The Psychological and Physical Side Effects 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

Opioid medications have been used for thousands of years to treat both pain and mental health problems. In the past 20 years, a resurgence of opioid prescribing in the United States has risen to unprecedented levels – increasing by more than 600% (Paulozzi & Baldwin, 2012). The United States consists of 4.6% the world's population and yet we consume 80% of the world's opioids (Solanki, Koyyalagunta, Shah, Silverman, & Manchikanti, 2011).This has been associated with a concomitant increase in admissions for treatment of opioid dependence and opioid overdose deaths (C. M. Jones, Mack, & Paulozzi, 2013). Though this increase in prescribing may be due to multiple reasons, a major cause is the belief medical professionals hold that opioids are generally safer than many alternatives including nonsteroidal anti-inflammatory medications (NSAIDs). This white paper will show that opioid medications are, in fact, very dangerous and should be used only after wise discernment and with great care.

Opiates are medications extracted from opium which comes from the poppy plant. The only true opiates are morphine, codeine, and thebaine. Opioid medications, are derived from or produce the same effect as opiates and include the semisynthetic opioids such as oxycodone, hydrocodone, oxymorphone, hydromorphone and heroin as well as the entirely synthetic medications: methadone, fentanyl, tapentadol and tramadol. The term opioids will be used throughout this paper as it includes all of the medications of concern.

Opioid side effects

Opioid medications have multiple psychological and physical side effects. However, often, medical providers do not fully consider the negative side effects when prescribing. Some of the opioid side effects are as follows:

Gastrointestinal

- **Constipation.** Constipation frequently occurs when taking opioid medications. Opioids slow down the normal peristaltic action of the intestines. Constipation may occur in as many as 40-95% of people (Benyamin et al., 2008). There is a prescription medication now that exclusively treats constipation secondary to opioid use.
- **Nausea and vomiting**. Nausea and vomiting are common side effects of opioid medications and also occur because of the reduced peristaltic activity of the stomach and small intestine. Nausea and vomiting may occur in 25% of people (Swegle & Logemann, 2006).
- **Gastrointestinal bleeding**. GI bleeding is commonly associated with NSAID medications and may also occur from opioids. Solomon et al showed that in the elderly using opioids, the incidence of upper gastrointestinal bleeding was 14 per 1000 patient years. This rate was identical to those on NSAID medications (Solomon et al., 2010).

Impaired recovery from injury or surgery

Opioids are often used to reduce pain to enhance recovery from injury or surgery. It has been commonly believed that by reducing pain in patients, they will resume activity more quickly and rehabilitative efforts will be more effective. However, the literature has shown that this is not true. Opioids following an injury delay recovery and increase the risk of permanent disability.

In a study of Workers Compensation claims for low back pain, Webster et al showed that even after controlling for injury severity, increasing opioid doses correlated with increasing length of disability. In other words, for those with equivalent injuries and levels of pain, those with no opioids did better than those with higher dose opioid treatment. The same study showed that opioids increased the risk of future back surgery (Webster, Verma, & Gatchel, 2007).

A study by Franklin et al showed that opioids prescribed within 6 weeks of injury *doubles* the risk of disability one year later (Franklin, Stover, Turner, Fulton-Kehoe, & Wickizer, 2008). In this study, after correcting for the severity of the pain, Franklin et al found that the use of opioids is a major risk factor for future disability: an important finding that should be considered before prescribing an opioid for acute pain.

Opioids taken before and after surgery can affect recovery and outcome. Patients taking opioids prior to back surgery have been shown to have worse outcomes with increased pain, decreased function and increased depression (D. Lee et al., 2014).

Those taking opioids prior to total knee replacement also have worse outcomes (Zywiel, Stroh, & Lee, 2011)

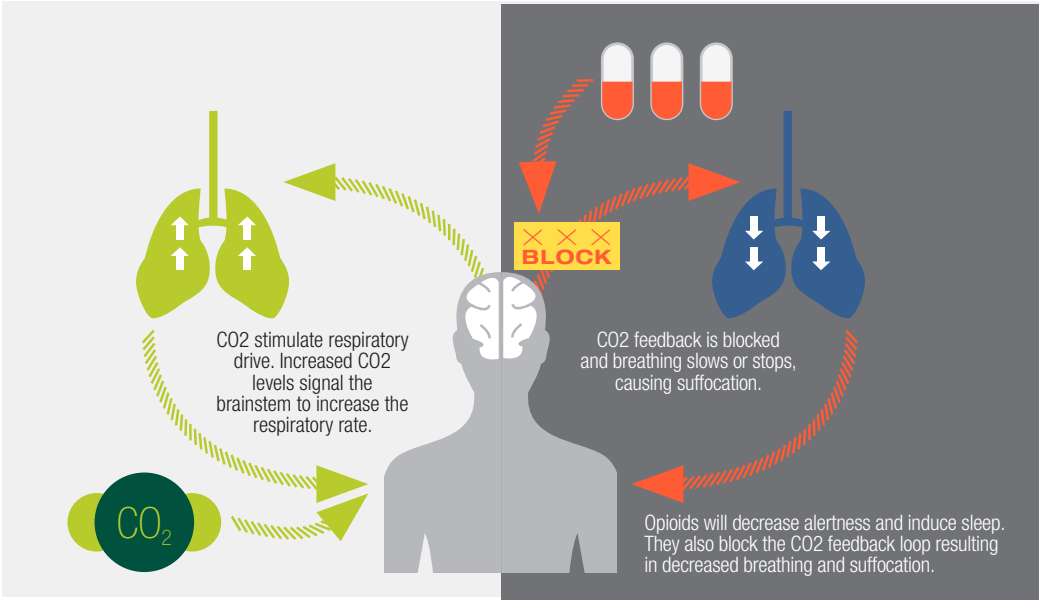
Opioids used following surgery are known to delay recovery. Modern surgical and postoperative procedures are designed to, among other things, reduce the use of opioids to speed recovery. Excessive pain, however, also has an adverse effect on recovery. It is, therefore, imperative to utilize a multimodal approach to pain relief and minimize the use of oral and long-acting opioids (Varadhan, Lobo, & Ljungqvist, 2010).

Cognitive impairment The effect of opioid medications on cognition is a complicated topic, and the following summary should not be considered an extensive review of the literature.

It is well known that larger doses of opioids are markedly impairing, leading to drowsiness, lethargy, and even death. The data on the effects of doses commonly used for the outpatient treatment of pain is more complex, because pain itself may compromise cognitive function. Therefore, studies evaluating the effect of opioids on cognitive abilities compared to healthy controls may not be representative of their effect on people in pain. However, as opioids impair cognitive abilities in healthy people (Cherrier, Amory, Ersek, Risler, & Shen, 2009) and people in pain experience cognitive impairment, it is reasonable to assume that those with pain who are on opioids likely have some cognitive impairment. At least one prospective study has demonstrated that those with chronic pain on opioid therapy have cognitive deficits including reduced spatial memory capacity and impaired performance in working memory assessment (Schiltenwolf et al., 2014).

Respiratory depression Opioids adversely affect the respiratory system. Carbon dioxide (CO2) levels in the blood stimulate our respiratory drive. As breathing slows down, CO2 levels increase, which stimulates the brainstem to increase the respiratory rate. Low oxygen levels do not stimulate breathing so sensitivity to CO2 levels is an important function of nerve cells in the brainstem. Opioids block that feedback loop. When an individual overdoses on an opioid, the high levels of opioid will decrease alertness and induce sleep. During sleep, it is the CO2 feedback loop that keeps people breathing but when blocked by the high levels of an opioid, breathing slows or stops and the person who has overdosed literally suffocates.

The effect of opioids on the respiratory system



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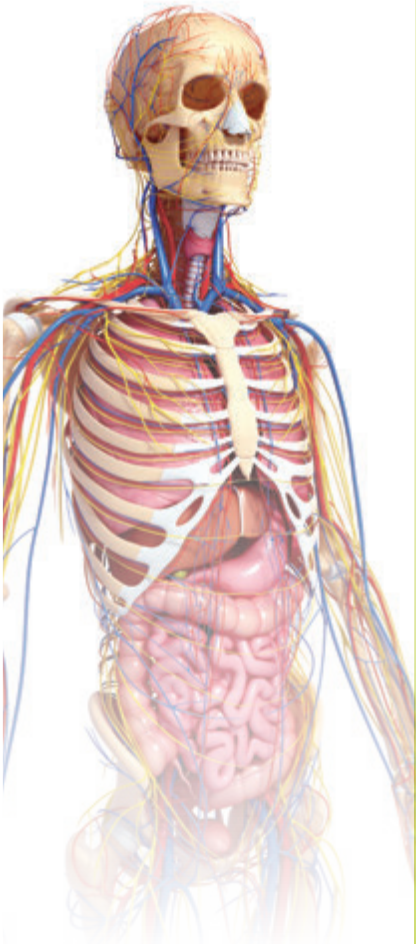


This is also problematic for individuals with lung disease or sleep apnea. People with chronic lung disease often need elevated carbon dioxide levels to stimulate them to breathe more deeply. Taking opioids will blunt this response, causing people with lung disease to breathe slower and therefore have low oxygen levels.

Sleep apnea is similar as people periodically stop breathing at night until their carbon dioxide levels get high enough to stimulate their brain to signal them to gasp for breath. When opioids interfere with this response the effect can be life threatening. Opioids have been shown to worsen the apnea episodes in those with sleep apnea (Jungquist, Flannery, Perlis, & Grace, 2012).

Endocrine – hypogonadism Chronic use of opioid medications can lead to several endocrine abnormalities. The most significant abnormality is a decrease in the production of gonadotropin releasing hormone (GNRH). This is the chemical that stimulates our body to produce sex hormones (estrogen and testosterone). A decrease in GNRH lowers sex hormone levels for both men and women. These low hormone levels will occur in over 50% of people on chronic opioid therapy (Reddy, Aung, Karavitaki, & Wass, 2010). Persistent low sex hormone levels produce multiple symptoms, which may include "loss of libido, infertility, fatigue, depression, anxiety, loss of muscle strength and mass, alteration of gender role, osteoporosis, and compression fractures and, in men, impotence, and, in females, menstrual irregularities, galactorrhea and infertility"(Katz, 2005). Another study found sex hormone levels were 30-70% lower in women on chronic opioid therapy compared to those who were not on opioids (Daniell, 2008).

Hyperalgesia Opioid-induced hyperalgesia (OIH) is another side effect of the use of opioid medications. Opioid hyperalgesia is a phenomenon where the body develops an *increased* sensitivity to pain secondary to opioid use (hyper – over or excess, algesia – sensitivity to pain). Pain is an important part of our body's defense system, warning us of current or impending damage or injury. As opioids decrease our brain's sensitivity to pain signals coming from the rest of the body, our brain begins to compensate by increasing our recognition of and sensitivity to pain. The pain neurons going to the brain actually change to make them more responsive to pain and increase our perception of pain. This change is called neuroplasticity of the nerve cell. Many mechanisms are believed to be involved in these changes (M. Lee, Silverman, Hansen, Patel, & Manchikanti, 2011). The result of this change is that after opioid levels decrease, our pain fibers are more sensitive than before consuming the opioid which results in an increase in pain.

Though the frequency of opioid-induced hyperalgesia is unknown, it is believed to be fairly common, and significant. Even after IV use of remifentanil (a very short acting opioid that is given intravenously) during surgery, postoperative patients had more pain and needed more opioids compared to those who did not receive this medication (Kim, Stoicea, Soghomonyan, & Bergese, 2014).

Patients who are on opioids for pain prior to orthopedic surgery have higher levels of pain and higher opioid needs after surgery suggesting OIH (D. Lee et al., 2014; Zywiel et al., 2011).

Opioid hyperalgesia presents clinically with increasing pain in a patient on opioids. Unfortunately, increasing pain can also mean disease progression or the development of tolerance to the current opioid dose. For these conditions, opioid doses are usually increased. In contrast, the treatment of opioid hyperalgesia is the decrease or discontinuation of opioids. Even experts in pain management may have difficulty recognizing and treating this complication appropriately.

Opioid use in the elderly A number of organizations have made recommendations for the treatment of pain in the elderly, many supporting the use of opioids because of concerns regarding side effects of the NSAID medications. The American Geriatric Society's pain treatment recommendations state the following:

> Nonselective NSAIDs and COX-2 selective inhibitors may be considered rarely, and with extreme caution, in highly selected individuals." Whereas their recommendation for opioids states: "All patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy. (Ferrell, Argoff, & Epplin, 2009. pg 1341 and 1342).

In fact, the use of opioids in the elderly is very risky. Solomon et al reviewed Medicare claims in Pennsylvania and New Jersey from 1999 through 2005. They evaluated medical outcomes in individuals who were taking one of three classes of medication: a nonselective NSAID, a COX-2 inhibitor NSAID (these are a special type of NSAID that do not have as many stomach complications. The only one available today is celecoxib – Celebrex®), and an opioid for pain. Their findings were remarkable. They found that compared to those taking a nonselective NSAID, those taking opioids experienced:

- A greater risk of having a cardiovascular event
- Equal rates of GI bleeding
- Four times as many fractures
- 68% greater risk for being hospitalized for an adverse drug event
- 87% greater risk of dying during the study period.

These were indeed surprising results but clearly showed that the opioid pain medications are very risky in the elderly; they should be used with extreme caution and only after extensive consideration and discussion regarding the likelihood of an adverse event (Solomon et al., 2010).

Solomon et al also showed that the risk of falls in the elderly taking opioids for pain increased by 64% compared to those taking NSAIDs. The risk of fracture of the humerus (the bone in the upper arm) was nine times greater for those on opioids. The risk of fracture of the hip was 3 times greater for those on opioids (Solomon et al., 2010). In a more recent study, Rolita et al showed that the risk of fall and fracture in the elderly was 3-4 times greater in those on opioid pain medications for control of the pain of osteoarthritis compared to those taking NSAIDs (Rolita, Spegman, Tang, & Cronstein, 2013). This is important because complications of hip fracture are a leading cause of death in elderly women, and up to half of elderly adults hospitalized for hip fracture never return to their previous level of function (Tinetti & Williams, 1997).

Brain Changes A number of studies have shown that significant changes to the brain that can occur with the use of opioid medications to treat pain. Younger et al showed that when individuals with chronic low back pain were administered oral morphine daily for 1 month, they had significant changes in the volume of several critical areas of the brain (some got bigger and some got smaller) compared to those who received placebo. Even after stopping the morphine and measuring for up to 4.7 months later, these changes persisted (Younger et al., 2011).

Other studies have shown that there are neuronal changes that occur with opioid use. These begin to occur early after opioid initiation and affect our response to opioids and the behavior associated with that response. These neuroplastic changes can begin as early as 24 hours after exposure to morphine (Dacher & Nugent, 2011).

Tolerance and withdrawal Tolerance occurs when the body has developed physiologic (both neuroplastic and chemical) changes that result in decreased effectiveness of the medicine necessitating a higher dose to get the same effect. Withdrawal is the unpleasant symptoms that develop upon decrease or discontinuation of that medicine. Brain changes and measurable withdrawal symptoms can occur after one dose of opioid medication (Rothwell, Thomas, & Gewirtz, 2012). In clinical practice, withdrawal symptoms can occur after five to seven days of opioid medication (Anand et al., 2010). Withdrawal symptoms may consist of myalgia (muscle pain), chills, sweats, anxiety, increased pain, rapid heartbeat, dilated pupils, yawning, diarrhea and nausea. Withdrawal is extremely unpleasant and can be relieved by taking another opioid dose. Tolerance and withdrawal are not considered addiction. Tolerance occurs because of the physiologic changes resulting from exposure to opioids. Withdrawal is the unpleasant physical and emotional symptoms that occur upon withdrawal of the opioid after tolerance has developed.

Morphine Milligram Equivalent (MME) is a convenient way to compare opioids of different strengths. Oxycodone, for example, is about **50% more potent** than morphine so **1 mg of oxycodone is equal to 1.5 mg of morphine** and therefore is said to be **1.5 MME**. 5 mg of oxycodone = **7.5 MME.**

$55.6 billion cost per year in 2007. **301 million** citizens in 2007. **$184.72** per person. **700 MME/ person** (Paulozzi & Baldwin, 2012). Calculates to **26 cents per MME.**

Addiction According to the American Society of Addiction Medicine:

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

> Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death. (American Society of Addiction Medicine, 2011)

Addiction is not a moral weakness but is a complex disease in which genetic predisposition, exposure to opioids, social stress, and mental health status all play a role. Some individuals believe that they were essentially addicted after their first dose – even if prescribed by a medical provider (Doe, 2012).

Death There is one factor that is often not considered when prescribing opioid pain medications – the overall increase in deaths. Opioids account for more deaths than any other medication. More than 16,000 people die every year from opioid overdose, which compares to about 3000 from upper GI bleeding from NSAID medications. Because of the illicit use of these medications, we have a situation that is unique to the opioids and other controlled substances, many of those who die are collateral deaths; these individuals were never prescribed the medication that killed them (C. Jones, Paulozzi, & Mack, 2014). The medical ethical principle of non-maleficence (do not harm) now extends beyond the exam room: the interaction between a physician and his/her patient may adversely affect the life and health of someone else who is not a part of the medical decision.

Opioids may lead to an increase in deaths that are frequently attributed to other causes. Opioid abuse often progresses to intravenous use, which may result in HIV or hepatitis C infections. Impairment from opioid medications may lead to unintentional death by motor vehicle crashes or workplace safety incidents. Opioid use may also lead to falls and increase mortality rates in the elderly.

It is also important to realize that the risk of death is markedly increased when opioids are taken with benzodiazepine medications. The combination of opioids and benzodiazepines are the leading cause of overdose deaths when multiple medications are involved (Calcaterra, Glanz, & Binswanger, 2013). Despite this danger, benzodiazepines are prescribed to about 30% of people on chronic opioid therapy (Nowak, Abou-Nader, & Stettin, 2014).

Side effects to society Unintentional death is one of many significant societal side effects related to the prescription of opioid medications. The diversion of opioid medications and the crime associated with that diversion are a significant problem for law enforcement and the public in many areas of our country. The sheriff in one North Carolina county in the southern Appalachian Mountains believes that the abuse of opioid medications accounts for at least 80% of the crime in his area (Christopher, 2014). Initially, the Appalachian Mountains and rural America were hard-hit but now the problem is pervasive in all areas of our society.

Opioids contribute to increased medical costs for patient care when used instead of non-opioid treatment of pain (White, Tao, Talreja, Tower, & Bernacki, 2012). Furthermore, treatment of those who are abusing or addicted to opioids is costly (Birnbaum et al., 2011).

Private businesses and industry lose a significant amount of money from the prescribing of prescription opioids. Opioid pain medications increase the cost of Workers Compensation and increase disability (Franklin, Rahman, Turner, Daniell, & Fulton-Kehoe, 2009; White et al., 2012). Even more problematic is the loss of worker productivity. A study in 2011 estimated that there was $55.6 billion in societal costs including $25 billion in workplace related costs secondary to opioid abuse (Birnbaum et al., 2011).

Every single prescription results in significant cost to society. Using the estimation of $55.6 billion per year for the societal cost of opioids, equals about 26 cents/morphine milligram equivalent (MME). A bottle of 20 Percocet (5mg) tablets would total 150 MME with a cost to society of about $39 (150 x .26).

Another significant cost to society is the marked increase in heroin use over the past few years. A recent study by the CDC showed of 28 states surveyed, heroin deaths doubled from 2010 to 2012 (Rudd et al., 2014). Four out of five heroin users started with prescription drugs (Muhuri, Gfroerer, & Davies, 2013). Typically, individuals will start misusing opioid pain pills, and when their habit becomes unaffordable (commonly $100-200 per day) they change to heroin, a cheaper alternative that produces the same effect (Mars, Bourgois, Karandinos, Montero, & Ciccarone, 2014). Heroin trafficking is becoming a major driver of crime in many communities. The IV use of heroin is leading to increasing rates of Hepatitis C.

Side effects of other pain medications

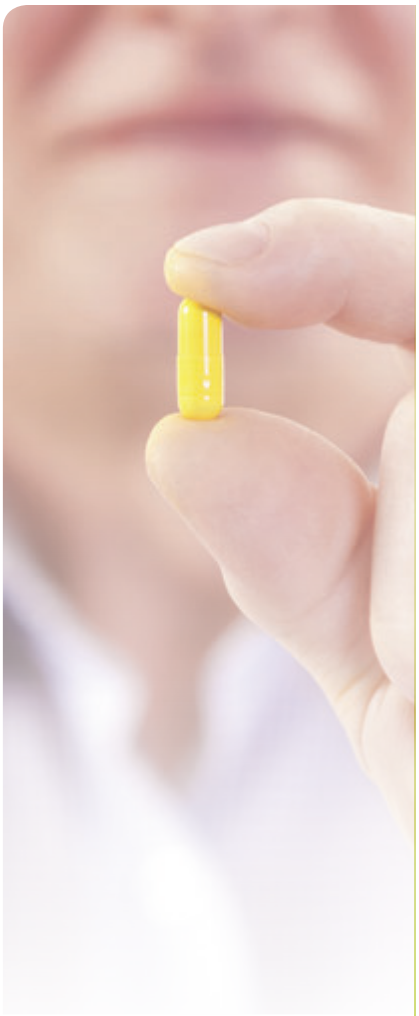
Nonsteroidal anti-inflammatory drugs (NSAIDs) Medical providers are always cautious when prescribing NSAID medications. This caution is appropriate as these medications can have several adverse reactions that can be life-threatening. Unfortunately, our fear of NSAID-related side effects contributes to our overprescribing of opioids. An examination of these side effects reveal that NSAIDs can be utilized safely – with caution.

Gastrointestinal side effects of NSAIDs NSAIDs are known to cause upper gastrointestinal irritation and bleeding. Approximately 3200 people die every year from GI bleeds secondary to the use of NSAIDs (Tarone, Blot, & McLaughlin, 2004). However, with some caution, NSAIDs can be used as a first or second line agent for pain. Lower doses of NSAIDs are less likely to cause GI bleeding. 200 mg of ibuprofen taken four times a day has the pain-relieving efficacy of 10 mg of morphine four times a day (Bandolier, 2007) and a side effect rate similar to placebo (Rainsford, Roberts, & Brown, 1997). If there is significant concern for GI complications, NSAIDs can be taken with a proton pump inhibitor (PPI) such as omeprazole (Prilosec®) to greatly decrease the risk of bleeding. Celecoxib may also be taken to reduce the risk of bleeding. Taking celecoxib with a PPI has a bleeding risk that is similar to placebo (Chan et al., 2007; Roth, 2012). Celecoxib now comes in a generic formulation and is getting much more affordable for patients.

Renal side effects of NSAIDs NSAIDs may also have a detrimental effect on kidney function. Medical providers are rightfully worried about recommending NSAIDs to anyone with an elevated creatinine. (Creatinine is a blood test that measures kidney function.) This detrimental effect is worse with some NSAIDs than it is with others. The renal effects of NSAIDs are dose-related. Lower doses are safer. The 200 mg dose of ibuprofen is very safe and can be used for a short duration even for those with moderate or severe renal insufficiency and acute pain (Nderitu, Doos, Jones, Davies, & Kadam, 2013).

Cardiac side effects of NSAIDs NSAIDs do have significant cardiac effects and should be used with caution in those with coronary artery disease. They appear to increase the risk of cardiovascular events in those with known heart disease and those at high risk for heart disease (Bhala et al., 2013). NSAIDs also interfere with aspirin, clopidogrel, and other blood thinners (Lamberts et al., 2014) and they should be used only after a thorough discussion of risks and benefits when there are no better options. Opioids also increase the risk of cardiac events and death and are not an appropriate alternative in the elderly (Solomon et al., 2010). Acetaminophen may be the safest pain reliever for those with known cardiac disease or those at risk.

Bone healing There is concern among physicians treating trauma that NSAIDs may delay healing after fracture, an appropriate concern since inflammation is an important

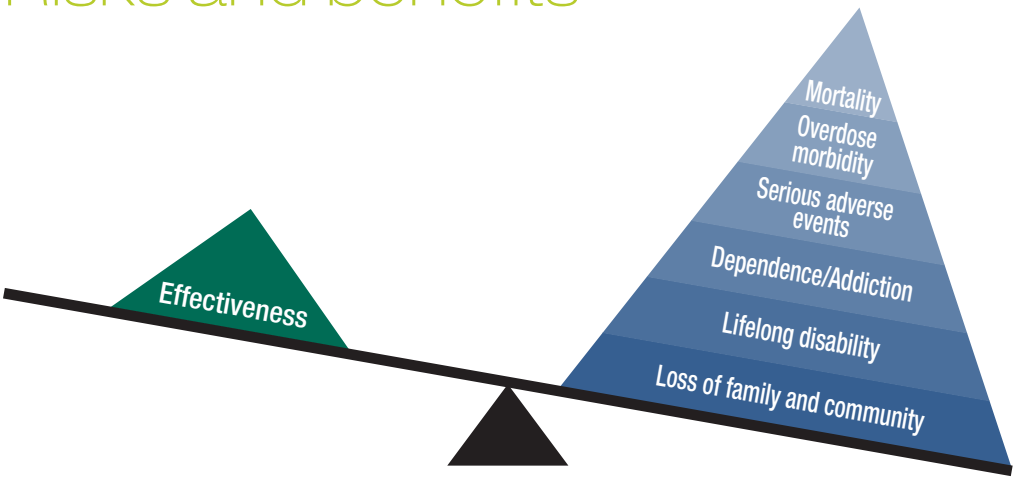


component of bone healing. Reduction of inflammation may impair the healing process. Some studies have confirmed that NSAIDs may have a small negative effect on healing but others have questioned this (Carley, 2005). Opioids may also have a negative effect on bone healing. As discussed previously, opioids decrease GNRH causing hypogonadism which is associated with decreased healing after fracture (Brinker, O'Connor, Monla, & Earthman, 2007). Animal studies have also shown that opioids impair healing after fracture (Chrastil, Sampson, Jones, & Higgins, 2013). These studies have not yet been done in humans.

The final answer on the effect of NSAIDs still eludes us. While some reviewers believe that NSAIDs should be used with great caution after fracture (Geusens, Emans, De Jong, & Van Den Bergh, 2013), others believe that NSAIDs are safe and have little or no effect on fracture healing (Kurmis, Kurmis, O'Brien, & Dalen, 2012; Taylor, Lindblad, & Kolber, 2014).

Acetaminophen Acetaminophen is likely the safest of all of the medications used for pain and is approximately as strong as the oral opioids (Gaskell, Derry, Moore, & McQuay, 2009; Toms, McQuay, Derry, & Moore, 2008), providing acceptable pain relief (Toms et al., 2008). While acetaminophen can cause liver damage when used in higher doses for prolonged periods of time, it is more likely to cause liver damage in individuals who are ingesting other liver-toxic drugs (alcohol in particular). For those with a healthy liver, 4000 mg per day or less is generally considered safe.

Risks and benefits



With an estimated 100 million people in the United States suffering from pain it is appropriate for treatment of pain to be a major health concern for our country (IOM, 2011). In an effort to improve pain treatment, medical providers have markedly increased their prescribing of opioids; consequently there has been a marked increase in abuse, overdose, and death.

There are potential side effects with all medications used to treat pain. For the past 20 years, medical professionals have had great concern regarding the side effects of NSAID medications and acetaminophen while largely ignoring the side effects of opioid medications. All medications must be used only after careful consideration and balancing of their risks and benefits. The NSC white paper, *Evidence for the Efficacy of Pain Medications* (nsc.org/painmedevidence), detailed why opioids are not more effective than NSAIDs for pain relief. Given that fact, along with the side effects described in this paper, it is very seldom that the benefit is worth the risk.

Conclusion

After considering the side effects of various pain medications in this paper, the evidence is clear that opioids are dangerous medications that should only be used with great caution when all other options have failed. In select circumstances, opioids may be used first-line for brief periods of time.

Call to Action

With this evidence of the opioid side effect profile and the knowledge of their limited effectiveness in relieving pain (Teater, 2014), the following actions are recommended:

- Medical providers should re-evaluate their prescribing habits. Opioids should be used rarely, only when indicated, and for a few days.
- Dental providers should rarely prescribe opioids and limit the prescription to 1-2 days.
- Public agencies, insurance companies, and pharmacy benefit managers should put restrictions on the use of these medications.
    - As tolerance and withdrawal can occur within 5 days of starting opioid therapy, any prescription over 5 days should require prior approval (Honey, Benefield, Miller, & Johnson, 2014).
    - Routine dental procedures, back pain, headaches, fibromyalgia and injuries that do not require hospitalization should require preapproval (Franklin, 2014).
- Insurance companies should develop mechanisms to facilitate non-drug treatment of pain including appropriate physical therapy and counseling.
- Everyone on chronic opioid treatment should have periodic evaluation to assess the risk of opioid-related side effects.

We need to change the paradigm of how we treat pain in this country. In the process, we will reduce the suffering from pain, save money, and save lives.

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