Review Article

Modulation of Pain in Osteoarthritis
The Role of Nitric Oxide

Celeste M. Hancock, PT, MS, DPT* and Cheryl Riegger-Krugh, PT, MS, ScD†

Background: Patients with osteoarthritis (OA) may experience severe pain, progressive loss of movement function, and disability. Many pain-relieving medications are not effective, and are not able to improve the existing pathology.

Objectives: This review summarizes (1) the pathology, mechanisms of pain production, and conservative management of OA with respect to pain; and (2) explains the role of nitric oxide (NO) in pain reduction and production, especially as related to OA.

Discussion: NO is produced in biologic cells by a family of enzymes referred to as the nitric oxide synthases (NOSs). The beneficial or harmful effects of different isoforms, constitutive NOS (cNOS) and inducible NOS (iNOS), respectively, suggest dual effects of NO in biologic structures. The harmful effects of NO are most often reported in the literature. We suggest that (1) NO via the beneficial cNOS pathway is decreased in joint structures exposed to chronic load-induced stresses and biochemical change-induced stresses, (2) monochromatic infrared light energy at an 890 nm wavelength, applied at the skin surface, is absorbed into blood vessels and stimulates production of NO in joints by the beneficial cNOS pathway, (3) NO from the cNOS pathway may help decrease the detrimental effects of NO induced by iNOS and produced in OA pathology, and (4) NO-based intervention may produce substantial pain relief without undesirable side effects.

Key Messages: (1) The roles of NO in nociception are dual and complex. (2) NO via cNOS, produced transiently in small amounts, can bring dramatic relief to people with painful OA.

Received for publication June 28, 2007; revised October 12, 2007; accepted October 13, 2007.

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Sources of Support: No funding. Disclaimers: None.

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Pain reduction is a primary goal for people with chronic pain, including patients with osteoarthritis (OA).1 Progressive loss of movement function and disability, which are directly related to the pain associated with OA, are major reasons for lost work time, eventual exit from the workplace, permanent disability, and large medical costs.2 Many pain-relieving medications are either not effective and/or have significant side effects.3 Few pain-relieving medications are capable of improving the existing pathology. One exception to this generalization is the class of disease-modifying OA drugs, most of which are currently in clinical trials and have not yet been approved for use in patients.3,4 Nitric oxide (NO)-based intervention seems at this time to produce substantial pain relief without undesirable side effects.5,6

Pain is the major determinant of decreased functional activity in people with OA, and movement function for people with OA is more related to the pain itself than to the disease status.7 Not surprisingly, therefore, pain relief is the major reason why people with arthritis seek medical advice.1 At the very least, pain reduction is sought for improvement in the quality of life or when joint replacement has to be delayed until weight is reduced or age criteria are met.

Pain-intervention methods that can improve or reverse OA pathology are actively sought in medicine, with the expectation that chronic pain will be simultaneously decreased. To this end, much research is now focused on NO, a compound with significant importance in medicine. In a cover story by Science in 1992, NO was noted as the “Molecule of the Year.” Three scientists, Robert Furchgott, Louis Ignarro, and Ferid Murad won the Nobel Prize in Physiology or Medicine in 1998 for their pioneering studies of NO. The first clues emerged from studies showing that if the inner layers of the cells (the endothelium) of an artery or vein were absent, the smooth muscle cells of the blood-vessel wall would lose their capacity to make the vessel relax. In 1986, they discovered that a previously unrecognized substance had to be present, which regulated the tone of the smooth muscle cells of the blood-vessel walls. This unrecognized...
mystery agent, an endothelium-dependent relaxing factor, was eventually identified as NO. NO has emerged as an important biologic mediator in almost all cell types and has effects on vascular tone, neurotransmission, immune function, morphogenesis, gene-expression regulation, and growth and repair of damaged tissues.5,8

We suggest that NO, used in a relatively new manner for pain relief, might enhance the body’s own natural production of low concentrations of NO via the stimulation of constitutive NOS (cNOS) through intervention with monochromatic infrared photo energy (MIRE). Also, it might improve the OA pathology. Intervention with MIRE, for example, when applied noninvasively at the skin surface, is speculated to stimulate the body to either produce the beneficial form of NO or release it from bound sites within the cells.9-11 Preliminary data from case studies in patients with knee OA documented by patient report that MIRE decreased pain, improved functional mobility, improved health-related quality of life, decreased the use of over-the-counter drugs, and had no reported detrimental side effects. Some patients reported improvement in sleep. One patient who was considering surgery stated that she no longer felt that surgery was needed at that time.9,12 Even though MIRE seems to be a beneficial approach to treatment, controlled clinical studies have not occurred, and the literature is not clear on the role of NO either in improving OA pathology or in reducing pain. However, use of MIRE in OA might prove to alleviate pain, because it reduces pain in other conditions such as neuropathy.13

The objectives of this paper are to
I. Review the pathology, the mechanisms of pain production, and the conservative management of OA with respect to pain.
II. Explain the role of NO in pain reduction in OA.

OA PATHOLOGY AND CONSERVATIVE MANAGEMENT OF OA PAIN

OA Pathology and Causes of Pain

OA is a disease of the entire synovial joint, which consists of articular cartilage, subchondral bone, intra-articular structures, synovial fluid, synovial membrane, periarticular soft tissue of tendon, ligament, muscle, fascia, and related nerves.14,15 All the structures in the synovial joint except the articular cartilage have pain fibers. Joints, other than synovial joints, might also have OA: in these cases, the joint structures present would be involved. OA pathology can cause pain in all of these structures, except in the articular cartilage. With disease progression, the articular cartilage becomes partially vascularized and innervated and might be associated with pain.16

OA is one of the most painful, functionally limiting, and disabling diseases that affects the musculoskeletal system.1 Pathology related to mechanical overload17-19 and/or biochemical changes (and most likely both)17-20 might not cause pain with initial articular cartilage degeneration. However, progressive OA usually involves increased subchondral bone density; eburnation of bone that exposes nerves, damage to the blood vessels at the tidemark between the articular cartilage and the subchondral bone; inflammation;16 and/or irritation of periarticular soft-tissue structures and related nerves, all of which can lead to pain.1,14-16 Of importance in this scenario is the loss of blood supply to previously well perfused structures; the result is ischemic pain16 mediated by loss of oxygen and nutrients to nerves. A palliative role might exist for improving blood flow by increasing local NO levels.

Articular cartilage thinning and erosion decrease the capacity of the cartilage to absorb shock; therefore, the cartilage might require bone to absorb more of the shock of loading; this in turn leads to increased density of the subchondral bone14,20 and can lead to bone marrow edema and pain.21 Edema can also compress capillaries and deprive tissues, including nerves, of oxygen.16 Lack of blood flow makes it impossible for healing to occur, even with oral medications, including analgesics. Surface fibrillation of articular cartilage increases with disease progression; and wear debris particles associated with surface fibrillation can create inflammation and harmful chemical changes. Surface fibrillation, if deep enough, wear debris, and the production of irritant mediators such as prostaglandins, kinins, cytokines, chemokines, ATP, serotonin, substance P, norepinephrine, and others can cause pain.22-24

Mechanisms of Pain Production in OA

Pain can be elicited with overload or damage to all joint structures, except the articular cartilage. Pain-producing mechanisms, both mechanical and chemical, joint structure sources of pain, and common types of pain are summarized in Table 1.

Conservative Management of OA Pain: Interventions for Pain Reduction

Pain is a protective mechanism that usually results from the stimulation of nociceptors when the stimulus exceeds the reactive threshold of the system. The purpose of pain is to increase the awareness of the potential for or the presence of damage and to provoke a response that will limit this damage.

Pain is multidimensional, dynamic, and results from complex changes in the peripheral and central nervous systems. In the case of peripheral OA, the pain originates at the site of damaged joints. Nerves might be sensitized to increased pain perception that lasts beyond the duration of the original noxious stimulus. This persistent nociceptive input leads to “neuronal plasticity,” with changes in spinal cord connections. These changes contribute to the variability in pain, and the shift from acute to chronic pain. Genetic predisposition, age, and psychosocial factors might also contribute.1,22,41 The mechanisms by which chronic pain, including OA pain, is maintained (even when the stimulus for the pain is removed) is relevant for patient management. Pain that is
TABLE 1. Mechanisms of Pain Production in OA

<table>
<thead>
<tr>
<th>Mechanism of Pain Production</th>
<th>Source of Pain</th>
<th>Commonly Associated Pain/Pain Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Trapped intravenous blood</td>
<td>Bone, nerve</td>
<td>Dull, aching, deep joint pain, occurring with WB &gt; 15/22–24* and also occurring at rest in advanced disease.15</td>
</tr>
<tr>
<td>with ischemia in subchondral</td>
<td>Vascularity, nerve</td>
<td>Throbbing, diffuse pain23*</td>
</tr>
<tr>
<td>bone14,15,21,25; impaired venous</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp or dull with WB/excessive compression &gt; shear on bone and nerve29,31*</td>
</tr>
<tr>
<td>drainage from bone marrow25;</td>
<td>Ligament, tendon, muscle, ligament or tendon to bone junction, joint capsule, nerve</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction29,31*</td>
</tr>
<tr>
<td>bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondral sclerosis25,26; bone remodeling/repair that leads to subchondal...</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
<td></td>
</tr>
<tr>
<td>2. Overload of bone and ST: a. In malaligned joints14,27–32</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>b. With joint laxity14,29,33,34</td>
<td>Ligament, tendon, muscle, ligament or tendon to bone junction, joint capsule, nerve</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>c. With malalignment and correlated/compensatory postures and motions at joint14,29,33,34</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>d. With high load14,29,35,36</td>
<td>Ligament, tendon, muscle, ligament or tendon to bone junction, joint capsule, nerve</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>3. Repetitive impulsive loading14,37; hard/fast loading without adequate shock absorption14; impact forces might lead to inflammation16</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp or dull at sites of correlated/compensatory postures or motions15 as noted with malalignment and joint laxity*</td>
</tr>
<tr>
<td>4. Microfracture from overload14,16</td>
<td>Ligament, tendon, muscle, ligament or tendon to bone junction, joint capsule, nerve</td>
<td>Sharp or dull with WB/excessive compression &gt; compression on bone and nerve29,33,34*</td>
</tr>
<tr>
<td>5. WB on eburnated bone14,16</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>6. Periosteal outgrowth: stretch/distension of nerve in bone might be accompanied by inflammation14 and angiogenesis15</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>7. Joint distension/stress at ligament bone insertion15</td>
<td>Joint capsule; ligament, bone</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>8. Nerve irritation: noxious mechanical stimuli (stretch, pressure, crush) in bone and in joint-related ST1,16,22</td>
<td>Nerve nociceptors22</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>9. Muscles fatigue with overuse39,40</td>
<td>Muscle, nerve</td>
<td>Sharp or dull with WB/excessive compression &gt; compression on bone and nerve29,33,34*</td>
</tr>
<tr>
<td>10. Muscle spasm38</td>
<td>Muscle, nerve</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>11. Excessive stretch of tight muscles with joint contracture39,40</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>12. Excess stretch of insertion of meniscus to capsule; tear of meniscus15</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>13. Movement across uneven joint surfaces, with crepitus (ie, osteochondromatoses, displaced torn meniscus)15</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>14. Inflammation</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>a. In synovium, with cartilage debris, fragments, crystals; release of proinflammatory cytokines/enzymes that further destroy cartilage16,20</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>b. Compression of synovial blood vessels, with swelling/distension within the joint capsule16</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>c. In bursae, with or without calcification35</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>d. In nerve, with peripheral and central sensitization of nerve nociceptors22</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
<tr>
<td>e. Chronic synovitis and angiogenesis16</td>
<td>Bone, nerve, vasculature, synovium</td>
<td>Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle, nerve, and accompanying sensory nerves16</td>
</tr>
</tbody>
</table>

(continued)
not addressed in a timely manner could be prolonged unnecessarily and compromise the health-related quality of life of the person with OA.

Pain is closely linked with physical activity, defined as exercise and daily functional movement, in people with OA. The links include the lack of pain warning that can occur with initial articular cartilage degeneration; pain with joint overuse, which can eventually lead to physical inactivity; pain with minimal physical activity for people who are sedentary; and pain with advanced OA pathology, first with activity and later even with rest.42–44

Wisely guided physical activity that improves the signs and symptoms of OA and avoids damaging mechanical loading is critical for people with OA.31 Unfortunately, pain and the fear of injury cause people with OA to resist physical activity.43 People with OA have often been instructed to avoid exercise; often, they are not instructed in how to exercise and move properly and safely. No single physical activity is universally recommended for people with OA, because people differ in risk factors such as weight, skeletal alignment, and movement-performance problems. Knee-joint skeletal malalignment and joint laxity are 2 situations for which physical-activity recommendations are modified from the standard physical therapy (PT) management for knee OA.31–34

“Nonpharmacologic treatments currently considered to have sufficient levels of scientific evidence are education, exercise, appliances, and weight reduction.”36,45 Because physical inactivity is the leading cause of overall morbidity and mortality for all people with and without pathology, it is important to promote and maintain pain-free and nondamaging physical activity in people with OA.32,41 It is of interest that physical activity causes an increased production of NO during the flow of blood through the muscle beds. This process, known as “shear stress,” occurs during the more rapid movement of blood along the surface of endothelial cells.5,8

Current PT standard care, including physical activity and other interventions for pain reduction, is included in Table 2. Every effort has been made to include currently available levels of evidence, including literature documentation and/or expert opinion.

The interventions leading to pain reduction, listed in Table 2, can occur by decreasing stress on overloaded structures, encouraging more normal tissue remodeling accompanying skeletal realignment therapies, improving muscle balance, decreasing the shock of high-impact loading on joints, decreasing nerve irritation, decreasing inflammation, improving appropriate flexibility and strength in joint structures, and by using other modalities. “International guidelines advocate nonpharmacologic treatments as first-line management for people with OA.”45

Pharmacologic interventions used to manage OA pain have variable success and can produce considerable side effects. The variable success of these medications might be due to their inability to control the multiple pain-generating factors in the numerous structures, inability to halt the pathology, and to effect disease-accompanying alterations in the blood flow. Medications/drugs used in treatment have been reviewed in several references.3,4,94 Because most pharmacologic interventions have side effects, people with OA often prefer nonpharmacologic interventions or, at least, as few pharmacologic interventions as possible.

MIRE, a nonpharmacologic treatment, has been cleared by the Food and Drug Administration for use in pain relief, produces no known side effects, and might be a good option to reduce pain for people with OA.9–11 In addition, Michlovitz and Nolan41 provided a literature review and stated that MIRE promotes vascular perfusion, enhances tissue oxygenation, nutrient delivery, removal of the waste products of metabolism, and increases ATP in human lymphocyte cells.

From these statements and on the basis of clinical experience, the authors interpreted this to mean that MIRE can slow down or prevent the deterioration of joint structures, possibly by decreasing acute and chronic inflammation, increasing blood flow, and promoting the healing of joint structures. We emphasize that MIRE is adjunctive to a comprehensive physical therapy/occupational therapy approach to pain in people with OA.

**NO PATHWAYS IN OA**

**NO Function in the Body and With OA Pathology**

NO is produced in all human cells by a family of enzymes called nitric oxide synthases (NOS).5,95–97 Synthases are enzymes that remain structurally the same while inducing chemical change and, in this instance, they synthesize NO from the amino acid, l-arginine.8,96
TABLE 2. Physical Therapy Interventions for Pain Reduction in OA

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Amount of Pain Relief</th>
<th>Level of Evidence/Expert Opinion</th>
</tr>
</thead>
</table>
| 1. Heat\textsuperscript{46} | 1. Temporary\textsuperscript{46}; level of pain relief not reported | 1. *Welch et al\textsuperscript{57}; few trials in OA, but in RA heat found effective, well liked, safe; recommended use for pain; †Mazzuca et al\textsuperscript{46}; heat-retention knee sleeve might reduce pain  
*Broseau et al\textsuperscript{56}; poor evidence; no significant pain relief  
†Hurley and Walsh\textsuperscript{46}; poor evidence; however, frequently used for pain |
| 2. Cold\textsuperscript{46} | 2. Temporary\textsuperscript{46}; level of pain relief not reported | 2. *Welch et al\textsuperscript{57}; few trials in OA; however, in RA cold found effective, well liked, safe; recommended use for pain  
*Broseau et al\textsuperscript{56}; poor evidence; no significant pain relief  
†Hurley and Walsh\textsuperscript{46}; poor evidence; however, frequently used for pain |
| 3. Ultrasound (US)\textsuperscript{50} | 3. Temporary\textsuperscript{50}; level of pain relief not reported | 3. *Robinson et al\textsuperscript{50}; US demonstrates no benefit in hip and knee OA over placebo; short-wave diathermy; poor evidence regarding use to decrease pain  
*van der Windt et al\textsuperscript{51} and †Gam et al\textsuperscript{52}; poor evidence for pain relief |
| 4. Low-level laser therapy (LLLT): infrared light, 684-904 nm\textsuperscript{53} | 4. Temporary\textsuperscript{53}; level of pain relief not reported | 4. *Broseau et al\textsuperscript{56}; LLLT effectiveness for pain relief not conclusive  
†Beckerman et al\textsuperscript{54}; RCTs: Stelian et al\textsuperscript{50}, delBie and Verhagen\textsuperscript{55}  
*Osiri et al\textsuperscript{56}; TENS and AL-TENS effective in pain control over placebo RCTs: Cheing et al\textsuperscript{57}  
*Hulme et al\textsuperscript{58}; PES effective in decreasing knee pain; RCTs: Trock et al\textsuperscript{59} Trock et al\textsuperscript{60}  
Zizic et al\textsuperscript{61}; variable treatment frequency, duration, dosage |
| 5. Transcutaneous electrical nerve stimulation (TENS); acupuncture-like TENS (AL-TENS)\textsuperscript{56} | 5. Significant: TENS: In one RCT, 256-min pain relief with 40-min duration of treatment\textsuperscript{57} | 5. *Osiri et al\textsuperscript{56}; TENS and AL-TENS effective in pain control over placebo RCTs: Cheing et al\textsuperscript{57}  
*Welch et al\textsuperscript{56}; poor evidence: no trials in OA, but in RA cold found effective, well liked, safe; recommended use for pain  
*Broseau et al\textsuperscript{56}; poor evidence; no significant pain relief  
†Hurley and Walsh\textsuperscript{46}; poor evidence; however, frequently used for pain |
| 6. Pulsed electrical stimulation (PES): electromagnetic field therapy\textsuperscript{58} | 6. Significant pain relief\textsuperscript{58}; small-to-moderate treatment effect in the knee | 6. *Hulme et al\textsuperscript{58}; PES effective in decreasing knee pain; RCTs: Trock et al\textsuperscript{59} Trock et al\textsuperscript{60}  
Zizic et al\textsuperscript{61}; variable treatment frequency, duration, dosage |
| 7. Manual therapy (MT): restoration of soft tissue and articular flexibility\textsuperscript{62} | 7. Significant pain relief; MT + supervised exercise, moderate-to-large combined-treatment effect | 7. RCT: Deyle et al\textsuperscript{52}; MT + supervised exercise effective vs. no treatment to decrease pain  
Other RCTs: Hoeksma et al\textsuperscript{53,64}; few studies in OA  
†Fitzgerald and Oatis\textsuperscript{65} |
| 8. Massage\textsuperscript{46} | 8. Temporary\textsuperscript{46}; level of pain relief not reported | 8. *Philadelphia Panel Clinical Practice Guidelines, 2001\textsuperscript{66}; no evidence that massage decreases pain  
†Hurley and Walsh\textsuperscript{46}; no trials in OA; massage used for subjective benefits |
| 9. Aquatics (Balneotherapy) | 9. Temporary; level of pain relief not reported | 9. *Verhagen et al\textsuperscript{57}; no evidence of efficacy/  
effectiveness to reduce pain; no SRs for OA; few RCTs: Foley et al\textsuperscript{68}, Patrick et al\textsuperscript{69}, Guillemin et al\textsuperscript{70}, Green et al\textsuperscript{71}, Nguyen et al\textsuperscript{72}  
*Welch et al\textsuperscript{57}; few trials in OA, but in RA cold found effective, well liked, safe; recommended use for pain  
*Broseau et al\textsuperscript{56}; poor evidence; no significant pain relief  
†Hurley and Walsh\textsuperscript{46}; poor evidence; however, frequently used for pain |
| 10. Therapeutic exercise; physical activity (land-based strengthening, aerobic, and combination programs) | 10. Significant pain relief established: small-to-moderate treatment effects | 10. *Fransen et al\textsuperscript{73}; *van Barr et al\textsuperscript{74,75}; RCT: Minor and Sanford\textsuperscript{76}; †Hurley\textsuperscript{77}; Strengthening exercise effective in decreasing knee pain  
*Broseau et al\textsuperscript{56}; *Westby\textsuperscript{78}; aerobic exercise effective in decreasing knee pain RCTs: Sharma et al\textsuperscript{31-33}; pain reduced if exercise is appropriate for subgroups of patients with joint laxity and malalignment  
RCTs: Sharma et al\textsuperscript{31}; varus/valgus knee alignment increase risk for medial/lateral knee OA progression; severity of pain is |
| 11. Patient education; disease process/self-management, not movement performance | 11. Significant pain relief: small, but significant pain-treatment effect | 11. *Warsi et al\textsuperscript{80}; †Reinsma et al\textsuperscript{81}; †Superio-Cabslay et al\textsuperscript{82}  
Numerous RCTs: education (self-management, home/class-based exercise, cognitive behavioral/coping, telephone, spouse) effective in decreasing pain  
*Warsi et al\textsuperscript{80}; varus/valgus knee alignment increase risk for medial/lateral knee OA progression; severity of pain is |
| 12. Management of skeletal malalignment and joint protection in weight bearing | 12. Significant pain relief established: small-to-large individual treatment effects | 12. RCT: Sharma et al\textsuperscript{31}; varus/valgus knee alignment increase risk for medial/lateral knee OA progression; severity of pain is |

(continued)
Isoforms are specific forms of the enzyme. There are 2 major isoforms of NOS: inducible NOS (iNOS), induced in cells by trauma, injury, or infection, and constitutive NOS (cNOS), continuously produced by, and active in, cells. Only one form of iNOS exists. 2 forms of cNOS are found in many cell types: eNOS (endothelial NOS) and bNOS or nNOS (brain or neuronal NOS, respectively). A third form, OA-NOS, recently identified in OA joints, will not be discussed further, as its clinical significance has not been determined.

We recommend the iNOS, cNOS, bNOS, and nNOS as the most descriptive and easy-to-use terminology. NO will be differentiated either as NO via cNOS or as NO via iNOS, representing its production via the constitutive or induced isoforms, respectively. NOS numerical terminology is used extensively in the literature, numbered by order of discovery and developed on the basis of chemical structure and other chemical characteristics. However, the simple term NOS provides no clue to the origin of NO and no information as to whether it was induced or generated from a constitutive isoform; hence, unfortunately, it is often used inappropriately.

NO serves as a fast-acting chemical messenger between and within cells. NO can be either beneficial or harmful. The beneficial or harmful role in tissues and organ systems is determined by the isoform, the amount (concentration) produced, the stimulus required for activation, the characteristic chemical

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**TABLE 2. (continued)**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Amount of Pain Relief</th>
<th>Level of Evidence/Expert Opinion</th>
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| a. Weight reduction (WR) | Small-to-large effect | associated with severity of varus/valgus alignment; Riegger-Krugh et al.:
| b. Footwear, orthotics | Small effect | skeletal malalignment can alter joint load distribution, produce correlated and compensatory motions and postures at adjacent/distant joints, and create pain; RCTs: Messier et al; WR decreases pain; but few RCTs; Felson et al: weight loss reduces risk of OA; might prevent pain in the future; Felson:
| d. Walking/work home devices | Effect not measured | c. *Brouwer et al: valgus brace decreases knee pain
| d. Walking/work home devices | Effect not measured | d. RCTs: Krebs et al: Contralateral cane use reduces peak acatabular contact pressure, which might impact pain in the future; Jackson et al: Walking, stationary bike generate lower in-vivo hip-pressure measurements than isometric hip/standing exercise; data challenges traditional protocols: clinician choice of exercise might affect pain;
| e. No RCTs regarding pain; historical evidence effective for pain relief in clinical practice | 13. Movement reeducation: to improve movement performance and prevent abnormal strategies; decrease impact loading in gait | 13. Significant pain relief established: size of treatment effect not described
| f. Household modifications | Effect not measured | 13. RCT: Voloshin et al: Muscle fatigue leads to decreased ability to absorb dynamic load, joint injury; Voloshin et al: increased walking speed increases dynamic loading/might induce pain; Radin et al: Repetitive impulsive loading increases joint loading; decreasing rate of loading might help decrease pain; McGibbon et al: repetitive stress from excessive muscle contraction can cause acatabular cartilage degeneration, which might lead to joint pain

behavior, and the chemical environment in which NO is generated. Contributions to the dual role of NO will be discussed in this section. Dual effects create confusion and confirm the complexity of the NOSs and NO in the body.

Controversy exists regarding the role of NO in OA. The destructive effects of NO are often reported in the literature versus the protective effects, and the isoform being discussed is not always specified.

The cNOS isoform is generally considered to be the beneficial healing form of NOS. This isoform is dependent on calcium as a stimulus for activation. NO via cNOS is thus regulated and produced in small quantities or low concentrations; it serves as a fast-acting chemical messenger for cell-to-cell communication in physiologic processes essential to healthy organisms, and promotes homeostasis. The cNOS synthase forms might promote pain reduction in OA, as described in the section NO and Pain Reduction in OA.

The iNOS isoform is usually considered to be the damaging form in which NO accumulates. The iNOS form, already bound to calcium (Ca$^{2+}$), is independent of Ca$^{2+}$ for activation. It produces NO in large quantities or in high concentrations, which might be harmful or even toxic, especially to OA cartilage and chondrocytes. Expression of iNOS in OA joints is induced by the exposure of the cells to proinflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-α, leukemia inhibitory factor, IL-17, and IL-6. Therefore, both iNOS and these cytokines are produced in response to tissue injury or mechanical trauma. Excessive production of NO via iNOS can lead to the reaction of NO with reactive oxygen species, resulting in oxidative injury and then destruction of cells.

Reactive oxygen species include compounds such as superoxides, which form reactive oxygen intermediaries such as peroxynitrite (ONOO$^-$) or peroxynitrous acid (ONOOH).

Also, NO dual roles are determined by characteristic chemical behavior, and are highly dependent on the variable physiologic and pathophysiologic chemical microenvironment in which NO is generated. NO is a molecule with potent, diverse actions in cartilage, bone, synovium, vascular, and nerve. NO is small, hydrophobic, highly diffusible, and has a short half-life (4 to 6 seconds) within the local cell microenvironment. NO, a reactive nitrogen species, might interact, with a strong affinity to oxygen or transition metals such as iron and sulfur, to produce beneficial or harmful effects. Beneficial reactions with NO include interactions with iron, containing substrates such as guanylate cyclase, in smooth muscle to cause vasodilation and the restoration of blood flow; and with sulfur to form nitrosothiols, such as hemoglobin, which either release NO for vasodilation or store NO for future beneficial use. An example of destructive reactions with oxygen has already been described.

Multiple conflicting NO effects in synovial membrane, cartilage, bone, nerve, and joint structures have been identified. It is not surprising that either an increase or a decrease in pain in OA has been linked to NO, probably because of an underappreciation of the isoform(s) involved. NO is only one of a multitude of mediators that can affect pain in OA. NO via iNOS, which is produced with inflammation, might participate in or induce cell injury; this could be the primary cause of chronic pain. Additionally, NO might play a role in other highly interrelated stimulators of structural damage and pain production in OA: inflammation; edema, vascular reactivity, and destruction; and nerve irritation and damage (Table 3).

**NO and Pain Reduction in OA**

NO via cNOS, produced transiently in small amounts, might bring relief to people with painful OA. Four pathways for pain reduction related to NO are proposed: the blood-flow pathway, which can normalize/restore the blood flow, thus reducing ischemic pain; the nerve-transmission pathway, which can restore nerve-membrane potential and conductance; the opioid-receptor pathway, which might stimulate the body’s normal pain-reduction pathways and open the ion channels at receptor sites to decrease nerve excitability; and the anti-inflammation pathway, which might reduce inflammation and, secondarily, promote improved oxygenation at the sites of pain. Reduction of inflammation and improvement in oxygenation affects not only the vascular system, but also the nerves themselves.

**Pain Reduction/NO and the Blood-flow Pathway**

In response to the shear stress of the pulsatile blood flow, a constant supply of NO via cNOS is generated by endothelial cells. The inner wall of the blood vessel, with its adjacent smooth muscle layer (tunica media), and its outer layer of epithelium (tunica adventitia) are illustrated in Figure 1.

With OA pathology, MIRE, which might induce local elevations in the physiologic amounts of NO via cNOS or by displacement of NO from hemoglobin, might be able to improve blood flow in the synovium and in the overly dense subchondral bone directly. MIRE might accomplish this by causing vasodilation, and restoring O$_2$, growth factors, and nutrients; secondary to the return of aerobic metabolism, MIRE might reduce acidosis in cells.

Michlovitz and Nolan believe that photo energy releases NO from red blood cells. Authors of this review believe that the photons of MIRE might alter the red blood cells passing near the light-emitting diodes, thus releasing NO from hemoglobin. Alternatively, MIRE photons might stimulate the production of NO by opening the endothelial cell calcium channels. When calcium is present, it binds to eNOS. L-arginine, in the presence of calcium-activated eNOS, produces NO. NO rapidly diffuses into the adjacent smooth muscle cells, where it binds to soluble guanylate cyclase (sGC).
Guanylate cyclase (sGC) is an enzyme that catalyzes the transformation of guanosine triphosphate to cyclic guanosine monophosphate (cGMP). Phosphorylation or the addition of a phosphate group to smooth muscle proteins via cGMP causes vascular relaxation; thereafter, it might cause a decrease in the pain due to the swelling that had caused local hypoxia or ischemia. Duarte and colleagues have also shown that NO via cGMP causes phosphorylation of the ATP-dependent potassium channel; they have proposed that this is one of the ways in which peripheral and central analgesia occurs when morphine is used to suppress pain. This is discussed below in Pain Reduction/NO and the Opioid Receptor Pathway. Additionally this vasodilation mechanism might improve nutrition via the synovial fluid, flush out the trapped blood in the subchondral bone, and promote the healing of soft-tissue injury or bone damage (Fig. 2).

### Pain Reduction/NO and the Nerve Transmission Pathway

Pain reduction also can be produced via a nerve-related mechanism in blood vessels, decreasing the irritation of the nerves in the synovium, bone, and soft tissues. Anytime there is loss of vascularity in the nerves themselves, pain is caused by abnormal nerve-impulse conduction or abnormal nerve-membrane potential. MIRE applied at the skin surface might act via the NO-cGMP pathway previously described (Fig. 2), to

![Blood vessel structure](image)

**FIGURE 1.** Blood-vessel structure.

**FIGURE 2.** Blood-flow pathway-vascular relaxation mediated by NO.

### TABLE 3. Stimulators of Pain Production in OA

<table>
<thead>
<tr>
<th>1. Inflammation</th>
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<td>Acute inflammation: sudden onset&lt;br&gt;Mechanical, chemical, or thermal stimuli at high threshold levels; pain by activation/sensitization of myelinated nerve in joint structures&lt;br&gt;Physical trauma&lt;br&gt;Acute synovitis&lt;br&gt;Chronic inflammation&lt;br&gt;Excessive mechanical, chemical, or thermal stimuli at high threshold levels; pain from prolonged activation of myelinated nerve, sensitization of unmyelinated nerve in joint structures&lt;br&gt;Excessive/repetitive overload in bone/joint soft tissues&lt;br&gt;Chronic synovitis with chronic edema, hypoxia, acidosis, poor perfusion of joints&lt;br&gt;Chronic irritation with activation of nociceptors via overstimulation of the immune system by proinflammatory mediators produced by invading immune cells&lt;br&gt;Mediators from resident cells, ie, cytokines, chemokines, nerve-growth factor, prostaglandins, ATP, others&lt;br&gt;Mediators from damaged cartilage, bone, and synovium, ie, hydrogen ions and kinins (bradykinin)</td>
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<th>2. Edema, vascular reactivity, and cellular destruction/damage</th>
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<td>Mechanical, chemical, or thermal stimuli at high threshold levels; pain by activation/sensitization of nerve in joint structures or peripheral nerve injury/growth&lt;br&gt;Acute synovitis&lt;br&gt;Chronic synovitis&lt;br&gt;Angiogenesis/new nerve innervation stimulated by inflammation, hypoxia, swelling&lt;br&gt;Vascularized/innervated articular cartilage; pain with innervation of cartilage via nerve from subchondral bone&lt;br&gt;Osteophyte formation via ossification/innervation of joint cartilage; pain via these new nerves stimulated by overload, hypoxia, and acidosis within cartilage&lt;br&gt;Normal loading with swollen joints; pain due to ischemia, reperfusion with joint-structure damage&lt;br&gt;Decreased cell energy sources (O$_2$, glucose, ATP) in smooth muscle cells of blood vessel walls; pain via altered nerve-membrane potential&lt;br&gt;Advancing age in cartilage/joint structures; pain possible with increased susceptibility of cells to destructive mediators</td>
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<th>3. Nerve irritation and damage</th>
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<td>Mechanical, chemical, or thermal stimuli at high threshold levels; pain by sensitization and activation of primary sensory afferent nerves; pain by sensitization of receptors to mechanical/other stimuli, direct receptor activation, or peripheral nerve injury/growth&lt;br&gt;Pain sensation transmitted by nociceptors&lt;br&gt;Sharp, sudden, well-localized pain transmitted from primary sensory afferent A delta fibers&lt;br&gt;Diffuse, dull, aching, or burning pain from unmyelinated C fibers&lt;br&gt;Increase in permeability of nociceptors at pain threshold and movement of ions across nerve membrane&lt;br&gt;Increase in nerve-membrane potential from stimuli at noxious levels to produce pain messages&lt;br&gt;Transmission of pain messages to higher central nervous system centers, where perceived as pain</td>
</tr>
</tbody>
</table>
decrease pain. NO produced by cNOS in nerve vasculature indirectly restores normal nerve-membrane potential and impulse generation by restoring blood flow, O₂, and nutrients to nerve cells. Clearly, vasodilation restores blood flow and results in pain reduction.¹¹,¹⁰²,¹⁰⁵,¹¹⁶

**Pain Reduction/NO and the Opioid Receptor Pathway**

Opioids decrease pain by decreasing nerve excitability either before or after afferent terminals are reached, and slow down or stop nerve transmission of pain information.¹¹⁹–¹²⁵ Opioid receptors in cells in joints are activated during inflammation²²,¹²³,¹²⁴,¹²⁶,¹²⁷ and bind with peptides such as endorphins, enkephalins, and dynorphins, which decrease both inflammation and pain.¹²² Intra-articular injection of morphine immediately before knee arthroscopy successfully reduces the need for postoperative analgesia.¹²⁸ The opioid-receptor pathway of pain reduction is proposed via a lock-and-key (opioid peptide-receptor) interaction on the nerve-cell membrane,¹²⁴ which stimulates NO production, regulates permeability of nerve membranes to calcium and potassium, and controls nerve-signal transmission to reduce pain¹¹⁹–¹²⁵,¹²⁹ (Fig. 3). MIRE, applied at the skin surface, is proposed by these authors to stimulate the calcium channels to open initially. Increased calcium binds to nNOS, and the activated nNOS + L-arginine produces NO. NO via the cGMP pathway acts on the nerve-cell membrane to open potassium channels and reduce calcium influx from calcium channels. It, thus, hyperpolarizes the membrane and stops pain transmission. Therefore, NO can act as a surrogate for opioids, bypassing the need for the drug to bind to the appropriate receptor. Tapping into the body’s natural opioid mechanisms via the use of MIRE might eliminate the side effects of opioid drugs: it seems to relieve pain in OA.

Other pain-reduction mechanisms via NO and nerve-transmission pathways are controversial. NO, via nNOS and iNOS, has been reported to be both antinociceptive and pronociceptive via the NO-cGMP pathway in the nerve.²²,²⁹ As noted above, this might be related to a misunderstanding of the concentrations of NO produced by iNOS or nNOS.

**Pain Reduction/NO and the Inflammation Pathway**

Inflammation in OA is accompanied by increased production of NO via iNOS in the synovium, bone, nerve, and cartilage,¹⁰⁵ which contributes to microvascular, nerve, and chondrocyte injury, and either initial or eventual pain.¹⁶ Increasingly, inflammation, hypoxia, acidosis, edema, angiogenesis, and new nerve growth have been described during OA,¹⁶,¹¹³,¹¹⁴ and each can be accompanied by pain. MIRE is proposed by these authors to promote homeostasis or oxidant/antioxidant balance in cells by stimulating the production of NO via cNOS. NO via cNOS is proposed to relieve pain by restoring the blood flow,¹¹ which had been compromised by the swelling and compression of capillaries. Decreasing the swelling, increasing the oxygen and nutrients to structures, and decreasing the waste products¹¹ and cytokine accumulation can collectively aid in restoring the normal nerve-membrane potential.¹¹,¹⁰⁰,¹⁰²

[FIGURE 3. Opioid-receptor pathway.](image-url)
MIRE at 890 nm

MIRE, at a wavelength of 890 nm (1 nm = 10^-9 m or one billionth of a meter) was chosen by the authors from numerous commercial MIRE units, because of its greater success clinically in pain reduction in these patients with knee OA. MIRE at 890 nm, absorbed by many cell types, can stimulate the production of NO via cNOS to reduce pain. MIRE at 890 nm is delivered to the joint using flexible 4 1/4" x 2 1/4"-treatment pads, each containing 60 near-infrared diodes. The uniform average power and total energy density from the diode array of each pad are reported to be 9.0 mW/cm^2 and 43.2 J/cm^2, respectively, per recommended 30-minute session. Eight treatment pads are available in the clinical model, and 2 to 4 in the home unit. The unit chosen delivers a short-acting thermal effect; however, the near-infrared light (MIRE) at 890 nm creates the NO-related treatment effect. Short-term elevations in NO increase cGMP, and the phosphorylation effects that follow sustain the blood flow for as long as 3 hours.

SUMMARY

The roles of NO in nociception are dual and far more complex than originally thought. The beneficial effects of NO can be described as antinociceptive, whereas the harmful effects are considered to be pronociceptive. NO via the cNOS pathway is decreased in joint structures exposed to chronic load-induced and biochemical change-induced stresses. NO-based intervention through cNOS is proposed to decrease pain and possibly improve OA pathology without detrimental side effects, by changing the cell microenvironments of the vascular and nerve pathways in joint structures. High concentrations of NO produced by iNOS are associated with injury, such as in OA; pain might be due to the side effects of these very high concentrations of NO. NO with MIRE at the 890-nm intervention can help decrease the detrimental effects of NO induced by iNOS and produced with pathology. The dual roles of NO have resulted in much confusion about the NO mechanism in pain production and reduction.

Future plans include studying comparative pain relief with MIRE at 890 nm and other modalities versus controls in people with OA, because positive clinical outcome measures have been demonstrated in preliminary studies. Our hope is that physicians and others will want to join this clinical and academic pursuit, to discover whether MIRE at 890 nm can provide a nonpharmacologic intervention that prevents pain; leads to better outcomes, including positive changes in health-related quality of life; and, perhaps, improves OA pathology, when combined with conventional, established PT interventions.

ACKNOWLEDGMENTS

The authors thank Tom Burke, PhD (retired, University of Colorado Medical School, Denver, CO), for thoughtful and pertinent suggestions during the early drafts of the paper. Additionally, the authors thank Michelle Bergman (Craig Hospital, Englewood, CO) for her technical assistance with illustrations.

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