

10 Pain Medication Myths

Challenges In Selecting the Appropriate Analgesic

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In recent years, an avalanche of evidence against opioid and nonsteroidal anti-inflammatory drug (NSAID) use has been published in medical journals, leading many physicians to re-evaluate the risk-to-benefit ratio of these medications. Nearly all publications in the past 5 years have either reported negative results or highlighted additional risks.

With such a clear focus on the negative aspects of these drugs, some providers have begun to raise several areas of concern. They question the medications' place in therapy; they wonder how to use them appropriately; and—perhaps most importantly—they are asking what safe analgesic therapies are left for their patients. Unfortunately, misinformation is pervasive, and this widespread uncertainty has resulted in greater difficulty interpreting new evidence and deciding on optimum pain-control regimens.

This commentary provides clarity on 10 analgesic medication myths selected by the authors.

Myth Number 1: NSAIDs Are More Dangerous Than Opioids

to GI bleeds annually was 7,215—of which less than half are typically attributable to NSAID use.⁶ This number is often compared with the data on opioid overdoses—15,597 deaths in 2009.⁷

But, in fact, only a single study directly compared toxicity between the 2 medication classes in a population that was predominantly older women (mean age 80 years).⁸ Because studies have shown the elderly (>65) are at 2 to 3 times increased risk of GI bleeds compared to younger patients, the survey should have reflected higher NSAID toxicity.^{8,9} However, compared to NSAIDs, opioids had an all-cause mortality hazard ratio of 1.87, with increased risk of hospitalization for adverse events, including risk of fracture, CV events, and bowel obstruction—all increased compared to NSAIDs.⁸

A number of additional factors contribute to NSAID toxicity and further skew the data. Sixteen percent of the population use NSAIDs and aspirin together chronically, which has been shown to double the risk of GI bleeds, and nearly 30% of GI bleeds are associated with aspirin use alone.^{4,10,11} In addition, 29% of the population believe that OTC NSAID use is safer than prescription NSAID use, and 40% of prescription NSAID users report taking OTC NSAIDs in addition to their prescription NSAIDs.^{12,13}

One major weakness with comparing opioid and NSAID toxicity is that opioid use and attributable mortality is tracked very closely, yet NSAID toxicity is based upon estimates. While risk of GI bleeds attributable to NSAID use has been studied, the increased risk of thromboembolic events or progression toward end-stage renal disease (ESRD) from NSAIDs is not yet clear. It is important to remember, however, that FDA recommendations are based on a meta-analysis of high-dose NSAID therapy, the results of which indicated increased CV risk was likely dose dependent as cyclooxygenase (COX)-1/COX-2 selectivity is lost at higher doses.^{13,14}

Despite these limitations, the prevalence data make it reasonably clear that NSAIDs are more widely used with lower mortality than opioids, despite rampant inappropriate NSAID use. Clinicians in all practice areas can make a significant difference by counseling patients to recognize the risks of all NSAID use in GI and CV disease. They should further counsel patients to avoid concomitant use of prescription and OTC NSAIDs and aspirin, and should provide strategies for gastric protection, if appropriate.

Myth Number 2: Extended-Release Opioids Are More Dangerous Than Immediate-Release Opioids

Is 30 mg of extended-release morphine somehow more potent than 30 mg of immediate-release morphine? And if not more potent, then does blunting the maximum concentrations (C_{max}) by slowly releasing the same amount of medication over a period of 10 to 12 hours (rather than immediate onset within 1-2 hours and elevated C_{max}) make it more dangerous? Conceptually, the idea is absurd. Yet interpretation of several studies recently has endorsed those exact conclusions.^{15,16}

Studies have shown an increased risk of adverse effects in patients on extended-release opioids. However, these studies often define chronic pain inappropriately and/or do not adjust for post-surgical pain and acute pain prescriptions. Chronic pain patients tend to be on opioids much longer than acute pain patients, and there is no question that longer exposure will lead to increased adverse effects.

Similarly, data from a recent study points out that the rate of overdose increases dramatically in the first 2 weeks of treatment with extended-release opioids. This led the authors to the inappropriate conclusion that the dosage form itself is more dangerous, and that short-acting opioids should be used if possible.¹⁵ This erroneous conclusion should have been recognized as an obvious struggle by today's health care providers with appropriate equianalgesic conversions when performing opioid rotations.^{17,18}

Increased doses due to lack of familiarity with some extended-release dosage forms is far more dangerous than the dosage form itself. For this exact reason, guidelines for chronic opioid therapy

recommend finding the correct dose with immediate-release opioids prior to conversion to an extended-release regimen. Also, patients receiving extended release opioids tend to be on higher doses and are sicker, with many comorbidities. Often, they are also on concomitant therapies, including benzodiazepines, compared with acute pain patients on immediate release opioids, who might otherwise be young and healthy.

The old adage, “start low and go slow,” continues to be the safest way to approach initiation, titration, or rotation of pain medications. This is an instance when clinicians can have a tremendous impact and save lives through expertise developed in performing accurate equianalgesic conversions, as well as educating others on dose reduction for cross-tolerance and identifying dangerous unintentional dose increases.

Myth Number 3: NSAIDs Should Be Stopped 7-10 Days Prior to Surgery or Interventional Procedures



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Discontinuation of NSAIDs 7 to 10 days prior to surgery (or procedures) is commonplace—but not evidenced-based. Stopping NSAIDs analgesics 1 week prior to interventional procedures is counterintuitive considering that NSAIDs mitigate the pain for which the intervention is indicated.

This recommendation reflects concerns about perioperative bleeding risk and assumes all NSAIDs have the same risk of bleeding as aspirin.¹⁹ But aspirin is highly selective for COX-1 and binds to Ser529, acetylating the NSAID binding site, thus causing irreversible inhibition that impacts platelets more than other cell types. This is because they are anucleated and remain inhibited for their entire life cycle (7-10 days).²⁰

Relatively low doses of aspirin (<81 mg) used chronically result in nearly total platelet inhibition.²⁰ All other NSAIDs bind reversibly and therefore result in increased risk of bleeding—but only for the time they are actively bound to the catalytic site, which depends on various factors. These include binding affinity, protein binding, COX selectivity, and terminal half-life.²¹ There are more than 6 distinct chemical classes of NSAIDs, each with unique characteristics and significant differences in clinical efficacy and tolerability.²²

In the absence of evidence for true bleeding risk of each NSAID, it is recommended that discontinuation prior to a procedure or surgery be made based upon pharmacology and pharmacokinetics. For example, NSAIDs with short half-lives like ibuprofen (2 hours) or diclofenac (2.3 hours) would be completely eliminated after 5 half-lives and less than 24 hours.

Even NSAIDs with longer half-lives like meloxicam (15-20 hours) or naproxen (12-17 hours) would be completely eliminated within 4 to 5 days.¹⁹ The American Society of Regional Anesthesia and Pain Medicine and the American College of Chest Physicians' evidence-based guidelines recommend using 5 elimination half-lives as the basis for discontinuation prior to a procedure or surgery.^{23,24}

While many surgeons and interventionalists no doubt believe caution is appropriate, many pain patients rely upon NSAIDs for mobility, and discontinuation for even a few days unnecessarily and significantly impacts their daily lives.²⁵ We should be advocating for individualized patient care rather than one-size-fits-all medicine.

Myth Number 4:

Naloxone in Suboxone Prevents Abuse When Used Off-Label for Pain

The naloxone component of Suboxone (buprenorphine with naloxone) was approved as a maintenance therapy for patients with opioid-abuse disorder. Adding naloxone to the formulation was intended as abuse deterrent technology to discourage intravenous abuse, but its effects are minimal and short-lived. Both naloxone and buprenorphine can induce withdrawal if administered while taking a pure μ -opioid agonist.²⁶

Suboxone contains a 4:1 ratio of buprenorphine to naloxone, giving buprenorphine a concentration advantage that is largely unnecessary for opioid dependence.²⁷ Buprenorphine has 2 to 3 times higher binding affinity for the μ -opioid receptor compared with naloxone, and a half-life that is 7 times longer.²⁸⁻³¹ Even when abused intravenously, the only advantage naloxone has over buprenorphine (in binding to opioid receptors) is faster absorption. This is due to buprenorphine's unique pharmacodynamic profile, which results in very slow binding kinetics with slow association (30 minutes) and extremely slow (166 minutes) and incomplete dissociation (50%) from opioid receptors, making displacement by other opioids nearly impossible.³² Upon arrival at the receptor site, buprenorphine easily displaces naloxone—essentially making naloxone unnecessary. Therefore, the abuse-deterrent advantage of naloxone is short-lived.

For example, buprenorphine displaces an equal concentration of fentanyl from 90% of opioid receptors. But unlike fentanyl, it takes 40 times the concentration of naloxone to reverse.³¹ Suboxone 2 mg/0.5 mg results in 36% to 50% receptor saturation, and 16 mg/4 mg results in 79% to 95% saturation of opioid receptors by buprenorphine.

One study allowed participants to challenge Suboxone (given at various doses) with IV hydromorphone

24 mg. The results of the study found that Suboxone 16 mg was highly effective at drastically decreasing euphoria in 75% of patients.³³ The delayed receptor binding kinetics are believed to contribute to decreased euphoria with buprenorphine, as compared to pure μ -opioid agonists. But it's clear that naloxone cannot block or remove buprenorphine from exerting its pharmacologic effects.

Buprenorphine's superior pharmacology and kinetic profile confers the abuse deterrence associated with Suboxone and not the naloxone packaged with it.

**Myth Number 5:
Butrans Patches Can Increase a Patient's QTc Interval**



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The buprenorphine transdermal delivery system (BTDS) has not been shown to increase QTc intervals to a clinically significant level at doses below 40 mcg per hour. Frankly, the FDA's judgment not to allow doses greater than 20 mcg per hour is both highly questionable and overly conservative.

The current FDA-approved package insert states that 40 mcg per hour (2 x 20 mcg/h) patches resulted in mean change in QTc prolongation of 9.2 ms (range, 5.2-13.3—anything greater than 5 ms is considered positive), whereas the results reported in the trial itself had QTc mean prolongations of 6.01 ms (3.2-8.8) when calculating the difference from placebo.^{34,35} However, the placebo arm of the study showed increases in QTc as high as 5.7 ms, which is beyond the threshold of concern cited by current FDA guidance. Should we ban placebo from trials as a comparator based on this "evidence"?³⁴

This question does become clinically significant for another reason—in essence, it severely limits the use of a highly useful dosage form, particularly for patients who struggle with compliance but have legitimate pain complaints. To illustrate, BTDS has been available internationally since 2001 and is widely used in Europe in a variety of dosage forms (35 mcg/h, 52.5 mcg/h, and 70 mcg/h). The lowest dose available internationally, therefore, is higher than highest dosage form currently available in the United States.³⁶

It is also important to keep relative buprenorphine dose in perspective. Sublingual products that contain buprenorphine are available in 2 formulations: Subutex (buprenorphine alone: 2 mg and 8 mg. Note: Subutex is no longer available, but generic version of buprenorphine are on the market) and Suboxone (buprenorphine/naloxone: 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, and 12 mg/3 mg). The 2 mg sublingual dose of Suboxone is roughly equivalent to the 20 mcg per hour patch, when factoring 30% absorption.²⁷ This seems to imply that sublingual buprenorphine, which is commonly used at doses between 16 and 32 mg per day, is being treated differently than transdermal products simply because the intended population is different.

Many studies evaluating QTc prolongation of sublingual buprenorphine compared to methadone are available. Suboxone is often recommended as an alternative to methadone for maintenance therapy when a person's QTc is greater than 500 ms—placing patient at risk for torsades de pointes (TdP) and sudden death.³⁷ In fact, it's rare, even in long-term studies of buprenorphine, to see mean QTc prolongation greater than 12 ms (+/- 4.1) despite high-dose therapy (16-32 mg), or QTc intervals greater than 450 ms without some genetic abnormality or drug interaction, particularly with chromosome P450 (CYP) 3A4 inhibitors—neither of which are routinely assessed in clinical practice.³⁸⁻⁴⁰

The decision to enforce such a low threshold of QTc prolongation needs to be re-examined with emphasis on clinical relevance because this becomes a significant barrier to drug approvals. The FDA plans sweeping changes to the drug approval process for opioids, yet many of the medications we currently rely upon would not be approved in the current environment, indicating it may be time to re-examine certain FDA decisions.⁴¹

Myth Number 6:

Opioids Do Not Work for Neuropathic Pain

Studies have refuted the above claim, showing that certain unique opioids, such as methadone, levorphanol, tramadol, and tapentadol, do have a benefit in the treatment of neuropathic pain.⁴²

All 4 of these medications exhibit opioid agonist activity, thus classifying them as opioid medications. However, each of these medications also exhibits an additional unique mechanism of action that becomes useful in the treatment of neuropathic pain.

Methadone and levorphanol both antagonize *N*-methyl-D-aspartate (NMDA) receptors and inhibit the reuptake of norepinephrine. NMDA receptor antagonists, including memantine, ketamine, orphenadrine and others, have been shown to successfully treat neuropathic pain.^{43,44} These studies suggest that if a pure NMDA antagonist, such as ketamine, can improve neuropathic pain, medications such as methadone and levorphanol should have similar benefits.^{45,46,47}

Tramadol and tapentadol both inhibit the reuptake of norepinephrine.⁴⁶ Norepinephrine has been demonstrated in non-opioid medications, including the serotonin-norepinephrine reuptake inhibitor duloxetine, to have a role in the treatment of neuropathic pain.⁴⁸ The role of norepinephrine in the treatment of neuropathic pain was demonstrated by Max et al. In that study, patients with neuropathic pain had better pain relief when treated with desipramine and amitriptyline, compared with fluoxetine or placebo—the efficacy of which was attributable to noradrenergic reuptake blockade.⁴⁹

These results can also be applied to opioid medications that have norepinephrine activity in the treatment of neuropathic pain. Therefore, atypical opioids with multimodal mechanisms of action should most certainly be utilized in the treatment of neuropathic pain.

This does not answer, however, whether drugs like morphine and oxycodone are ineffective for neuropathic pain. We do not believe opioid monotherapy is appropriate or especially effective for neuropathic pain. Clinically, we have observed that opioid monotherapy seems effective temporarily (a few months) but tolerance is developed much faster than it should be, and doses tend to escalate much faster than when these agents are utilized for discogenic or musculoskeletal pain.⁴² The author (TA) runs a high-risk clinic where most (90%) of the high-dose opioid (>300 mg/d MEDD) patients have had dose escalation in an attempt to manage an element of neuropathic pain.

Myth Number 7:

Tapentadol Increases the Risk of Serotonin Syndrome

The utility of compounds that block the reuptake of norepinephrine have already been identified as beneficial in the treatment of chronic pain.⁴⁹ Tapentadol has 2 mechanisms of action: opioid agonist and norepinephrine reuptake inhibitor. Both mechanisms allow tapentadol to provide benefits to patients with neuropathic pain.^{50,51} Unlike tramadol, which inhibits reuptake of both norepinephrine and serotonin, tapentadol has limited interaction with serotonin transporter proteins and minimal effect upon serotonin reuptake. A compound without serotonergic activity would carry no risk of contributing to serotonin syndrome.⁵² Therefore, the risk of serotonin syndrome is drastically reduced and nearly nonexistent with the use of tapentadol.⁵³

The package insert states: “Potentially life-threatening serotonin syndrome has occurred with concomitant use of tapentadol and serotonergic agents or agents that impair metabolism of serotonin.” But these are case reports from post-marketing studies and therefore do not have a black-box warning for serotonin syndrome.⁵⁴ A paper by Nossaman et al states there is a risk of serotonin syndrome with both tramadol and tapentadol; however, all 8 studies that were referenced to make this claim include the use of tramadol, not tapentadol.⁵⁵ While the package insert for tapentadol does warn against serotonin syndrome, the simple fact is that the evidence is lacking, both chemically and clinically.

Myth Number 8: Methadone Is a Long-Acting Opioid

As noted above, methadone has both opioid receptor agonist activity and NMDA receptor antagonist activity, creating a distinct pharmacologic profile. Methadone has been demonstrated to be useful in the treatment of chronic pain and neuropathic pain, and has a role in the medical management of substance-use disorders.⁵⁶ However, the unique pharmacokinetic properties of methadone present dosing and titration challenges to many prescribers.

Looking at the pharmacokinetics of the drug can easily refute the argument of whether or not methadone is a long-acting opioid. Methadone has a very long serum half-life (24-36 hours, with outliers as long as 60-150 hours).⁴⁵ A serum half-life is not the same as duration of action. Methadone’s onset of action is within 30 minutes to 2 hours, and due to the long serum half-life, methadone can build up slowly in a patient’s tissue, which can be falsely interpreted as “prolonged duration of action.”

Methadone is not a long-acting or extended-release medication, and this is reflected in its daily dosing of usually 3 to 4 times per day.^{45,57,58} However, due to its extended half-life, these unique properties allow methadone to be stopped abruptly without a significant risk of precipitating acute-onset withdrawal. Additionally with methadone, if patients experience withdrawal symptoms, those symptoms usually appear 3 to 5 days later, not 2 to 3 days later as with other opioids—reflecting the drug’s long half-life.⁵⁹ Finally, while the onset is similar to most opioids, the duration of analgesia is not (6-12 hours). This further lends evidence to the need for multiple daily dosing and to the potential of reaching toxicity with frequent dosage increases.^{59,60}

Myth Number 9: Topical NSAIDs Increase Risk of CV Disease and GI Bleed



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As noted, the FDA has twice taken action to increase awareness of the increased risk of adverse CV and GI events. These events may occur at any time during therapy and without warning. The risk for serious events is greater in elderly patients.⁶¹ These actions raise the question of whether these same warnings can be applied to topical formulations of NSAIDs.²

To best answer this question, the NSAID diclofenac, which exists in many dosage forms, can be used. A typical dose for diclofenac tablets is 50 mg by mouth 3 times daily. This dose generates a C_{max} of 2270 ng/mL. The higher the drug's C_{max} , the greater the toxicity observed. In comparison, diclofenac gel generates a C_{max} of 58.3, which is nearly 40 times lower than that generated by the tablet.⁶² Moreover, the serum levels are so low and the percent of bound diclofenac to albumin is so high that the level of drug available to cause toxic effects at any given time is miniscule.

To date, no cases have been reported involving any topical of nonsalicylate NSAID leading to a toxic effect that is assigned to the NSAID class. Further research is needed to support the claim that, even at small serum concentrations, patients exposed to chronic topical NSAIDs have an increased risk for CV disease.

Myth Number 10: NSAIDs Lead to Increase of Bone Fusion Time and Decreased Healing Rate

This claim lacks conclusive evidence to support NSAID therapy delaying bone healing. Current literature on this topic only exists in animal models such as rabbits, dogs, goats, mice, and rats. These results cannot be extrapolated to humans, and, furthermore, the longest study conducted in animals was only 12 weeks. Fractures can take months to heal, and therefore these animal studies do not provide conclusive evidence that short-term NSAID use has any effect on long-term bone healing.

Additionally, in 2008, Scott Ruben, MD, significantly advanced this argument and published over 20 papers regarding positive results with the use of COX-2 selective NSAIDs in orthopedic surgery patients. However, this argument was revealed to contain falsified data.⁶³ These events further contributed to the negative association of the use of NSAIDs in the postoperative patient.

Review articles conducted by Pountos et al, Vuolteenaho et al, and Kurmis et al concluded that research on this topic is lacking and further data is needed to conclude whether or not NSAID therapy leads to an increase in time to bone fusion.⁶⁴⁻⁶⁶

Conclusion

Much of the increased risk and many of the adverse effects suspected with these medications can be addressed through appropriate monitoring or counseling by providers. Furthermore, providers who follow their patients closely can help dispel myths surrounding these medications.

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