Evidence for the efficacy of pain medications

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About the Council

Founded in 1913 and chartered by Congress, the National Safety Council (nsc.org) is a nonprofit organization whose mission is to save lives by preventing injuries and deaths at work, in homes and communities, and on the road through leadership, research, education and advocacy. NSC advances this mission by partnering with businesses, government agencies, elected officials and the public in areas where we can make the most impact – distracted driving, teen driving, workplace safety, prescription drug overdoses and Safe Communities.

Overview

Opioids have been used for thousands of years in the treatment of pain and mental illness. Essentially everyone believes that opioids are powerful pain relievers. However, recent studies have shown that taking acetaminophen and ibuprofen together is actually more effective in treating pain. Because of this, it is helpful for medical professionals and patients to understand the history of these opioid medications and the potential benefits of using nonsteroidal anti-inflammatory drugs (NSAIDs) instead.

Extracted from the seedpod of the poppy plant, opium was the first opioid compound used for medicinal purposes. The active ingredients of opium are primarily morphine, codeine, and thebaine. Opium and its derivatives have had more impact on human society than any other medication. Wars have been fought and countless lives have been lost to the misuse, abuse and overdose of opioids. It is also clear, however, that many received comfort from pain when there was no other alternative. For thousands of years, opium products provided the only effective treatment of pain and were also used to treat anxiety and depression. Tolerance, dependence, and addiction were identified early as a problem with opioids.

In 1899, the Bayer Company produced and introduced aspirin for wide distribution. It became the first significant alternative to opioids for treating pain. Aspirin not only relieves pain but also reduces inflammation and is in the class of NSAID medications. Aspirin was commonly used for mild pain such as headache and backache. Other NSAID medications followed with the development of ibuprofen in 1961, indomethacin in 1963, and many others over the next 20 years. While these drugs are not addictive or habit-forming, their use and effectiveness were limited by its side-effects and toxicity. All NSAID medications share some of the same side-effects of aspirin, primarily the risk of gastrointestinal irritation and ulcer. These medications can also adversely affect renal function.

Acetaminophen was created in 1951 but not widely distributed until 1955 under the trade name Tylenol®. Acetaminophen is not an opioid nor an NSAID. Tylenol soon became another medication that was useful in the treatment of pain, offering an alternative to the opioid medications and to aspirin. Acetaminophen avoids many of the side effects of opioids and NSAIDs but carries its own risk with liver toxicity.

Efficacy in acute pain

Since the development of acetaminophen, medical professionals have had the choice of three different classes of medications when treating pain. Those decisions are usually made by considering the perceived effectiveness of each medicine and its side effects along with the physical status of the patient. For example, acetaminophen should not be taken by someone with advanced liver damage, NSAIDs should not be given to an individual with advanced kidney disease or stomach ulcers, and opioids pose a potential risk to anyone with a personal or family history of addiction.

Although many have long been believed that opioids are the strongest pain medications and should be used for more severe pain, scientific literature does not support that belief. There are many other treatments that should be utilized for treating pain. Studies have shown NSAIDs are just as strong as the opioids.

Number Needed To Treat When considering the effectiveness or the strength of pain medications, it is important to understand one of the statistical measures used in clinical studies: the number needed to treat (NNT). NNT is the number of people who must be treated by a specific intervention for one person to receive a certain effect. For example, when testing pain medications, the intervention is the dose of pain medication and the effect is usually 50 percent pain relief. Fifty percent relief of pain is considered effective treatment, allowing people increased functional abilities and an improved quality of life (Cochrane.org, 2014). So the question becomes, how many people must be treated with a certain dose of a medication for one person to receive 50 percent pain relief (effective relief)?

A lower NNT means the medicine is more effective. A product with an NNT of 1 means that the medicine is 100 percent effective at reducing pain by 50 percent - everyone who takes the medicine has effective pain relief. A medicine with an NNT of 2 means two people must be treated in order for one to receive effective relief. Or, alternatively, one out of two, or 50 percent, of people who take the medicine get effective pain relief. An example of a medicine that would not be a good pain reliever would be one with a NNT equal to 10. In such a case, you would have to treat 10 people for one to receive effective pain relief.

Basically, the medication with the lowest NNT will be the most effective. For oral pain medications, an NNT of 1.5 is very good and an NNT of 2.5 would be considered good.

Organizations that have reviewed treatment of acute pain

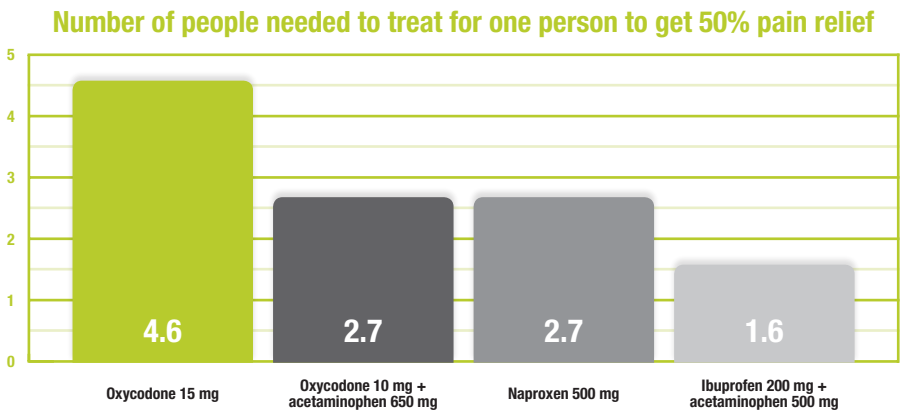
The Cochrane Collaboration Several organizations have examined the comparative effectiveness of the oral medications. The Cochrane Collaboration is one of those organizations. Its website reads that it is:

"A global independent network of health practitioners, researchers, patient advocates and others, responding to the challenge of making the vast amounts of evidence generated through research useful for informing decisions about health. We are a not-for-profit organisation with collaborators from over 120 countries working together to produce credible, accessible health information that is free from commercial sponsorship and other conflicts of interest." (Cochrane.org, 2014)

The Cochrane Collaboration is highly respected globally for its scientifically rigid, independent reviews.

Several Cochrane reviews have examined the treatment of postoperative pain. Postoperative pain is often studied because it is an example of acute pain where there has been tissue trauma resulting in pain. It also occurs in a controlled environment (hospital or medical office) where rigorous experimental protocols can be followed. The results of these reviews are as follows:

- **Oxycodone 15 mg:** The NNT is 4.6. Since it is hard to conceptualize 4.6 people, consider that you would have to treat 46 people for 10 to get 50 percent relief of their pain. Thirty-six of those 46 people would not get adequate pain relief. (Gaskell, Derry, Moore, & McQuay, 2009)
- **Oxycodone 10 mg + acetaminophen 650 mg:** The NNT for this combination treatment (Equivalent to two 5 mg Percocet pills) is 2.7. Clearly this is better than oxycodone alone. Acetaminophen adds significant benefit. (Gaskell et al., 2009)
- **Naproxen 500 mg (or naproxen sodium 550 mg):** The NNT for this is also 2.7. Naproxen is not an opioid. It is an NSAID medication. Naproxen sodium is known to many as the brand name over-the-counter (OTC) medicine Aleve®. (C Derry & Derry, 2009)
- **Ibuprofen 200 mg + acetaminophen 500 mg:** The combination of these two OTC medicines provided the best pain relief of all, with an NNT of 1.6. (CJ Derry, Derry, & Moore, 2013)



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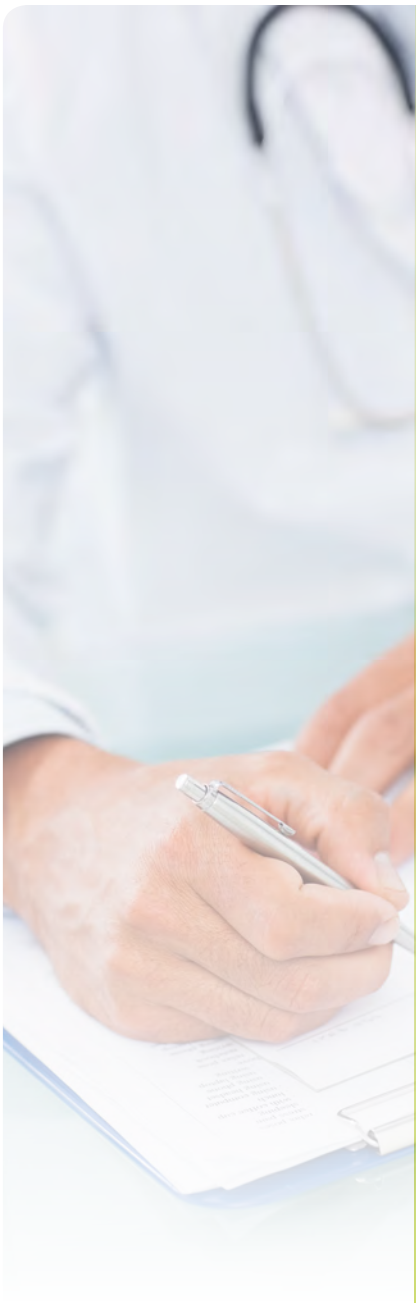

Bandolier Bandolier is an independent organization in Europe that produces reports on evidence-based medicine. In 2003, Bandolier issued a report on the treatment of acute pain. Its evaluation compared many studies and concluded that the opioid medications were no more effective than the NSAIDs (Bandolier, 2003). In 2007, Bandolier produced a table comparing the efficacy of many different oral and injectable medications for pain. The below excerpt from that table shows the relative strengths of some commonly used medications. Notice that an injection of 10 mg of morphine is roughly equivalent to an oral dose of OTC ibuprofen.

Medication	Type of medication	# of patients studied	NNT
Diclofenac 100 mg	Prescription NSAID	545	1.8
Celecoxib 400 mg	Prescription NSAID	298	2.1
Ibuprofen 400 mg	Prescription NSAID	5456	2.5
Naproxen 400 mg	Prescription NSAID	197	2.7
Ibuprofen 200 mg	OTC NSAID	3248	2.7
Oxycodone 10 mg + acetaminophen 1000 mg	Prescription opioid	83	2.7
Morphine 10 mg intramuscular	Injectable opioid	948	2.9
Oxycodone 5 mg + acetaminophen 325 mg	Prescription opioid	149	5.5
Tramadol 50 mg	Prescription opioid	770	8.3

(Bandolier, 2007)

Types of acute pain

Dental pain A recent review article in the *Journal of the American Dental Association* addressing the treatment of dental pain following wisdom tooth extraction concluded that 325 mg of acetaminophen (APAP) taken with 200 mg of ibuprofen provides better pain relief than oral opioids. Moore et al. concluded, "The results of the quantitative systematic reviews indicated that the ibuprofen-APAP combination may be a more effective analgesic, with fewer untoward effects, than are many of the currently available opioid-containing formulations." (Moore, 2013, p. 898)

Back pain A recent review article in *The Spine Journal* looked at multiple treatment options for the treatment of sciatica – back pain with a pinched nerve with symptoms radiating down one leg. They found that non-opioid medications provided some positive global effect on the treatment of this disorder, while the opioids did not. When looking at the symptom of pain, opioids appeared to have no significant effect. The non-opioid medications did appear to have a positive effect on the pain, but these results did not reach statistical significance. (Lewis et al., 2013)

Radcliff et al. looked at patients who received opioids initially for treatment of lumbar disc herniation compared with those who did not. They found that those receiving opioids had a higher rate of surgery and that, overall, there was no significant difference four years later. Opioid medications were associated with an increased crossover to surgical treatment. Four years after the initiation of treatment, 16 percent of those who received opioids at the start were still on opioids, whereas only 5 percent of those who were treated with non-opioids initially were on opioids after four years. They concluded that those who were initially treated with opioids had a higher rate of surgery and a greater chance of being on opioids four years later but no significant change in overall outcome (Radcliff et al., 2013).

Severe pain Few studies have been done to determine the effectiveness of various medications in severe pain after extensive trauma. However, the Cochrane Collaboration has conducted a review of the most effective treatments for renal colic pain. This happens when a kidney stone gets stuck in the ureter leading from the kidney to the bladder, obstructing the flow of urine. Many consider renal colic to be one of the most severe pains humans experience. The Cochrane Collaboration concluded that NSAIDs and opioids are both effective. The review does mention that "(10 out of 13) studies reported lower pain scores in patients receiving NSAIDs." NSAIDs also had fewer side effects and required fewer rescue medications, or additional pain medication. (Holdgate & Pollock, 2004)

In summary, regarding acute pain, it is frequently stated that NSAIDs and acetaminophen should be used for mild to moderate pain, and opioids should be used for severe pain. There is, however, no scientific evidence to support this recommendation. In fact, the evidence seems to indicate that NSAIDs are more effective for severe pain. The combination of acetaminophen and an NSAID may be the strongest option available for oral treatment of acute pain.

Treating chronic pain

Despite the widespread use of opioid medications to treat chronic pain, there is no significant evidence to support this practice. A recent article reviewing the evidence regarding the use of opioids to treat chronic non-cancer pain concluded, "There is no high-quality evidence on the efficacy of long-term opioid treatment of chronic nonmalignant pain." (Kissin, 2013, p. 519)A recent Cochrane review comparing opioids to placebo in the treatment of low back pain came to a similar conclusion. This review said that there may be some benefit over placebo when used for short term treatment, but no evidence supports opioids are helpful when used for longer than four months. Although there is some benefit over placebo when used short term, there is no evidence of benefit over non-opioid medications when used for less than four months. (Chaparro et al., 2014)

Several other reviews have also concluded that no evidence exists to support long term use – longer than four months – of opioids to treat chronic pain. (Kissin, 2013; Martell et al., 2007; McNicol, Midbari, & Eisenberg, 2013; Noble et al., 2010)

Epidemiologic studies have also failed to confirm the efficacy of chronic opioid therapy (COT) for chronic non-cancer pain. A large study from Denmark showed that those with chronic pain who were on COT had higher levels of pain, poorer quality of life, and were less functional than those with chronic pain who were not on COT. (Eriksen, Sjøgren, Bruera, Ekholm, & Rasmussen, 2006)

In the last 20 years in the U.S., we have increased our consumption of opioids by more than 600 percent. (Paulozzi & Baldwin, 2012) Despite this increase, we have not decreased our suffering from pain. The Burden of Disease study in the *Journal of the American Medical Association* (JAMA) showed that Americans suffered as much disability from back and neck pain in 2010 as they did in 1990 before the escalation in the prescribing of opioids. (Murray, 2013) A study in JAMA in 2008 found that "Despite rapidly increasing medical expenditures from 1997 to 2005, there was no improvement over this period in self-assessed health status, functional disability, work limitations, or social functioning among respondents with spine problems." (Martin et al., 2008, p. 661)

It is currently estimated that more than 9 million Americans use COT for the treatment of chronic nonmalignant pain (Boudreau et al., 2009) When we consider the proven benefits of this treatment along with the known risks, we must ask ourselves how we can ethically continue this treatment.

The reality is we really don't know if COT is effective. Anecdotal evidence and expert opinion suggest it may be beneficial in a few, select people. However, epidemiologic studies suggest that it may be doing more harm than good.

Terminal care

The treatment of incurable cancer, end stage lung disease, and other end-of-life situations are notable examples where opioid medications are absolutely indicated. Although opioid pain killers are not very good medications for the treatment of pain, they are very strong psychotherapeutic agents. They are excellent at relieving anxiety and treating depression for a limited time. Opioids cause beneficial changes to brain serotonin, epinephrine, norepinephrine, dopamine, and endorphins. For short-term, end-of-life situations, these neuropsychiatric effects are likely beneficial.

For terminal care, opioids are the medications of choice.

How did we get here?

So why do so many in both the general public and medical field believe opioids are so much stronger? Here are likely reasons:

1. When given intravenously, opioids have no ceiling effect. Higher doses given intravenously have powerful psychotherapeutic effects allowing the patient to relax or sleep. Unfortunately, the side effect of respiratory depression also gets worse with increasing doses and will limit the amount that can be used unless the patient is closely monitored or on a ventilator.
2. The powerful psychotherapeutic effects of opioids help relieve the emotional distress of pain. These psychotherapeutic effects are likely much stronger than the pain relieving effects. (The opium wars were not fought because of pain relieving effects.) Pain is usually associated with significant emotional distress. Unfortunately, those individuals who have the most emotional distress are more likely to become addicted.
3. The WHO pain ladder. In 1986, the World Health Organization convened a panel of experts to recommend the best way to treat cancer pain. The result was the WHO pain ladder. It recommends that practitioners use NSAIDs and acetaminophen for mild cancer pain but then change to weak or strong opioids for more severe pain, or if NSAIDs and acetaminophen are not effective. While many pain specialists reference the WHO pain ladder regarding effective treatment of pain, it is noteworthy that these recommendations are based on expert opinion (the weakest source of recommendation) and intended for *cancer* pain. (Vargas-schaffer, 2010)
4. The pharmaceutical companies have done a good job marketing opioids, so many doctors have come to believe opioids are actually stronger than other medications. (Van Zee, 2009)

Safety

Safety of NSAIDs, acetaminophen and opioids will be thoroughly addressed in a future white paper. The paper will explain that NAIDS and acetaminophen are safer than the opioids. When taken in over-the-counter doses, ibuprofen and acetaminophen have safety profiles approaching placebo.(Rainsford, Roberts, & Brown, 1997)

Conclusion

The opioid medications are often referred to as "powerful painkillers." In fact, the evidence shows that they are mild to moderate painkillers and less effective than over-the-counter ibuprofen. They have, however, powerful side effects that harm hundreds of thousands of individuals every year in the U.S. Even if one disregards the public health problems created by the use of opioid pain killers, these medications still are not a good choice for the treatment of acute pain – regardless of the severity. In some situations, limited use is appropriate. But in the majority of situations in which opioid painkillers are used today, they are not appropriate. The standard of care in the practice of medicine today is to provide the best treatment that causes the least harms. When there is a treatment that is proven to be both more effective and safer, it is the treatment of choice.

The implication of this data for policymakers is critical. By implementing policy that puts restrictions on opioid prescribing to protect public health, policymakers will also improve the treatment of pain by guiding prescribers to use medications that are more effective.

It is also important for the medical and dental communities to address this inadequate and unsafe treatment of pain and change practice standards to guide care that is more appropriate for what our patients need and deserve.

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