NSAIDs and Bone Healing

Data both support and refute the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the healing process following musculoskeletal or orthopedic injury.\(^1\)–\(^5\)

**Orthopedic Effects of NSAIDs**\(^3\)

- NSAIDs inhibit prostaglandins, which leads to a reduction in pain and inflammation.
- Bone healing and the formation of new bone may be inhibited by NSAIDs due to reduction of prostaglandin’s effects on osteoclasts and osteoblasts.

**Gastrointestinal Effects of NSAIDs**\(^3\)

- COX-1 inhibition reduces cytoprotective prostaglandins present in the stomach lining which enhances GI adverse effects of NSAIDs.
- Theoretically, COX-2 selective NSAIDs should have less GI adverse effects by not inhibiting the COX-1 pathway, but minimal COX-1 activity is possible and may lead to some GI adverse effects.
- Non-selective NSAIDs are more likely to cause GI adverse effects due to inhibition of both COX-1 and COX-2.

**Evidence supporting impairment in bone healing with NSAIDs**

In rats, there was a higher incidence of nonunion and reduced bone healing post-operatively with celecoxib when compared to acetaminophen (APAP).\(^2\) None of the rats in the APAP and control (methylcellulose) groups had a nonunion; most (73%) had a complete union of the fractured bone. In the celecoxib groups, 26% of rats had a nonunion, and only 21% had a complete union. The differences between the celecoxib groups and the APAP and control groups were statistically significant. These results support the argument that NSAID treatment for pain following acute orthopedic injury can lead to inhibition of healing at fracture site.\(^2\)

In humans, NSAIDs demonstrated a reduced fusion rate in a retrospective study from 1989 to 1994.\(^5\) Total of 83 patients underwent spinal fusion surgery and 73 patients were followed for almost 4 years post-surgery. Patients taking NSAIDs for more than 3 months had a fusion rate of 37%. Patients not taking NSAIDs post-operatively had a fusion rate of 93%. NSAID use post-operatively in orthopedic injuries may significantly reduce healing of fusion rate and new bone growth.\(^5\)

**Evidence to refute impairment in bone healing with NSAIDs**

In rats, there was no difference between selective COX-2 inhibitors and non-selective COX inhibitors in fracture healing after musculoskeletal injury.\(^4\) Neither parecoxib nor diclofenac treatment inhibited bone healing when administered for 7 days after injury and compared to saline control. All fractures healed by forming a callous in all 3 treatment groups. No nonunion or fracture reduction occurred.\(^4\)

Where do we go from here?

The lack of published evidence in prospective human studies makes it difficult to draw a definitive conclusion on whether NSAIDs inhibit healing after a musculoskeletal injury. Variables that may affect healing outcomes with NSAID treatment:

- Drug – Which agent is used?
- Dose – High or low?
- Duration – short- or long-term?
- Demographics – age, race, gender

Studies describe a reduction in healing with NSAIDs, making it important to assess the benefit versus risk in treating certain patients with NSAIDs following acute orthopedic injury.\(^1\)–\(^5\)

NSAIDs have many potential adverse effects, especially gastrointestinal. In certain patient populations, it may be clinically reasonable to choose other methods of analgesia.

**By Holly Anderson, PharmD Candidate**

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Vedolizumab is indicated for the treatment of moderate to severe Crohn’s disease and ulcerative colitis in adult patients with inadequate response, loss of response, or intolerance to standard therapy (corticosteroids, immunomodulators, or TNF-α inhibitors) or in patients with corticosteroid dependence. Vedolizumab is used to achieve and maintain clinical response and remission in these patients.

The GEMINI program is a series of vedolizumab studies. Three double-blind, placebo-controlled trials have been completed. The GEMINI I trial enrolled 895 patients with ulcerative colitis, while the GEMINI II and III trials studied patients with Crohn’s disease (n=1115 for GEMINI II; n=416 for GEMINI III). The open-label GEMINI-LTS trial, studying long-term treatment with vedolizumab, is currently ongoing.

The GEMINI I and II trials each included an induction phase and a maintenance phase. In the induction phases, patients were randomized to receive either vedolizumab 300 mg or placebo at 0 and 2 weeks or open-label vedolizumab treatment. In the maintenance phases, patients who responded to vedolizumab at week 6 were randomized to receive placebo or vedolizumab 300 mg at 0, 2, and 6 weeks. At week 6, the remission rate was similar between groups; however, the clinical response rate was greater in the vedolizumab group. At week 10, both remission and clinical response rates were significantly greater with vedolizumab compared to placebo.

**Limitations of the GEMINI trials**

The results of the GEMINI studies are limited by the set duration of induction therapy. Although 6 weeks was effective, a longer induction period may be better. Rare, serious adverse effects such as progressive multifocal leukoencephalopathy (PML) may not have occurred in the studies because the trial durations were too short or the number of patients may not have been large enough; therefore, the risk of these adverse effects is unknown.

In the GEMINI I and II trials, adverse events occurred in 52% of vedolizumab patients and in 45% of placebo patients. The most common adverse events were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, and cough. Hypersensitivity reactions, infections, liver damage, and progressive multifocal leukoencephalopathy are potential severe adverse events with vedolizumab treatment.

Patients should be monitored for these adverse events.

Vedolizumab was effective at inducing clinical response and remission in patients with moderate to severe Crohn’s disease and ulcerative colitis. The GEMINI-LTS study will provide more useful information on the long-term safety and efficacy of vedolizumab treatment.

**By Andrea Friend, PharmD Candidate**

**REFERENCES:**

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Movantik™ (naloxegol) for Opioid-Induced Constipation

 Constipation is the most common gastrointestinal side effect associated with opioid use and can decrease patients’ quality of life.¹ Naloxegol, a newly approved oral medication, antagonizes the peripheral mu-opioid receptors, lessening opioid-induced constipation.²,³ Naloxegol does not alter centrally-mediated analgesia produced by opioids.² The PEGylated chemical moiety of naloxegol is a P-gp substrate, which decreases its penetration of the blood-brain barrier.²

Contraindications²,³
- Naloxegol should not be used in patients with or at risk for gastrointestinal obstruction.
- Naloxegol should not be used with strong CYP3A4 inhibitors which will inhibit the metabolism of naloxegol.
- Naloxegol should not be used in patients with hypersensitivity reactions to naloxegol.

Renal & Hepatic Dose Reductions²,³
- In patients with a CrCl < 60 mL/min, the naloxegol dose should be reduced to 12.5 mg daily. If the reduced dose is tolerated, then the naloxegol dose can be increased to 25 mg daily.
- No adjustments are necessary for mild to moderate hepatic impairment; however, naloxegol should not be used in patients with severe hepatic impairment, as its safety in this population has not been established.

Safety & Efficacy¹

Design: Two identical randomized, double-blind, multicenter, placebo-controlled, phase three clinical trials

Inclusion: Both trials included patients who were 18-84 years of age and were taking 30-1000 mg of morphine or morphine equivalents daily for non-cancer pain for at least 4 weeks prior to study enrollment. Patients had symptoms of active opioid-induced constipation. Investigators confirmed active constipation upon review of the diary after two weeks, then randomized patients to study treatments.

Treatments: Patients were randomized to receive naloxegol 25 mg (n=446), naloxegol 12.5 mg (n=445), or placebo (n=446) once daily for 12 weeks. Rescue laxative treatment (bisacodyl and an enema if needed) was allowed for patients who did not have a bowel movement for 72 hours.

Primary Endpoint: Response rate during the 12-week treatment period for both studies. Response was defined as three or more spontaneous bowel movements weekly in addition to an increase in one or more spontaneous bowel movements from baseline for at least 9 of the 12 treatment weeks and at least 3 of the 4 final weeks of treatment. Bowel movements were not included if they occurred within 24 hours of rescue laxative treatment.

Results: Naloxegol 25 mg treatment resulted in an increased response rate compared to placebo in both studies (44.4% vs. 29.4% and 39.7% vs. 29.3%). The 12.5 mg dose group had a significantly greater response rate in one study, but not the other. In patients with inadequate response to laxative treatments, the response rate was still higher with naloxegol 25 mg compared to placebo (48.7% vs. 28.8% and 46.8% vs. 31.4%).

Adverse events (with an incidence of 5% or greater): abdominal pain, diarrhea, nausea, flatulence, vomiting, upper abdominal pain, back pain, and headache. More serious adverse related events include gastrointestinal perforation and symptoms of opioid withdrawal.

Conclusion: Naloxegol was safe and effective compared to placebo for the treatment of opioid-induced constipation in adult patients with non-cancer pain.

Study Limitations: The use of rescue laxative treatment may have affected the results, although bowel movements within 24 hours of rescue treatment were not included in the response rate. The subjective ratings for diagnosis of opioid-induced constipation may have biased the study results. In addition, bowel movements were recorded by the patients in daily electronic diaries and failure to document bowel movements may have under- or overestimated the efficacy of naloxegol.

By Cara Laslovich, PharmD Candidate

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A concussion is a mild traumatic brain injury where the brain smashes into the skull as a result of a bump or jolt to the head or if the lower body is shaken violently. Concussions are common in contact sports such as football, basketball, or soccer. Most concussions are not life-threatening but can be serious. Also, if you have suffered from one concussion, you are at greater risk for having another.

Symptoms of a concussion generally fall into 4 categories: thinking, physical, sleep, and emotional (see table below). These effects may be short lived, lasting days to weeks; however, they can occur months to years after the initial injury.

You may miss early symptoms because most people do not know they have suffered a concussion. Concussions can also be missed because symptoms may occur hours after the initial injury.

When should you seek medical attention? Go to an emergency department if any of these signs are present:
- Very drowsy or if someone cannot wake you up
- Pupil in one eye is larger than the other
- Experiencing seizures
- Cannot recognize people or places
- Increasing confusion, anxiety, or agitation
- Any unusual behavior
- Loss of consciousness

Medications that increase bleeding (such as Coumadin® [warfarin], Plavix® [clopidogrel], and aspirin) can be especially dangerous in a concussion due to bleeding in the brain. Contact the emergency department if you are currently taking these medications and a concussion is suspected.

A physical examination will be performed to test reflexes and mental status. The healthcare provider may also check the nose and ears for any signs of bleeding. A CT scan may also be used to rule out any bleeding in the brain.

How is a concussion treated?

The brain will recover on its own. Most concussions get better in 7-10 days. Time and rest are the two main focuses of concussion recovery. No optimal time has been decided on. Rest for the brain does not simply mean sleep. Things that can stimulate your brain should be avoided, like TV, video games, cell phones, or computers.

Most other treatments are for symptoms—take Tylenol® (acetaminophen) for headaches, ice any lumps on the head, and treat any cuts that may have occurred. Athletes should not return to play until they have been cleared by a healthcare provider. Recovery is a slow progression of physical and mental activities until they can be performed without symptoms. Avoid anything that may cause a jolt or bump to the head.

What are the effects of a concussion?

See table below for short-, medium-, and long-term effects of concussions. Second impact syndrome (SIS) may also occur after a concussion. SIS results when concussions recur without enough time to heal between injuries. SIS can lead to the swelling of the brain, coma, and even death.

By Caelon Vecchio-Miller, PharmD Candidate

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<th>PHYSICAL</th>
<th>EMOTIONAL</th>
<th>SLEEP</th>
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<tr>
<td>Cannot think clearly</td>
<td>Headache, fuzzy or blurred vision</td>
<td>Feeling irritable</td>
<td>Sleep more than normal</td>
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<tr>
<td>Feeling slower than normal</td>
<td>Nausea and vomiting or dizziness</td>
<td>Feeling sad</td>
<td>Sleep less than normal</td>
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<tr>
<td>Difficulty concentrating</td>
<td>Difficulty balancing, sensitive to light and sound</td>
<td>Feeling more emotional than usual</td>
<td>Difficulty falling asleep</td>
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<tr>
<td>Having a hard time remembering new information</td>
<td>Feeling run down or no energy</td>
<td>Feeling nervous or anxious</td>
<td>Difficulty waking up</td>
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<table>
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<tr>
<th>Concussion Consequences:</th>
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<td><strong>Short-Term</strong></td>
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<td>These side effects usually last a few days but can last up to 10 days.</td>
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<tr>
<td>Symptoms: Headaches</td>
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<tr>
<td>Sleep disturbances</td>
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<tr>
<td>Difficulty paying attention</td>
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<tr>
<td>Lethargy</td>
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<tr>
<td>Sensitivity to light or sound</td>
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### NSAIDs References (from page 1)


### Vedolizumab References (from page 2)


### Concussion References (from page 4)


Basic Facts about Brand and Generic Drugs

Brand Drugs:
- Are new chemicals discovered and made by a drug company
- Go through many different steps of testing in animals then humans to prove the drug is safe and effective
- Require at least two different approvals from the FDA before being sold
- Take many years (and a lot of money) to create and test
- Are given several years of “patent protection” saying other companies can’t make a generic
- Aren’t always successful—about 6 drugs fail to get approval for every 1 drug that makes it to market

Generic Drugs:
- Are not new chemicals (same active ingredient as the brand drug)
- Have a faster, one-step approval through the FDA
- Do not have to go through the long animal and human testing period (since the brand drugs already did)
- Only have to be “as good” as the brand drug
- Can be made by many different companies (unlike the brand drug), leading to competition and lower prices for the public

Why Are Brand Drugs So Expensive?
It takes billions of dollars and many years to create a new brand drug. During the patent-protected time, the drug will cost more money because the drug company needs to earn back the extra money it spent on research. Without competing companies to lower prices, the price of these new brand drugs can be very high. This may seem unfair to the patient, but what if this system was different?

New system: Other companies can make “generic” versions of a new drug as soon as that new drug was put on the market. What would this do?

⇒ Many companies would be able to produce the drug almost as soon as it was approved.

⇒ The drug would cost less money as each company tries to make its drug cheaper, and sell more than other companies.

⇒ Over time, the drug would barely cost more than the raw materials that make up the tablet or capsule.

While this system is better for the person buying the drugs, it is very bad for the company that spent all the time and money to discover the new drug. As a result, drug companies would have no reason to create new drugs. It would be much cheaper to let other companies do all the research and then just copy the drug and sell it at a lower price! With the new system, everyone would suffer because no company would be willing to discover new, life-saving drugs.

Even though this new system would mean cheaper drugs, it would also mean that new drugs that might save many lives would never be discovered. Imagine a world where there was no treatment for headaches or back pain because common drugs like aspirin or ibuprofen were never created! Just like you wouldn’t work 40 hours every week if you didn’t earn a paycheck, drug companies wouldn’t make new drugs if they could only charge the price of the materials to make the tablet or capsule.

Drug Companies Aren’t “The Enemy”
Even though people see drug companies as greedy or “the enemy”, the truth is that the brand-vs.-generic system is good for the consumer. Drug companies have a reason to create new drugs because they know they can earn back the cost of making and testing the new drug. The extra cost of making a new drug will be earned back by the time its patent protection period ends. Then generic versions become ready for sale, and the brand-name drug can choose to compete with the lower price.

So why do brand drugs still cost more even after generic drugs are available? This is because people tend to trust a “tried-and-true” brand product much like when people buy brand-name paper towels instead of the cheaper store-brand. Generic drugs have to prove that they are equally as powerful as the brand version before the FDA will allow the generic drug to be sold. Because generic drugs must have the same active ingredient and must be just as effective means that generics are nearly identical to the brand drug, but cost 80-85% less. Imagine buying a $100,000 European sports car for only $20,000 just because it has a different paint job and an American-company symbol on the hood. This is the level of savings that generic drugs can provide.

To learn more about brand and generic drugs, visit the FDA Web site at: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/default.htm

By Micah Miller, PharmD Candidate

REFERENCES:


PATIENT INFORMATION:
Managing Cold Symptoms in Children Less Than 2 Years Old

When your baby is sick with the common cold, it can be a stressful for both you and your child. Deciding how to treat your child’s cold can be confusing since children 2 years and under cannot take over-the-counter cold medicine. You can safely comfort your child and manage the symptoms with the following options.

Rest:
Your child needs energy for the body to fight off the sickness, so getting enough rest is one of the most important ways your child will start feeling better.

Fluids (6 months and older):
Giving your child enough fluids is very important to keep the mucus in the sinuses and chest thin and loose so the mucus is easier to clear.

Pain Relief:
Often, colds can cause a fever, a sore throat, or ear aches. Acetaminophen (children 3 months or older) or ibuprofen (children 6 months or older) can safely be used in children to lower the fever and provide pain relief.

Saline Nasal Drops
Saline nasal drops can help loosen the nasal mucus and relieve congestion. The saline will thin the mucus making it easier to remove. It is important to remember to only use the saline drops for no more than 3 days because using saline too much can dry out your child’s sinuses.

How to use saline nasal drops:
Lay your child down and gently tilt the head back. Drop 2 to 3 drops of saline into each nostril. Try and hold your child’s head still for 30 seconds to allow the saline to soak into the mucus.

Bulb Syringe
A bulb syringe can be used to relieve congestion by clearing the mucus from your child’s nose.

How to use a bulb syringe:
Squeeze bulb then gently insert tip inside the nostril and release bulb to allow the mucus to be suctioned back into the bulb. Remove tip, then squeeze bulb onto a tissue to clear the contents inside of the bulb. Repeat in the other nostril as needed. It is helpful to use the bulb after saline drops so the mucus is easier to remove.

Humidifier:
Having a humidifier in your child’s room where he or she sleeps and plays allows your child to breathe in moist air which can loosen mucus and relieve congestion in the sinuses and chest.

Honey (1 year old and older):
One-half to one teaspoonful of honey can be used in children 1 year and older to help soothe a cough. The honey coats the throat and may provide comfort for a child with a sore throat or a cough.

By Britney Selvig-Bellew, PharmD Candidate

REFERENCES: