trial-and-error approach; often various NSAIDs are tested and doses titrated. As mentioned above, most comparative NSAIDs trials focused on gastrointestinal and cardiovascular safety and the underlying assumption was that the distinct compounds were equally effective at doses administered in the trial. However, only a few outcome studies have associated a measure of the pharmacological response to a COX inhibitor—as an index of the actually attained activity of a dose in vivo—rather than a standard dose with reduction in pain relief.\(^{92,93}\) Indeed, no study has selected the comparator doses based on biochemical indices of drug activity in vivo to assure comparison of equipotent doses across treatment groups. Thus, comparative pain relief is usually the only measurement available to determine whether the assumption of equipotency of the comparator drugs and/or doses has been met. However, if efficacy assessments in a trial indicate that dosing may not have been equipotent, there may be little interest in highlighting this problem. For example, the authors of TARGET (“Therapeutic Arthritis Research and Gastrointestinal Event Trial”), which compared the investigational COX-2 selective NSAID lumiracoxib with naproxen and ibuprofen, apparently found differences in the analgesic efficacy between the treatment groups (e.g., patient’s global assessment across the three groups: \(P = 0.0153\)), but failed to report exactly which study drug differed in efficacy.\(^{94}\)

A recent meta-analysis compared the analgesic potency of various doses of eight chemically distinct NSAIDs assessed in 74 randomized clinical trials in 58,556 patients with knee or hip osteoarthritis.\(^{95}\) The authors conducted a Bayesian network analysis to enable indirect comparison of 23 NSAIDs or NSAID doses each with placebo. Measures of symptom relief included change in pain levels on a VAS at \(\approx6\) weeks of treatment vs. baseline and improvement of physical ability using arthritis inventories. Effect sizes were reported as fractions of the standard deviation. The “minimally clinically important difference,” was set to an effect size of \(0.37\) SD units, which corresponded to an absolute change of \(-9\) mm on a VAS vs. placebo. The probability
that patients on a particular NSAID would reach this threshold was calculated. A comparison of the maximally approved daily doses is shown in Figure 4. Etoricoxib 60 mg/d (not approved in the US) and diclofenac 150 mg/d ranked as the most potent regimens and had a probability of 1.0 to reach a “minimally clinically important difference” (MCID), was assumed to be –0.37 SD units (–9.0 mm on a VAS vs. placebo). Right panel: Probability that patients reach MCID.

Figure 4 Comparison of NSAID efficacy. Data are published previously.95 Measures of symptom relief included change in pain levels on a VAS at ~6 weeks of treatment vs. baseline. Left panel: Effect sizes are fractions of the standard deviation. The “minimally clinically important difference” (MCID), was assumed to be –0.37 SD units (–9.0 mm on a VAS vs. placebo).

DIFFERENCES IN ANALGESIC EFFICACY IN CARDIOVASCULAR OUTCOME STUDIES

SCOT and PRECISION were the most recent prospective clinical trials to compare the cardiovascular safety of traditional NSAIDs with the COX-2 selective NSAID, celecoxib.15–18 Both were designed as noninferiority studies with cardiovascular events as the primary outcome. Both had a relatively high noninferiority threshold to begin with and then their power was adjusted from 90% to 80% when event rates, enrollment, and retention of patients turned out to be below anticipated rates.15–18 SCOT (n = 7,297 patients) detected a small risk increase with celecoxib in the on-treatment analysis of the primary cardiovascular outcome vs. all traditional NSAIDs combined and, thus, formally failed to show noninferiority of celecoxib.15,16 Unconventionally, the authors based their main conclusion on a secondary analysis, which observed noninferiority of celecoxib vs. traditional NSAIDs in the intention-to-treat population.16 By contrast, the on-treatment analysis, which is considered the more conservative approach in safety trials and was appropriately selected as the primary outcome,23 was deemphasized. The analysis of PRECISION (n = 24,081 patients) demonstrated a noninferior cardiovascular safety profile of celecoxib when compared with ibuprofen and naproxen.17,18 These conclusions, suggesting that celecoxib’s cardiovascular risk profile is similar to that of traditional NSAIDs, have important implications for the management of pain. However, there are multiple concerns with both studies (which we discuss in detail14,23) that question the validity of their results. A major concern is that in both studies the assumption of equipotency of the comparator drugs was violated14,19–23; the comparator drugs are unlikely to have provided similar pain relief.

In SCOT, the traditional NSAIDs and celecoxib were given in standard doses and adjusted as necessary up to the maximum approved dose (celecoxib up to 400 mg/d) to provide adequate pain relief. However, the doses that were actually consumed were not measured and prescription data were only available in a subpopulation. Because prescription occurred on an “as needed” basis, the average daily dose (reported as the total dose of medication prescribed per number of days before study discontinuation) is diluted by periods in which no drug was prescribed. This type of dosing information is not very helpful in the evaluation of equiptomy; much more granular information would be needed. However, a strong indication that celecoxib was less effective than the other NSAIDs is that discontinuation was asymmetrical across the groups. The withdrawal rates were significantly higher in the celecoxib group (51% discontinued) than in the traditional NSAID group (30% discontinued, P < 0.001), which was twice as frequently attributed to lack of efficacy in the celecoxib group than in the traditional NSAID group (23% vs. 10%, no P-value reported).

In PRECISION, NSAID doses were also titrated to provide sufficient pain relief; however, dosing was continuous (not “as needed”).17,18 Thus, the reported average daily doses are useful in the evaluation of likely potency—although daily consumption of NSAIDs over extended periods of time does not necessarily reflect clinical reality, where treatment is often intermittent. Mean (±SD) daily doses were 209 ± 37 mg/d (permitted dose 200 or 400 mg/d) for celecoxib, 852 ± 103 mg/d (permitted dose 750 or 1,000 mg/d) for naproxen, and 2,045 ± 246 mg/d (permitted dose 1,800 or 2,400 mg/d) for ibuprofen. Because only two dosing levels were permitted, we can estimate how many patients were up-titrated to the higher dose in each arm. This showed that patients in the naproxen and ibuprofen arms were 2–3 times more likely to receive the higher daily dose than in the celecoxib arm.97 Given the lower analgesic potency of celecoxib seen in the comparative meta-analysis (see above and Figure 5), it seems unlikely that this difference can be explained by largely adequate pain relief on the lower celecoxib dose. Although it has been argued that 200 mg already provides maximal symptomatic relief in most patients,98 closer inspection of the comparative dosing data of celecoxib does not support this claim (Figure 5). The SUccessive Celecoxib Efficacy and Safety Study-1 (SUCCESS-1) compared pain relief during 12 weeks of 200 mg/d with 400 mg/d celecoxib in osteoarthritis patients.98 Approximately 4,400 patients were included in each dosing arm.
Interestingly, the authors chose to report the comparative pain relief (in mm VAS) separately for 16 regions (the study was conducted in 39 countries) rather than as a single aggregate analysis. The mean treatment difference with 95% confidence intervals for these 16 regions. Region 1 is the United States.

Figure 5 shows the mean treatment difference with 95% confidence intervals for these 16 regions. While only one region, the United States (region 1 in the figure), showed a statistically significant dose effect, the majority of regions have a point estimate that reflects better efficacy of the higher dose. A formal summary analysis across all regions is not possible, because the numbers of patients enrolled in each region have not been reported. Thus, it seems unlikely that in PRECISION fewer patients were up-titrated to the higher celecoxib dose because 200 mg/d provides maximum pain relief. A more plausible explanation is that the maximal dose was capped at 200 mg/d for treatment of osteoarthritis patients by regulatory agencies in most countries where the trial was performed. Since ~90% of the study population consisted of osteoarthritis patients, this would be expected to introduce significant bias toward a lower, less effective dosing of celecoxib on average across the entire trial.

Several lines of evidence support this notion. First, the analgesic efficacy assessed on a VAS was significantly lower \((P < 0.001)\) on celecoxib than on naproxen (Figure 4b). Ibuprofen was also less potent than naproxen \((P < 0.01)\), but ibuprofen was not different from celecoxib \((P < 0.38)\). As discussed above, these differences were detectable despite the large variability of the data (see interindividual variability section above). It has been argued that these differences are clinically irrelevant because they fail to reach a “minimally clinically important difference” of ~13.7 mm (VAS). Indeed, the average difference between the treatment arms were less than ~1 mm (VAS). However, as discussed above, the “minimally clinically important difference” has been established as a threshold to predict whether an individual patient responds to the drug or not (“I feel slightly better” vs. “I feel no change”). It has not been validated as a measure to discriminate at the population level between two NSAIDs. Moreover, the –13.7 mm cutoff, which has been established for shoulder pain originating from various etiologies not limited to arthritis, appears too stringent even for its intended purpose, since the average pain relief afforded by the study drugs never reached that threshold throughout the trial (Figure 3b). Second, a lower efficacy of celecoxib is supported by a higher incidence of both clinically assessed arthralgia and osteoarthritis flares on celecoxib \((P < 0.003)\) compared to ibuprofen in PRECISION. Finally, the rate of discontinuation due to “lack of efficacy” was numerically higher in the celecoxib arm (9.4% celecoxib, 8.4% ibuprofen, 8.2% naproxen; \(P\)-values were not reported). A less effective analgesic dose of celecoxib than the comparators is likely to reflect less suppression of both proinflammatory and cardioprotective prostaglandins, biasing the trial towards minimizing its cardiovascular risk and favoring the declaration of noninferiority.

CONCLUDING REMARKS

Inattention to variability in pain relief between chemically distinct drugs has biased clinical trials addressing the comparative cardiovascular safety of celecoxib vs. traditional NSAIDs. SCOT and PRECISION, both funded by the maker of celecoxib, have apparently not compared equipotent doses. Due to this and other limitations, they provide no conclusive answer as to which of the compared NSAIDs has the most favorable safety profile for patients who require daily pain relief for arthritis, particularly when they have cardiovascular risk factors or established cardiovascular disease. Future studies need to focus on the comparisons of equipotent doses, for example by using measures of drug exposure and biochemical markers of drug activity. At the same time, it seems timely to focus resources on the study of pain relief by NSAIDs.

Deeper research into the efficacy of NSAIDs has long been neglected, although clinicians are well aware of the high variability of efficacy between patients and between distinct drugs in the class. We should seek:

1. A better understanding of mechanisms involved in the sensation of pain and their susceptibility to be affected by COX inhibition;
2. An improved ability to phenotype pain and to identify the underlying mechanisms in an individual patient so that COX inhibitors are prescribed to patients who are most likely to respond;
3. A better understanding of the factors that affect the dose-response of an NSAID in an individual patient. These may include genetic and nongenetic factors, such as the microbiome, which alter the disposition of the drug, but also environmental/nutritional factors that affect COX enzyme function;
4. A better understanding of mechanistic differences between chemically distinct NSAIDs such as their ability to penetrate inflamed tissues and the CNS, or the relative potency with which COX-1 and COX-2 are inhibited, given that both isoforms play roles in inflammation and pain.

Inhibitors of the COXs continue to play an important role in pain management, both as short-term therapies and for chronic conditions such as osteoarthritis and inflammatory diseases.
diseases with a marked inflammatory pain component, such as the arthritides. The recognition that liberal prescription of narcotics has contributed to the ongoing opioid epidemic is likely to increase further the use of NSAIDs. Expanding the focus of future research beyond the gastrointestinal and cardiovascular safety of these drugs to pain relief will provide a better understanding of the risk–benefit relationship, as well as facilitate the rational selection of an appropriate analgesic regimen for an individual patient.

Man’s fate is according to his pains.

—Hesiodes 752.

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CONFLICT OF INTEREST
The author declares no conflicts of interest.

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