

Viewpoint

A Bayesian Network Concept for Pain Assessment

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Abstract

In this study, we propose an approach that provides a useful data summary related to a patient's experience of pain. Because pain is a very important but subjective phenomenon that currently has no calibratable method for assessing it, we suggest an approach that uses calibratable biomarker sensors with the patient's self-assessment of perceived pain. We surmise that such an approach may only be able to clearly distinguish between cases in which the available evidence is consistent. However, this information may provide clinicians with valuable insights, and as research progresses into how biomarkers are related to pain, more specific insights may emerge regarding how specific evidence inconsistencies may point to particular pain causes. We provide a brief overview of pain science, including the types of pain, contemporary pain theories, pain, and pain assessment techniques. Next, we present novel approaches to pain sensor development, including an overview of research on pain-related biomarker sensors and artificial intelligence methods for summarizing the evidence. We then provide some illustrations of the implementation of our approach. Some specifics are presented in the Methods section of this paper. For example, in a set of 379 patients, we observed 80% evidence of consistency and 5 types of inconsistencies. Information regarding the gender and individual differences in cyclooxygenase-2 and inducible nitric oxide synthase data on reported pain could contribute to the inconsistency. Different causes of inconsistencies are also attributed to cultural or temporal variability of cyclooxygenase-2 and inducible nitric oxide synthase (as well as their serum variation and half-life), visual analog scale, and other tools. We emphasize that this presentation is illustrative. Much work remains to be done before implementing and testing this approach in a clinically meaningful context.

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KEYWORDS

pain science; pain biomarkers; novel biosensors; Bayesian network; artificial intelligence; AI evidential reasoning; pain self-report; probability of pain levels; cyclooxygenase-2; COX-2; inducible nitric oxide synthase; iNOS

Pain and the Scope of This Work

Pain is largely subjective yet critical to assess for clinicians to provide proper care. A major challenge (much discussed in the literature) is that, at this time, there is no objectively calibratable way to measure pain. This study aims to present a novel approach to address this problem. Rather than seeking a specific calibratable pain scale, we propose an approach that combines calibratable measures of pain-related biomarkers with patient self-assessments of perceived pain using artificial intelligence (AI) methods that can at least provide a view of the extent to which available evidence is consistent. We postulate that with an appropriate set of evidence, we may discover specific patterns of evidence that will provide valuable insights that clinicians may use to improve pain care. We present a modest illustration of an approach to this problem by using two pain-related biomarkers, cyclooxygenase-2 (COX-2) and inducible nitrous oxide synthase (iNOS), and a Bayesian network (BN) model. The reader should keep in mind that this illustration is only an example and is not meant to be *the* answer. Much work remains to be done and will require a dedicated team of pain experts, including those knowledgeable in pain care and neurology, with biochemical or molecular biology of pain mechanisms.

A Brief Overview of Pain

Pain Defined

According to the International Association for the Study of Pain, pain is an unpleasant sensory and emotional experience associated with, or resembling that is associated with, actual or potential tissue damage [1]. One common distinction is between acute and chronic pain. Acute pain is typically caused by the stimulation of peripheral nerve endings because of inflammation or trauma or interference with nerve pathways (neuropathic) because of the nerve being severed (for example, during surgery). Tissue healing generally results in the cessation of

acute pain. Chronic pain arises in acute pain situations, generally when the acute pain is very intense or lasts for an extended period. It is important to remember that in most situations, acute pain serves as a critical protective mechanism in preventing further tissue injury. By reducing the risk of continued trauma, the tissue can heal more rapidly and the pain will subside. The main challenge in dealing with intensive acute pain is to prevent the overuse of strong opioids, morphine, codeine, and cocaine, leading to addiction through the euphoria created using these medications.

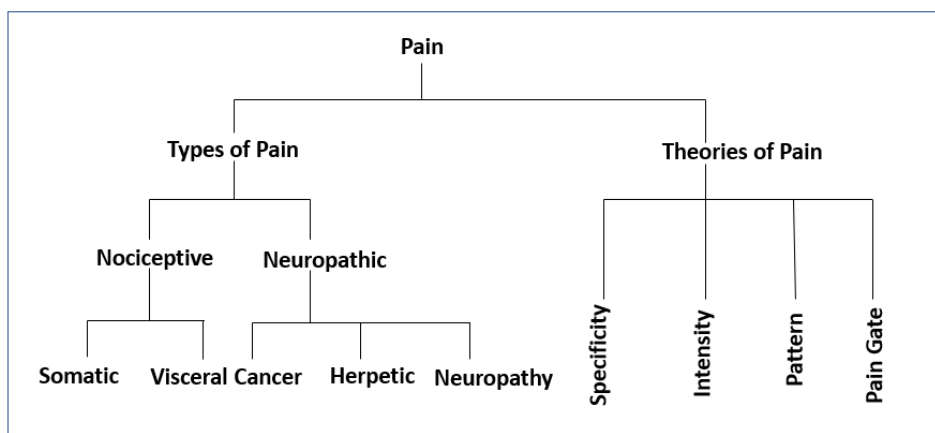
According to the National Health Interview Survey of 2019, a total of 50.2 million or approximately 20.5% of American adults experience chronic pain, with the most common examples being back pain and hip, knee, or foot pain [2]. Chronic low back pain affects a significant segment of the population. It is a heterogeneous disease that includes several causes of pain syndromes, latent molecular pathologies, genetic and psychological factors, and a history of injury. The Institute of Medicine has estimated that chronic pain affects approximately 100 million adults in the United States, with an estimated annual cost of up to US \$635 billion [3].

Pain is perceived centrally and is strongly influenced by physical, physiological, and social or cultural factors. Another distinction often made is between pain caused by tissue damage (sometimes called inflammatory or nociceptive) and pain caused by nerve damage (neuropathic), where nerve signals may not be driven by local tissue damage.

Types of Pain

Depending on the quality, quantity, and duration, pain can be categorized into 2 major types: nociceptive and neuropathic pain. Distinguishing them is very important if proper treatment is to be achieved, because their causes and treatments are different. Figure 1 shows the classification of the major types of pain and contemporary theories of pain.

Figure 1. Classification of the major types of pain and contemporary pain theories.



Nociceptive Pain

Nociceptive pain can be attributed to tissue damage. Whole or undamaged neurons report damage, and pain is experienced [4]. It can be subdivided into somatic and visceral (gut) pain. This pain may be localized, constant, and often with an aching or

pulsating quality. Nociceptive pain can be experienced as razor sharp, dull, or aching. Visceral pain is a subtype of nociceptive pain that involves the internal organs and tends to be episodic and poorly localized [5]. This type of pain is usually acute and is responsive to nonsteroidal anti-inflammatory drugs and

opioids [6]. Examples of this type of pain include inflammation, burns, bruises, bone pain, and myofascial pain.

Neuropathic (Nerve) Pain

Neuropathic pain results from an injury or the malfunction of the peripheral or central nervous system [7,8]. This pain is often precipitated by an injury that may or may not involve actual damage to the nervous system [9]. Nerves can be permeated or compressed by tumors, suppressed by scar tissues, or inflamed by infections. This pain frequently involves burning, piercing, or electric shock qualities [9]. This type of pain may persist beyond the apparent healing of any damaged tissue. Neuropathic pain is often chronic and tends to have a less robust response to treatment with nonsteroidal anti-inflammatory drugs and opioids but may respond well to other drugs such as antiseizure and antidepressant medications [9]. Neuropathic problems tend to be irreversible, but partial improvement is often possible with proper treatment [7,8].

Examples include postherpetic neuralgia, nerve injury, cancer pain, phantom limb pain, entrapment neuropathy, and peripheral neuropathy (widespread nerve damage) [7,8]. Diabetes is among the many causes of peripheral neuropathy, but it can also be caused by chronic alcohol use, chemotherapy, vitamin deficiencies, and numerous other medical conditions, many of which may sometimes go undiagnosed [9].

Theories of Pain

Several theories of pain have been postulated for centuries to explain the mechanisms underlying pain perception [10-13]. The most modern theories include the specificity, intensity, pattern, and gate control theories of pain.

The specificity theory teaches that when specific nociceptive receptors in the periphery are stimulated, they transmit signals to the brain's pain center, which ultimately produces the perception of pain. This theory holds that the amount of pain is related to the amount of tissue damage. Assuming that the free nerve endings are the pain receptors, the theory has failed to find the pain receptors or the fibers specifically devoted to transmission, and it does not account for people who continue to experience pain long after the injury has healed.

The intensive (or summation) theory of pain asserts that pain is not a unique sensory experience but an emotion that occurs when a stimulus is stronger than usual. According to this theory, pain results from excessive stimulation of the sense of touch, with summation occurring in the dorsal horn cells. This explains why some form of summation must occur for subthreshold stimuli to become unbearable. The pattern theory of pain states that any somesthetic sensation occurs through a particular neural firing. This asserts that there are no specialized receptors. Pain occurs when the rate and pattern of sensory inputs exceed a threshold. The intensity evokes a pattern of impulses that are interpreted by the brain as pain.

The gate control theory claims that pain operates at the spinal level. It recognizes experimental evidence that supports the specificity and pattern theories. It carefully discusses the shortcomings of the specificity and pattern theories and attempts to bridge the gaps between the 2 dominant theories.

According to the pain gate control mechanism, Melzack and Wall (1965 [11]) accepted that there are nociceptors (pain fibers) and touch fibers. The pain gate mechanism was proposed as an alternative to the specificity theory of pain, which holds that pain is a specific modality with its own specialized sensors, neuronal pathways, and centers [14] and the pattern theory, which maintains that the stimulus intensity of nonspecific receptors and central summation are critical determinants of pain [15]. The pain gate control mechanism postulates that injury is transmitted from pain receptors to the central nervous system (CNS) via two types of nerve fibers: (1) small unmyelinated fibers (C-type) and (2) large myelin-containing fibers (A delta type), which transmit sharp, brief pain rapidly via the peripheral nerves through a gate mechanism. Larger-diameter nerve fibers pass through the same gate. If other subcutaneous stimuli are transmitted, the "gate" through which the pain impulse must travel is temporarily "blocked" by the other stimuli. The brain is unable to acknowledge pain impulses when transmitting other stimuli. When the gates are open, pain impulses flow freely.

The theory, as originally propounded, states that the opening or closing of the "gate" depends on the relative activity of large-diameter (normal receptors) and small-diameter (pain receptors) fibers. It teaches that activity in large-diameter fibers tends to close the "gate," and activity in small-diameter fibers tends to open it [12]. Garrison and Foreman [16] support this theory, demonstrating that the cell activity of dorsal horn neurons decreases during transcutaneous electrical nerve stimulation (TENS) application to somatic receptive fields. Ultimately, this can potentially transmit noxious information to supraspinal levels. These findings support the "gate control theory of pain" in that less noxious information would be involved in the pain perception process. Garrison and Foreman [16] also showed that there is a differential effect in that more cells respond to conventional high-frequency, low-intensity TENS variables than they do to low-frequency, high-intensity ALTENS variables.

Biochemical Nature of Pain

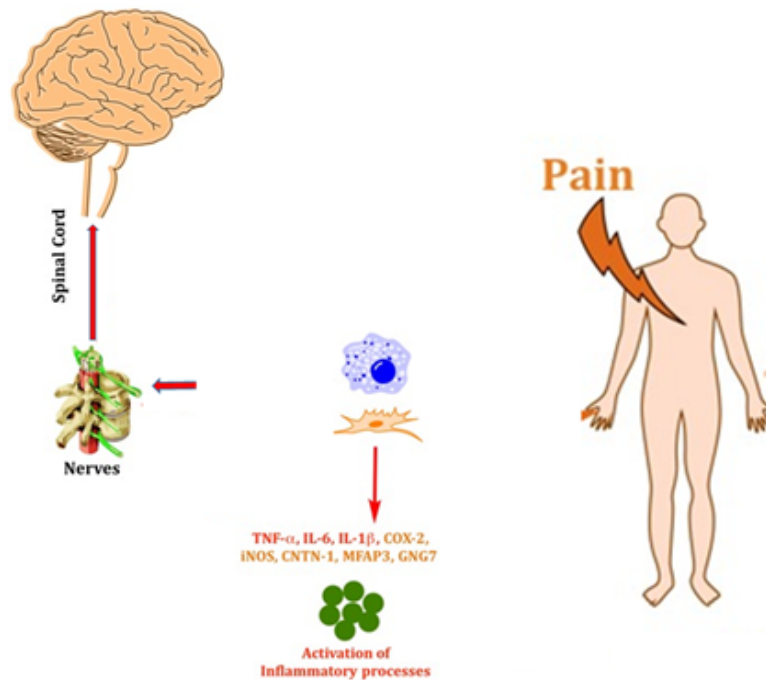
Inflammation has been associated with pain. In a unifying theory of pain, the biochemical theory origin of pain asserts that regardless of the type of pain, whether acute pain or chronic pain as in arthritis, migraine, back or neck pain from herniated disks, complex regional pain syndrome or reflex sympathetic dystrophy pain, fibromyalgia, interstitial cystitis, neuropathic pain, or poststroke pain, the underlying basis is inflammation and the inflammatory response [17-19]. Therefore, irrespective of the characteristics of the pain, whether it is sharp, dull, aching, burning, stabbing, numbing, or tingling, it is asserted that all pain arises from inflammation and the inflammatory response. However, pain could be subjective, with pain reported without any tissue damage or underlying pathophysiological cause. Studies have shown that stress, anxiety, and other psychological factors may be responsible for the elevation in biomarkers.

According to the unifying theory of pain pioneered by Omoigui [17-19], the origin of all pain is inflammation and the inflammatory response. Biochemical mediators of inflammation include cytokines, neuropeptides, growth factors, and

neurotransmitters. Irrespective of the type of pain, acute or chronic pain, peripheral or central pain, and nociceptive or neuropathic pain, the underlying origin is inflammation and the inflammatory response. The activation of pain receptors, transmission and modulation of pain signals, neuroplasticity, and central sensitization are all one continuum of inflammation and the inflammatory response. This theory proposes the reclassification and treatment of pain syndromes based on the inflammatory profile. Every pain syndrome has an inflammatory

profile consisting of the inflammatory mediators present in the pain syndrome. The inflammatory profile may vary from one person to another and may vary in the same person at different times. The key to the treatment of pain syndromes is to understand their inflammatory profiles. The concentrations of several substances, namely substance P, calcitonin gene-related peptide, bradykinin, and various cytokines, are measurably elevated in the milieu of the active trigger point, indicating a chemical inflammatory response (Figure 2).

Figure 2. Biochemical signaling mechanism and the role of biomarkers in pain activation. COX: cyclooxygenase; GNG7: G-protein subunit gamma 7; IL: interleukin; iNOS: inducible nitric oxide synthase; MFAP: microfibril-associated protein; TNF: tumor necrosis factor.



Inflammatory pain is felt through multiple mediators released at inflammation sites that send information to the CNS. At the inflammation site, arachidonic acid is released by phospholipase A2 into the cell membrane. Cyclooxygenase-2 (COX-2) catalyzes the conversion of arachidonic acid into prostaglandin G₂ (PGG₂), and the peroxidase further reduces PGG₂ to prostaglandin H₂ (PGH₂), which is eventually converted into prostanoids, prostacyclin, and thromboxanes. These products bind to various receptors that signal pain in the CNS. Extensive literature supports the relationship between COX-2 and pain, with the amount of COX-2 being proportional to the magnitude of pain. In addition, many of the most widely used pain medications (eg, aspirin and nonsteroidal anti-inflammatory drugs) act through the COX-2 pathway, implying that, among other things, the detection of COX-2 could represent a direct measure of pain [20-28].

The fundamental origin of inflammatory pain is the activation of pain receptors, which leads to pain transmission (Figure 2). At the biochemical level, several factors are essential including neurotransmitters, cytokines, and growth factors. Despite the underlying biochemical nature of pain, few studies have focused on medical assessments to determine the nature of pain at the molecular level. It is important to remember that in most situations, acute pain serves as a critical protective mechanism in preventing further tissue injury. By reducing the risk of

continued trauma, the tissue can heal more rapidly, and the pain will subside. The main challenge in dealing with intensive acute pain is to prevent the overuse of strong opioids, which can lead to addiction to the euphoria created by the use of these medications.

Chronic pain presents a very different challenge. The perception of pain, particularly chronic pain, is a process that uses partial, multimodal, and noisy information to create the perception of a potential bodily threat even long after the tissue has healed [29]. The issue of addressing chronic pain is challenging, because, following tissue healing, there is no peripheral stimulation—that is, there is no pain source, but there is a sensation of pain. Pain arises directly within the CNS, usually through central sensitization. Central sensitization results in 3 pain-related outcomes: hypersensitivity, pain in response to nonnoxious stimuli, and pain response outside the area of injury. These responses are mediated in the dorsal roots of the spine by several chemical agents, including substance P and prostaglandins such as cyclooxygenases.

On the basis of these pain theories, we propose an approach that acquires accurate measurements of biomarkers of the underlying pain processes. One approach is to develop analytical biosensors that can accurately measure pain markers. A biosensor is an analytical device that consists of a recognition element (eg,

enzymes, antibodies, nucleic acids, cells, or micro-organisms) combined with a transducer or detector element that responds to the interaction of an analyte, allowing for an easy method of measuring and quantifying data. Owing to their fast response, simplicity, cost-effectiveness, and portability, biosensors can be used for continuous monitoring point-of-care analysis and do not require highly trained staff.

Conventional Methods of Pain Assessment

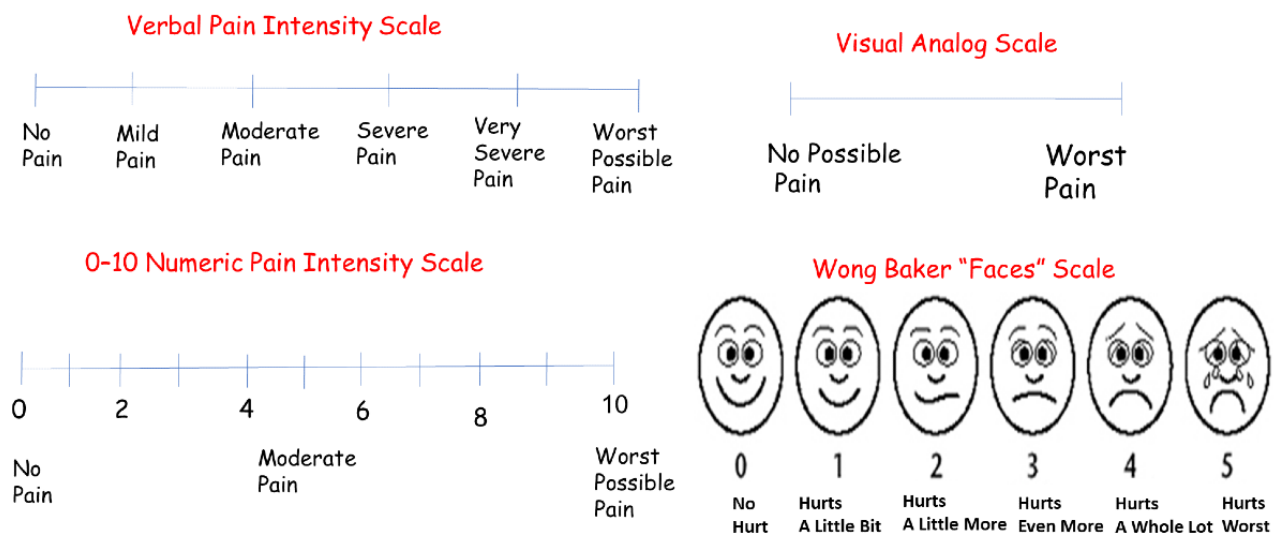
Currently, most pain measurements are based on patients' self-reports. For example, the visual analog scale (VAS) [30], McGill Pain Questionnaire [31], Wong-Baker Faces Scale [32], and Descriptor Differential Scale [33] have all been used as self-rating instruments for pain measurement in clinical and research settings. Figure 3 shows the different scales used to assess the levels of pain.

Despite the wide use of pain assessment tools, there is also an awareness of their inherent unreliability, as evidenced by reports on discrepancies [34-38]. Therefore, attempts have also been made to augment self-reports with other more objective measures, such as behavioral measures (eg, motor response,

behavioral responses, facial expression, crying, sleep patterns, decreased activity or eating, body postures, and movements) [39-42]. Additional pain assessment methods include physiological measures such as changes in heart rate, blood pressure, oxygen saturation, palmar sweating, respiration, and sometimes neuroendocrine responses [43].

Conventional methods of assessing pain involve multisensory approaches or expensive devices such as brain imaging in a laboratory setting [44-47]. The feasibility and accuracy of this expensive advanced instrumentation in clinical settings remain challenging. A review article evaluated the current state of pain biomarkers developed using several commonly used methods, including structural magnetic resonance imaging, functional magnetic resonance imaging, and electroencephalography, with a model classification accuracy of 70% [46]. A study used functional MRI data during a visual stimulation task to distinguish between patients with fibromyalgia and healthy controls and recorded an accuracy of 82% [45]. Another study involving a combination of electrocardiograms to predict pain in healthy adults produced 75% to 81% accuracy [48]. A study has explicitly reported the use of microneedle-based biosensors for pain-free high-accuracy measurement of glycemia in interstitial fluid [49]. None had reported array self-reports using BN and pain-related biomarkers and biosensors.

Figure 3. Common pain assessment scales.



Rationale for Pain Sensor Development

The driving force behind the need to develop a pain sensor for the objective quantification of pain is that when different participants with the same disease or trauma report vastly different pain levels, it is tempting to assume that this reflects the differences in pain sensitivity. However, there are 2 reasons why this may not be true. First, although the diagnosis may be superficially the same, the severity of the disease or trauma may differ. Second, one might argue that the physical causes of pain may be initially similar across patients (eg, extraction of 2 wisdom teeth) but that these causes develop differently owing to differences in patients' pathophysiological conditions. Although better predictions of pain could be achieved through better characterization of pathology, there are reasons to doubt

that differences in pathology are the only or even a major explanation for individual differences in pain.

Large differences in reported pain are ubiquitous and large when the cause of pain is homogenous and well defined (eg, surgery) as for illnesses with diffuse or unknown causes (eg, fibromyalgia). Inflammation and other physiological parameters are poorly correlated with pain intensity among patients with rheumatoid arthritis [50], and several studies have failed to find an association between the extent of breast surgery and acute postsurgical pain [51,52]. Most importantly, individual differences in reported pain are equally large for precisely controlled experimental pain stimuli [53].

In using either the VAS pain intensity ratings or the Wong-Baker Faces Scale [53,54], which is not only subjective but may only

be qualitatively applied to patients with language or mental capacity difficulties, the variability in pain ratings of patients with the same disease or trauma is enormous. This occurs despite differences in individual pain sensitivity, and some clinical conditions experienced are more painful than others. Pain sensitivity can be estimated only through well-controlled experimental pain stimuli. Such estimates show substantial heritability but are equally critical environmental factors. The genetic and environmental factors that influence pain sensitivity differ across pain modalities. For example, genetic factors that influence cold-pressor pain have little impact on phasic heat pain and vice versa [53]. Individual differences in pain sensitivity can create complexities in diagnosis, because low sensitivity to pain may delay self-referral. The inclusion of patients with reduced pain sensitivity can attenuate treatment effects in clinical trials unless this is carefully controlled. Measures of pain sensitivity are predictive of acute postoperative pain, and there is preliminary evidence that heightened pain sensitivity increases the risk of future chronic pain conditions [54]. Experimental pain modalities have been suggested for use as predictors for future pain conditions, along with a careful assessment of each individual's pain sensitivity to prevent, evaluate, and treat pain. We propose a calibratable biomarker sensor and AI coupled with the patient's self-assessment of perceived pain. We surmise that such an approach may only be able to clearly distinguish between cases where the available evidence is consistent. However, this information may provide clinicians with valuable insight. Furthermore, as research progresses into how biomarkers are related to pain, more specific insights may emerge as to how specific evidence inconsistencies point to particular pain causes.

AI Methods for Summarizing Evidence

There is a long history of AI work that focuses on what is sometimes called evidential reasoning. These methods include BN [55], the Dempster-Shafer theory [56], and fuzzy logic and its derivatives [57,58]. For our present purposes, we will focus on Bayes nets and leave the possibility open that if our approach seems to stress the limitations of Bayes nets, other options may be available.

BN Proposal

Overview

The approach we propose is to devise a BN that will consider what evidence is available and report how the available evidence may be interpreted as a distribution of the likelihood that the participant is experiencing different levels of pain. This is similar to the proposal by Hill et al [59]. As a starting illustration, we consider only three forms of evidence: (1) a

participant self-reports pain on a 0 to 5 scale (Figure 3), (2) a measured value of serum levels of COX-2 on a similar 0 to 5 scale, and (3) a measured value of inducible nitric oxide synthase (iNOS) on a 0 to 3 scale.

The process of developing a BN involves 2 basic steps:

1. Identify the key concepts needed in the domain, where each concept becomes a node in the network, and the causal relationships among them (known or assumed) are specified as directed links between the nodes. A node that has a "causal" influence on another node is called a parent node and the influenced node, the child. The nodes without links are assumed to be statistically independent. Figure 4 shows an example of a BN that can be applied to the pain domain. Each node is coded as a finite set of possible levels. For example, Figure 4 illustrates a node for "experienced pain" that may take any of the 6 levels: 0=no pain and 1, 2, 3, 4, and 5=most severe pain. This is the node we assume cannot be directly observed, and thus must be inferred from the other evidence.
2. Specify the set of parameters that will determine the probabilities to be computed. These consist of prior probabilities for each node and conditional probabilities of the child's probability, given knowledge of the parent's state. If a node's value is known, then the known level is assigned a probability of 1 and all other levels are assigned a probability of 0. If a node has no parent nodes and is unknown, then its prior probabilities are assigned to its levels. If a node is unknown but has one or more parent nodes, its posterior probabilities are computed using Bayes theorem (A is the child and B is the parent; in Figure 4, COX-2 is a parent and experienced pain is a child; equation 1):

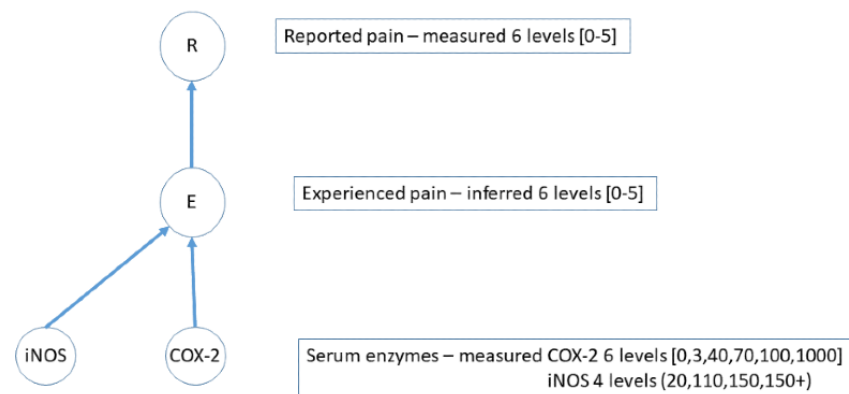
$$P(A|B) = \frac{P(B|A)P(A)}{P(B)} \quad (1)$$

where P(A) and P(B) are the prior probabilities, and P(A|B) is the conditional probability of A given the level of B. The usual approach assumes that all levels of a node's priors are the same (the principle of equal ignorance). However, in some applications, we may have the knowledge that the priors are not the same, and we can use this knowledge. If B is a set of parents rather than a singleton, a chain rule applies. Suppose it is the parent that is unknown (here, B is the child and A is the parent; in Figure 4, experienced pain is the parent and reported pain is the child). In this case, we compute the posterior probabilities for each level (i) of the parent node using the following (equation 2):

$$P(A_i|B) = \frac{P(B|A_i)P(A_i)}{\sum_{j=1}^n P(B|A_j)P(A_j)} \quad (2)$$

Figure 4. Illustrative Bayes network graphic for the pain application. COX: cyclooxygenase; E: experienced; iNOS: inducible nitric oxide synthase; R: reported.

Concept Sketch 2021-07-23



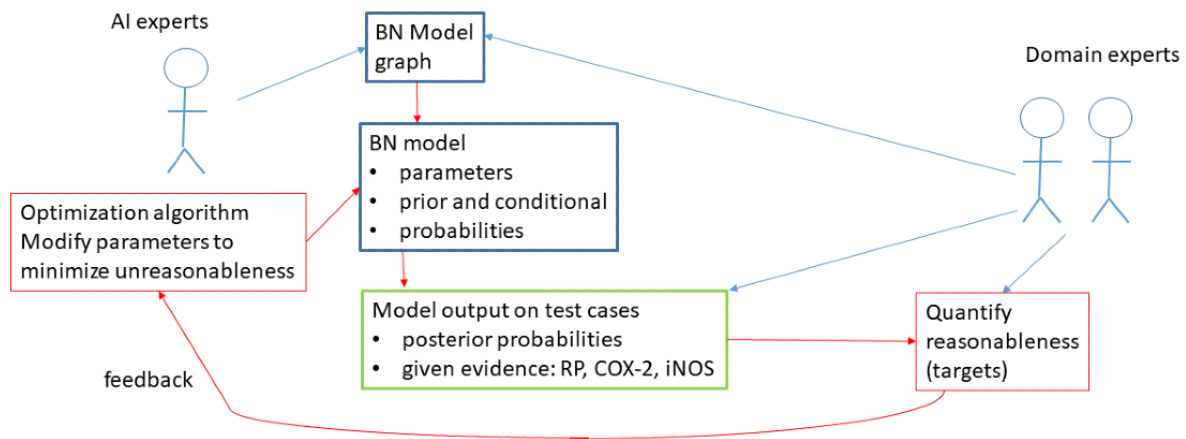
Approach to Setting BN Parameters When No Ground Truth Knowledge Exists

Each node in a specified graph requires a prior probability estimate. As mentioned earlier, one may always assume (by the principle of equal ignorance) that each level of a node has equal prior probability. If we have the knowledge or even reasonable consensus from experts that some probabilities other than all-equal are better, say, for a particular application or population of patients, we may set them accordingly. Such assumptions can always be tested using the methods described next.

The difficult challenge in devising a BN for an application is specifying the conditional probabilities for the parent-child

links. One rarely has sufficient knowledge at this fine level of detail. However, what we may be able to accomplish with an adequate pool of domain experts is a specification of “reasonableness” tests for the final probabilities. That is, we ask the experts to say how the probabilities for the different levels of experienced pain (which we can never know with any certainty) “should” come out for some set of test cases. This set of test cases should span a “representative” range of possibilities of evidence combinations. With such information, it should be possible to set up an optimization procedure that can set the required conditional probability parameters to closely approximate the desired output behaviors of the system. This approach is illustrated in Figure 5.

Figure 5. An optimization approach for setting the conditional probability parameters for the Bayes network (BN). AI: artificial intelligence; COX: cyclooxygenase; iNOS: inducible nitric oxide synthase; RP: reported pain.



Some Illustrations of What Might be Accomplished

Our Patient Samples

Our earlier study explored the potential utility of serum COX-2 and iNOS as objective measures of pain in 102 American patients [60]. Sandwich enzyme-linked immunosorbent assay was used to determine COX-2 and iNOS levels in the blood serum. At the same time, statistical analysis was performed using Pearson product-moment correlation coefficients,

regression, and receiver operating characteristics analyses. Our follow-up study examined the relationship between COX-2 and iNOS in the blood serum of >500 Turkish patients with different types of pain (Sadik, OA, unpublished data, November 2021) and assessed their potential as pain biomarkers. Serum COX-2 and iNOS levels were examined along with the level of pain caused by different types of pain, including lumbar or vertebral; lung; osteoporosis; inflammation; and fatigue, headache, or malaise related to problems. The data (Sadik, OA, unpublished data, November 2021) are now used to develop the current BN

concept. For more details on our patient samples, see the Methods section.

Proposed Output From the BN

The BN will estimate the probabilities that the pain the participant is experiencing takes each of the possible levels: 0, 1, 2, 3, 4, and 5. Figure 6 shows the method for exhibiting these estimated probabilities as histograms. The left example shows the computed probabilities when the evidence is fully self-consistent, all pointing to no pain experienced. The right illustration shows computed probabilities when the evidence is not consistent; the participant reports experiencing pain at level 4 (out of 0-5), although the COX-2 evidence points to no pain (out of 0-5), and the iNOS evidence points to a pain level of 1 (out of 0-3). The probabilities over all levels must sum to one. The reader may notice in Figure 6 that we have modeled some “leakage” of probabilities to pain levels adjacent to the levels of the evidence. These behaviors are embodied in our choices of model parameters (conditional probabilities).

Because there is, as yet, no verifiable sensor for experienced pain, such a system would be capable of implementing some form of expert consensus as to how the available evidence

should be combined. The best clinical decision support system can alert the caregiver to the extent that the available evidence is consistent. One possibility is to provide additional evidence that may be valuable in reconciling the situation.

Clearly, a point where important decisions are needed involves mapping actual measured biomarker values into the chosen discrete node levels for biomarkers, such as COX-2 and iNOS. Our current working model, the mapping, is presented in Tables 1 and 2. We hasten to point out that these decisions are provided for illustration purposes.

Evidently, the design of the system output can involve a small amount of creativity. Here, the primary source of guidance will be expert opinions from clinicians knowledgeable in this domain. There may be significant disagreements among pain experts, but it seems reasonable to assume that some considerable consensus may be reached regarding the nodes that should be included. Of course, it is always possible to explore different models for different applications. However, a significant challenge remains regarding the setting of many required internal probability parameters. For this, we propose the approach described in Section 3.1. For a somewhat differing approach, the reader may consult Hill et al [59].

Figure 6. Illustrations of envisioned Bayes network (BN)–clinical decision support system output. (A) consistent evidence (B) inconsistent evidence. COX: cyclooxygenase; iNOS: inducible nitric oxide synthase.

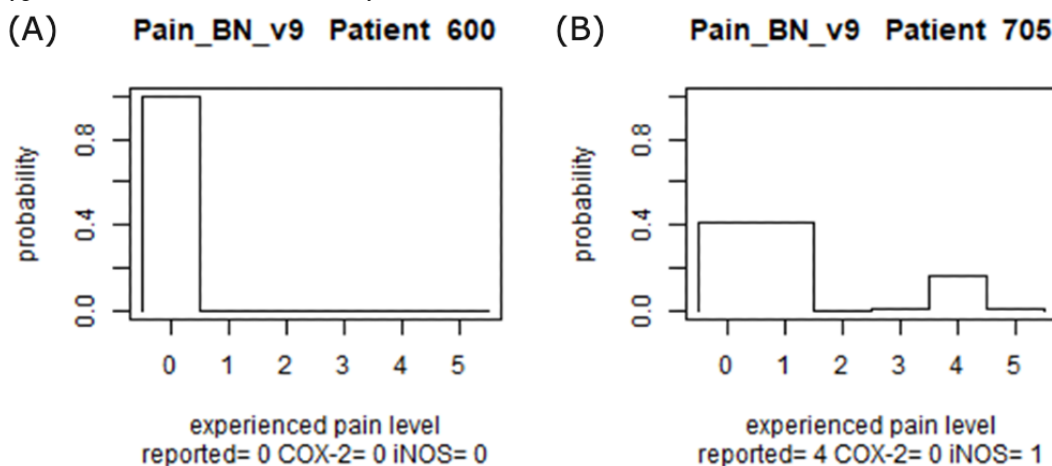


Table 1. Mapping measured values for cyclooxygenase-2 (COX-2) into experienced pain levels.

COX-2 measurement (ng/ml)	COX-2 code	Level of experienced pain most likely
<3	0	0
>3 to 40	1	1
>40 to 70	2	2
>70 to 100	3	3
>100 to 1000	4	4
>1000	5	5

Table 2. Mapping measured values for inducible nitric oxide synthase (iNOS) into experienced pain levels.

iNOS measurement (ng/ml)	iNOS code	Level of experienced pain most likely
<20	0	pain_0
>20 to 110	1	pain_1
>110 to 150	2	pain_2
>150	3	pain_3,4,5

Some Pain Evidence Examples

Figure 7 shows a distribution from our patient samples as to how consistent or not is the observed evidence that our BN model uses. We quantified the number of steps (node levels) that differed between the reported pain and biomarker levels. If a patient’s difference was fewer than 3 steps for both biomarkers (an arbitrary threshold for illustration purposes), we called it “consistent” and colored it green. Of the 379 patients with all 3 pieces of evidence, 302 (79.7%) had consistent evidence. This suggests that our goal of using these biomarkers to corroborate reported pain may be reasonable. If one or both biomarkers was “inconsistent” (>2 steps different), we highlighted those patients in yellow. The 77 inconsistent patients fell into 5 groups:

1. A total of 8 patients with high COX2, low reported pain (RP), and low iNOS
2. A total of 31 patients with high RP, high COX2, and 0 iNOS
3. A total of 11 patients with high RP, low COX2, and low iNOS

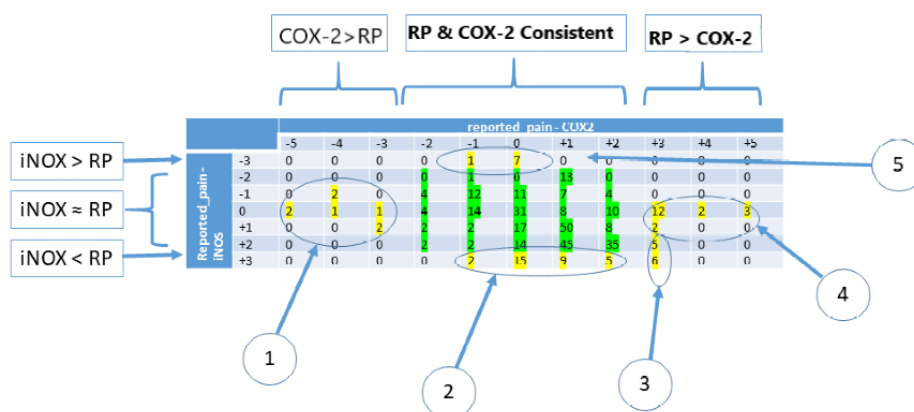
4. A total of 19 patients with high RP, high iNOS, and low COX2

5. A total of 8 patients with high iNOS, 0 RP, and low COX2

A reasonable next step would be to explore the data from these patients for other evidence that may help explain these observations.

The inconsistent evidence may be attributed to cultural or temporal variability of COX-2 and iNOS (as well as their serum variation and half-life), VAS, and other tools. Tables 1 and 2 assume that each categorized COX-2 and iNOS measurement most likely corresponds to a given pain experience. However, it is necessary to perform “sensitivity analysis” for greater precision. Inconsistencies may also be caused by potential miscalibration in pain management [35-37,61]. Ongoing work now includes supplementary information regarding the time-of-day data the biomarkers were taken and measured. The time-course measurements are being compared with other collected data. Information regarding gender and individual differences in COX-2 and iNOS data on RP is also being recorded. Different causes of inconsistencies could be attributed to memory bias and cognitive effects such as exaggerations or underestimations when reporting pain.

Figure 7. The distribution of evidence consistency or inconsistency in our samples. COX: cyclooxygenase; iNOS: inducible nitric oxide synthase; RP: reported pain.



Summary

We have presented an approach to building a clinical decision support system to help clinicians assess the pain experienced by a patient. We base our approach on ongoing research into new biosensor technologies that we hope will soon make available quick, inexpensive, and minimally intrusive measures of biomarkers related to pain. Such evidence will then need AI technology to offer clinicians an easy-to-grasp summary of the available evidence and perhaps suggestions for useful next steps. We present a simple Bayes net model as a prototype. Preliminary

data on 379 patients suggest that this approach is appropriate, because the majority (302/379, 79.7%) of participants showed reasonable consistency between the biomarker data and the patients’ self-reported pain. These data also showed 5 distinct types of inconsistencies, suggesting follow-up exploration of factors that might account for these inconsistencies. However, much work remains to be done. First, a community of clinical pain experts must be assembled to help define how such a prototype might be further developed (perhaps using alternative AI methods) to be of practical value. Portable biosensors need to be developed to allow for an easy method for measuring and

quantifying data. Owing to their fast responses, simplicity, cost-effectiveness, and portability, biosensors can be used for continuous monitoring of point-of-care analysis and do not require highly trained staff to operate.

Methods

Biomarkers or Biosensors

In 2018, the National Institutes of Health launched the Helping to End Addiction Long-term Initiative to stem the national opioid public health crisis [60,62]. One component of the Helping to End Addiction Long-term Initiative is to support biomarker discovery and rigorous validation to accelerate high-quality clinical research on pain [62,63]. Biomarkers are objectively measured and evaluated as indicators of either normal or pathogenic biological processes or responses to therapeutic interventions. Multiple studies have observed significant differences in proinflammatory cytokines (eg, interleukin 6 [IL - 6], tumor necrosis factor α , IL - 8, and IL - 1 β) in relation to pain intensity [63-65]. Serum protein levels and mRNA expression of tumor necrosis factor α have been shown to be significantly higher in participants experiencing a greater intensity of chronic pain. Biomarkers may be used alone or in combination to assess the health or disease state of an individual [66,67].

Our group conducted extensive research in this area, identifying COX-2 and iNOS or nitric oxide synthase 2 as good candidates for this purpose [58,60,62,63,65,68-71]. COX, also known as prostaglandin H₂ synthase, is a key bifunctional enzyme in the biosynthetic pathway that leads to the formation of prostanoids, including prostaglandins, prostacyclins, and thromboxanes. COX exists in different isoforms [72,73], COX-1, COX-2, and COX-3. COX-1 is an oxidoreductase enzyme constitutively expressed in many cell types. It is presumed to be responsible for the synthesis of housekeeping prostanoids that are critical for normal physiological functions such as regulating vascular homeostasis, gastric mucosa protection, and renal integrity [74]. COX-3 is a variant of COX-1, which has retained intron-1 during translation and is found in human tissues in a polyadenylated form [75]. It is a selective splicing product of COX-1 mRNA with 633 amino acids with less activity in the production of prostaglandin E₂, and it is mainly found in the hypothalamus, spinal cord, and pituitary choroid plexus. COX-2, on the other hand, is usually undetectable in healthy tissues but is rapidly induced and found to be upregulated in a variety of pathophysiological conditions such as neurological diseases [24], pain [76], inflammation, and cancer infection [13,77,78]. Some studies have indicated that the level of COX-2 at the point of inflammation translates to the degree of inflammation and may thus be used to determine the level of inflammatory pain [18]. Nitric oxide (NO) is a highly reactive free radical and, at the same time, an important signaling molecule involved in

different functions [79]. Its inducible form, “iNOS,” is expressed in macrophages and other tissues in response to infection or inflammation, generating large amounts of NO in the blood [24,80]. Increased NO levels have been observed during inflammation and arthritis; therefore, iNOS can be considered a pain biomarker.

In addition to these biomarkers, preliminary results from our laboratory indicated that Contactin-1 (CNTN-1) could also be a promising pain biomarker. This is supported by previous studies that pointed to CNTN-1 as a pain suppressor [81,82] and found antibodies against CNTN-1 in patients with chronic inflammatory demyelinating polyradiculoneuropathy [26]. CNTN-1 levels have been shown to decrease in blood in high-pain states, with convergent evidence in other tissues in human studies for the involvement of pain. Anti-CNTN-1 autoantibodies block or decrease the levels of CNTN-1 in chronic inflammatory demyelinating polyneuropathy [22] and have been considered a bona fide pain marker [81-84]. Moreover, human G-protein subunit gamma 7 plays a strong role in signal transduction with decreased levels in high-pain states (ie, it is a pain suppressor gene with transdiagnostic evidence for involvement in psychiatric disorders) [85,86]. Its expression is decreased by omega-3 fatty acids [87,88]. Microfibril-associated protein 3 provides the most robust empirical evidence as a strong predictor of pain in both men and women. It decreases in expression in the blood during high-pain states [28,84,89,90].

Patient Recruitment

The General Secretary approved the institutional review board of the Manisa State Hospitals Union. The study was conducted at Manisa Merkez Efendi State Hospital, Manisa, Turkey. The participants included in the study were recruited from emergency, internal medicine, gynecology, general surgery, clinical microbiology, chest, urology, and physical therapy clinics. Only participants aged ≥ 18 years, who consented to participate were included in the study. All participant recruitment and data collection were performed by nurses at the clinics.

Patients were excluded from data analysis if they (1) aged < 18 years, (2) did not provide sufficient description during anamnesis to determine their level of pain, and (3) had a blood sample not sufficiently large for analysis (Figure 8).

The survey questions were incorporated into the initial intake and anamnesis questions provided by the nurses. The survey questions are presented in Multimedia Appendix 1. The survey questions included information such as participant's age, gender, smoking and alcohol habits (Figure 9), chronic disease, long-term medication, surgery history, the reason for and duration of the pain, and pain medication before coming to the hospital.

Figure 8. Flowchart of patient recruitment. COX: cyclooxygenase; iNOS: inducible nitric oxide synthase.

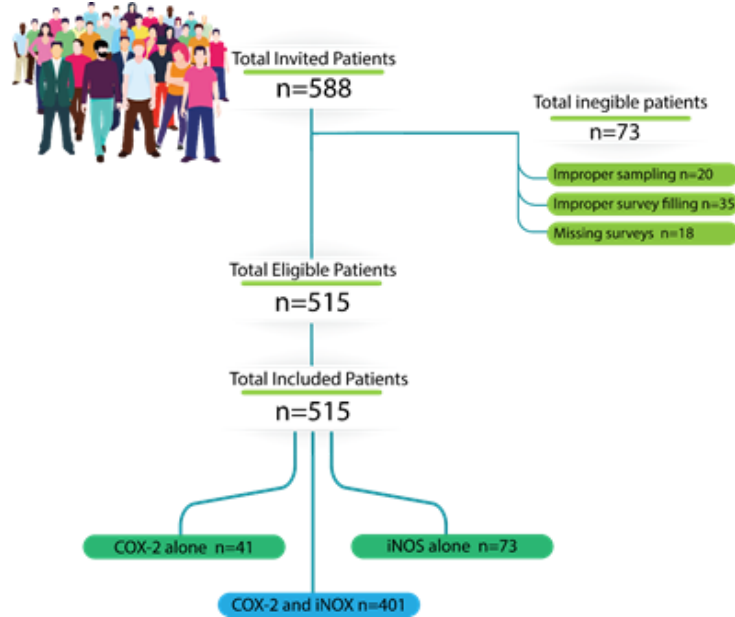
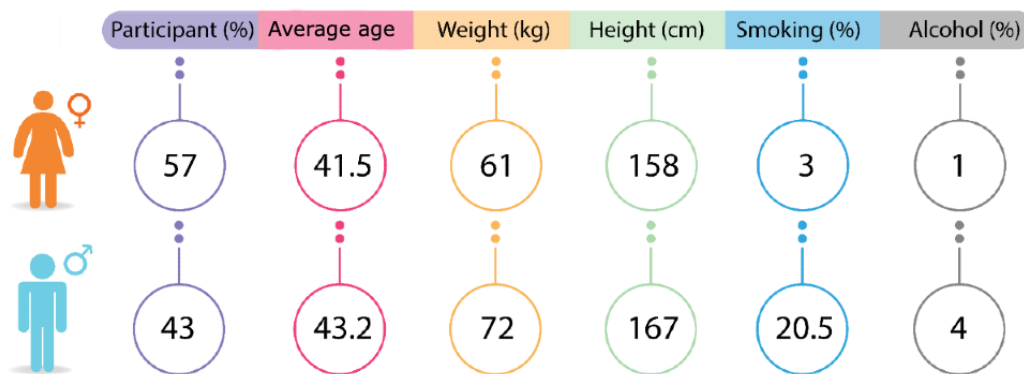


Figure 9. Demographic and habit distribution of patients.



Age and Height Are Averages

Following this initial questioning, patients were informed of the study. Informed consent was obtained if the patient agreed to participate in this study. Blood samples were collected via the leftover serum from blood samples taken for routine analysis. During the informed consent process, the participants consented to the use of their leftover serum; no patients were asked to donate blood samples specifically for the study.

The pain level for each participant was classified by the nurse performing anamnesis based on the patient’s responses to the survey questions. Pain level was classified from 0 to 5 as 0=no

pain, 1=feeling pain but not disturbing, 2=feeling pain and little disturbing, 3=severe pain and requiring painkiller intake, 4=very severe pain and distraction from working and requiring urgent painkiller administration, and 5=unbearable pain requiring urgent painkiller administration and rest as well as causing anxiety. Each pain level with characteristic conditions was explained to the patients, who were asked how they felt and if they had taken painkillers before they arrived at the hospital.

A sandwich enzyme-linked immunosorbent assay was used to monitor the levels of COX-2 and iNOS in the serum, as reported elsewhere [68].

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Survey form.

[\[PNG File , 71 KB-Multimedia Appendix 1\]](#)

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Abbreviations

- AI:** artificial intelligence
- BN:** Bayes network
- CDSS:** clinical decision support system
- CNS:** central nervous system
- CNTN-1:** Contactin-1
- COX:** cyclooxygenase

IL: interleukin
iNOS: inducible nitric oxide synthase
NO: nitric oxide
PGG2: prostaglandin G2
PGH2: prostaglandin H2
RP: reported pain
SUNY: State University of New York
TENS: transcutaneous electrical nerve stimulation
VAS: visual analog scale

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