

# PEN



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Paul Clement

**P**ain and hemophilia go hand-in-hand. During a joint or muscle bleed, blood fills the joint cavity or makes muscles swell. Nerves alert the brain, prompting the body to respond. The result? Pain. Repeated joint bleeds cause the joint cartilage to deteriorate, causing arthritis. The result? Long-lasting chronic pain.

Good pain management can help you or your child get through the short-term acute pain of bleeds as well as long-term chronic pain. Many options exist for treating and managing pain, from ice to opioids. Yet many people with hemophilia—for personal, cultural, or religious reasons—don't take advantage of these options. Instead, they live in pain.

Let's explore what pain is, identify some of the misunderstandings around pain management, and see how to overcome some barriers, so you can achieve the best pain relief for your hemophilia.

## Types of Pain

Pain is either *acute* or *chronic*. Acute pain lasts hours, days, or a few months, while the body is healing. Chronic pain lasts six months or longer. Acute pain is considered necessary, even beneficial—

alerting our bodies to danger or injury, and prompting us to react (think: touching a hot stove), protect ourselves, rest, and get treatment. Chronic pain, on the other hand, can affect us physically and mentally and, if not properly managed, can be destructive and debilitating.

For people with hemophilia:

- **Acute pain** is usually caused by bleeding that leads to swelling in joints and muscles. Acute pain resulting from a bleed is often described as sharp, tender, or throbbing.
- **Chronic pain** is usually caused by arthritis in joints, a consequence of bleeds that have damaged the joint's cartilage. Chronic pain is often described as aching and tiring. Pain level may vary during the day: higher in the morning, and then decreasing through the day as the joint is used.

Acute pain and chronic pain require different treatment approaches. But in both cases, the goal of pain management is not necessarily to *eliminate* the pain through the use of drugs, but to *reduce* it to a level that makes the pain manageable.

Acute pain is usually treated quickly and effectively by physicians and parents. Treatment involves not only reducing the level of pain, but also eliminating the cause of the pain.

# welcome



I was raised in the 1960s in a big family that often shunned doctors and hospitals. We were like pioneers of old times. I had six brothers who basically said “Just suck it up!” when I got hurt. In fact, getting hurt while riding motorcycles, skiing, or climbing

trees—and not complaining about it—was a badge of honor. I badly sprained an ankle while playing volleyball in high school in Dr. Scholl’s sandals (remember those?). My foot immediately turned black and hurt, but I just kept on playing, hobbling on one foot. No one was going to call me a wimp! Luckily, none of us kids ever had any major illness or accident.

But having a child with hemophilia changed my views on pain. There is perhaps no pain as bad as watching your little child suffer. And not having the experience of pain management, I had to learn the hard way about pain treatment options. When my son had a psoas bleed at age 10, we stayed up ’til dawn, watching Marx Brothers movies to keep him distracted and laughing, though there were many groans and tears. At times, the pain was relentless. It never even dawned on me to request a prescription painkiller. I didn’t think children could have them! I simply didn’t understand his level of excruciating pain.

Fortunately for you, Paul Clement presents a thorough review of pain and pain management in this issue of PEN. We have many options, but there isn’t a one-size-fits-all when it comes to pain management. And we have to be careful of dosing, and of hidden ingredients in other over-the-counter products when using prescription pain meds. We need to understand the causes of pain, and learn about appropriate treatment options based on cause.

Use this comprehensive issue as a guide. Bring it with you to the hemophilia treatment center if you need to discuss pain management with your physician. Pain has purpose...and pain can be managed.

*Laurie Kelley*



**Pain  
Relief**

In the past, it was incorrectly believed that only men could have hemophilia, and women with the gene were labeled asymptomatic “carriers.” It’s now recognized that women are not just carriers of hemophilia, but can also have hemophilia and experience symptoms if less than 50% of their factor is active. Most diagnosed patients are male. For editorial simplicity in PEN articles, when we refer to a person with hemophilia, we may alternately use “he,” “she,” or “they.”

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Corey Pierce

## Pain Is Not the Problem...

# IT'S THE SOLUTION

The bleeding disorder community has a pain problem, but it's not the problem of *too much pain*. The real problem is a misunderstanding of pain and its importance for our survival. Many people with bleeding disorders have come to devalue pain, because pain is often characterized as a mysterious and uncontrollable inevitability. A fallacious concept like “spontaneous bleeding” has sowed a seed in many minds that the actions we engage in are divorced from how our bodies respond. If the pain we experience is seen as inevitable, or with clouded causes, then we're left with no other option than to manage the best we can, or trick ourselves into thinking the pain doesn't exist.

If given the option to never feel pain again, many people would take this deal in a heartbeat. But only later would they truly understand the horrors of living without pain. What if you took this deal? Well, rare medical conditions like congenital insensitivity to pain (CIP) suggest that you shouldn't be too attached to your fingers and toes. And you'd better hope to never get an infection or have heart failure, because you'll be without the best warning sign nature ever created: *pain*. In short, your life would end much sooner. Living without pain is not a blessing—it's a tragic, brutal curse.

If you want to understand pain, know that it results from a set of factors. Pain doesn't arrive out of nowhere, and it's rarely attributable to a single cause. For example, the mild ankle pain I am experiencing as I write this is not only the result of countless past ankle bleeds, but also the result of (1) standing for two hours straight while making an elaborate meal yesterday; (2) wearing “cool” shoes with no heel drop yesterday; (3) running three days ago even though I was sore; (4) eating inflammatory foods yesterday; (5) being dehydrated today; (6) slightly twisting my ankle on a tree nut while intently looking at a mailbox on a recent run; (7) not being able to ice myself after physical activity (my roommate has needed the ice more after his recent surgery);

(8) not yet knowing my mileage limit while running (running is new for me since COVID-19); (9) switching to a new running shoe (is it helping or hurting?); (10) walking a mile on uneven sand recently. And so on...

If you look critically at what contributes to pain, you'll see that it's possible to improve your underlying condition by changing how you navigate through this world. By examining the obvious—and subtle—contributing factors to pain, you can create a template in your mind for what you should be doing and also avoiding. In my earlier example, there are complex interactions between my physical awareness, my activity level, and my shoes that I can monitor and refine over time, as I get used to my new activity—running. This introspective, reflective process is often at odds with the objectives of using pain medications.

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Paul Clement

## PATIENT DEATHS:

# ASSOCIATION

## Not Causation

This past spring, a patient contacted us at LA Kelley Communications about social media posts concerning deaths of people on Hemlibra® (emicizumab-kxwh). The patient asked us what we thought: Are the number of deaths abnormal, or to be expected? Were the deaths actually caused by Hemlibra? What's the truth about these deaths?

The social media posts were generating fear and concern. Of course, published numbers of deaths are always frightening, but let's put it in perspective. Are deaths of people using hemophilia therapies unusual, or to be expected? Should you be concerned? What do you need to know to help identify misinformation?

*Just because there is an*  
**ASSOCIATION**  
*between 2 things,*  
that does not mean  
**1** *thing* **CAUSED**  
*the other to happen.*

### Reported Deaths

The deaths of patients on Hemlibra mentioned in these social media posts came from a quarterly “Reported Fatalities” of patients on Hemlibra: a publication of Hemlibra’s manufacturer, Genentech/Roche, available online to the public.<sup>1</sup> Note that Genentech/Roche is the *only* pharmaceutical company to publish a document like this for a hemophilia therapy.

As of June 30, 2020, Genentech reported 44 fatalities of people having been treated with Hemlibra. These deaths are worldwide cases in Asia, Australia, Europe, and North America, out of more than 7,200 people treated with Hemlibra since phase III clinical trials began in 2015. Most important, none of the 44 deaths was found to be *caused* by Hemlibra.

Because other pharmaceutical companies don’t publish global fatality statistics of people taking their hemophilia products, let’s look at deaths of people taking some hemophilia drugs as reported on the Food and Drug Administration’s (FDA) Adverse Event Reporting System (FAERS) Public Dashboard.<sup>2</sup> This will help us make more equal comparisons.<sup>3</sup> The FDA’s definition of an “adverse event” is any undesirable experience, including death, *associated* with the use of a medical product in a patient.

Hemlibra was first approved for treating people with hemophilia A with factor VIII inhibitors in November 2017, and for people without inhibitors in October 2018. From 2018

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1. Genentech's quarterly update of Reported Fatalities with emicizumab: [www.emicizumabinfo.com/patient.html](http://www.emicizumabinfo.com/patient.html). The website was created for people with hemophilia A and their caregivers in the US.  
2. FDA Adverse Event Reporting System (FAERS) Public Dashboard: [www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard](http://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard)  
3. When making comparisons, it's important to know the total number of patients treated with a particular product. Although we know more than 7,200 patients have been treated with Hemlibra worldwide, we don't know the total number of patients on other products, because this info isn't public.

# richard's review

Linda Weaver's Studio

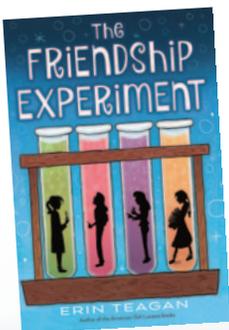


Richard J. Atwood



## Interesting Fictional Teens

**D**o you ever wonder whether teenage fictional characters with bleeding disorders can foreshadow the future of our community? I pondered this question because some recent novels caught my attention. These novels include young protagonists with bleeding disorders who may represent the next generation of leaders. Decide for yourself if the following novels provide any insights.



### **The Friendship Experiment**

*Erin Teagan*

Houghton Mifflin Harcourt, 2016

In this young adult novel (also appropriate for adults), Madeline Avery Little, or “Maddie,” aspires to become a microbiologist, just like her deceased grandfather.

Now in the sixth grade, Maddie conducts experiments. And her

father conducts research on von Willebrand disease (VWD) at the local university, partly because it's personal: VWD runs in the family. Both Maddie and her older sister have VWD. Maddie keeps a medical diary (logbook), wears a

medical bracelet, treats herself with a nasal spray, and worries that laughing could cause a nosebleed. She creates a crisis in her father's lab due to her negligence, and then she loses the friendship of her classmates after they read her personal notebook with its nasty comments about them. Maddie's sister self-medicates with Maddie's medicine, causing a medical crisis requiring hospitalization. Overwhelmed, Maddie realizes she needs to fix her messes with “I'm sorry.” She also learns that there is no such thing as a “friendship experiment,” because life is too complicated and too unpredictable. The author received expert advice to accurately portray VWD.

### **Kick**

*Mitch Johnson*

Usborne Publishing, 2017

Budi, who lives in Jakarta, the capital of Indonesia, is almost 12 and small for his age. He no longer attends school, and now works in a factory sewing together football boots—shoes for exportation that he can't

afford to buy. Budi loves football (“soccer” in America) and dreams of becoming a professional footballer. Yet he shares a family curse. Along with his grandfather, his father, and his dad's twin brother, Budi has a bleeding disorder—his blood doesn't clot properly. Budi's mother treats his skin



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# Chronic Pain, CAM, and YOU

Laurie Kelley

**P**ain is highly personal. No two people experience the same feeling of pain, even when it's the same injury, like a muscle bleed, or experience, like childbirth. A joint bleed may feel tingling to one, stabbing to another, or throbbing to someone else. Mike Birmingham, a man with hemophilia A, writes in his blog *The Bleeding Edge*, "Pain is pretty deeply personal. I personally have never been able to figure out what to say when a nurse asks me to describe my pain."<sup>1</sup>

But it's especially personal when trying to describe the level of pain. Doctors often ask patients to rate their pain on a scale of 1 to 10. But what is a 1? What is a 10? A level 8 to one person might be a level 3 to another. Matt Rollins, who has hemophilia A, notes, "The HTC [hemophilia treatment center] will understand that most of us older guys have a base pain level that stays steady at a 5 or 6 every day. We've gotten used to that level of pain and this is our 'normal.' What's difficult is when you go to an ER and try to relay that same information." This is critical when people with bleeding disorders try to explain their level of pain to their doctor. Not appreciating or understanding how much pain a person is feeling may lead to an inefficient treatment for that pain.

Bonnie Charles interprets her pain at lower levels when

compared to people without a bleeding disorder. "I feel like what would be painful to someone else is just the norm for me. And I don't find it painful because I've learned to live with it."

Because pain is so personal, medication may not be the first—or the only—option for chronic pain. Instead, both patient and physician can consider different types of *complementary and alternative medicine* (CAM) to learn how to handle chronic pain. And like pain, CAM can be highly personalized as well.

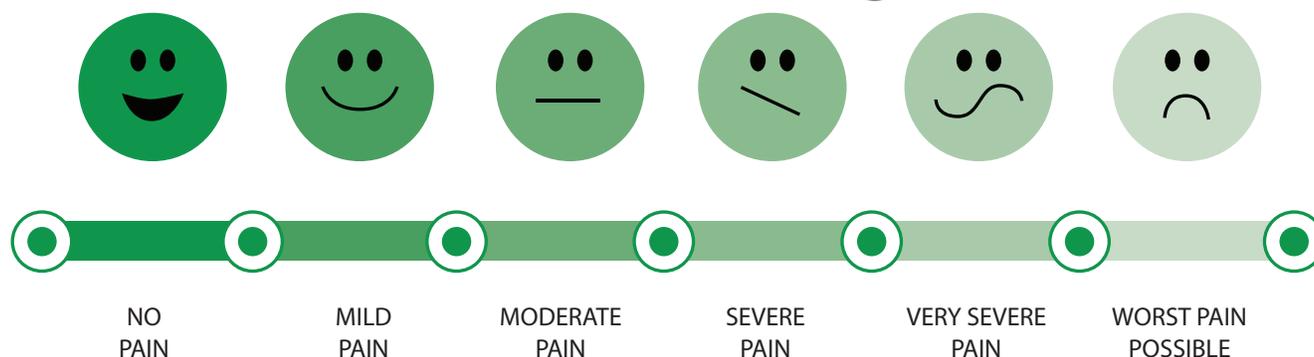
## What Is CAM?

CAM is any *adjunct* (additional) therapy, like massage, used along with conventional medicine. It's an important part of a *multimodal* or multidisciplinary approach to pain management. It's also important in *integrative medicine*, which focuses on the whole person and makes use of all appropriate therapeutic approaches, healthcare professionals, and disciplines to achieve optimal health and healing. Here are some of the most common CAM therapies:

*Relaxation Therapies.* Relaxation teaches you to relieve tense muscles, reduce anxiety, and alter your mental state. Mindfulness meditation helps you focus attention on a specific object or

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## FACES Pain Rating Scale



1. mbirmingham.blogspot.com

For chronic pain, where eliminating the *cause*—for example, joint damage—may not be possible right away, the goal of treatment is to improve your ability to function by (1) reducing the *level* of pain, and by (2) addressing the psychological issues that accompany chronic pain. Eliminating the cause of chronic pain in hemophilia may require surgery, such as joint fusion or joint replacement. But even without surgery, there are still many things you can do to manage your pain so it has less effect on your physiological well-being, your ability to sleep, and your daily activities.

## Managing Acute Pain

Bleeding into joints and muscles causes acute pain. To limit acute pain, you must *stop the bleeding as soon as possible* with your prescribed factor concentrate or bypassing agent.

Using additional, or *adjunct*, therapies can often help reduce swelling and pain. Adjunct therapies are designed to increase the effectiveness of the primary therapy, often allowing you to use a lower dose of pain medication, and possibly for a shorter time. In some cases, adjunct therapy can reduce or eliminate pain without pain medication. One adjunct treatment that helps reduce pain from bleeds and speeds healing is RICE: Rest, Ice, Compression, Elevation.

*Rest* the injured body part for 24 to 48 hours to prevent reinjury of the site.

*Ice* the site for 10 to 15 minutes at a time, using a gel-filled cold compress, Cryo/Cuff®, or bag of frozen peas or crushed ice wrapped in a towel, four to eight times a day. Wait at least 40 minutes before reapplying. Icing reduces blood flow to the injured area, which helps control bleeding and swelling. Ice also

helps numb pain. To avoid freezing and damaging the skin, limit the time when the ice or cold object is directly on the skin.

*Compress* the affected area with an elastic bandage to help reduce bleeding and swelling.

*Elevate* the injured body part above the heart to help reduce swelling and the throbbing sensation common in lower extremity bleeds.

If RICE alone doesn't reduce your pain enough, you may need a pain medication, or analgesic. Most people with hemophilia use over-the-counter (OTC) analgesics to treat mild to moderate acute pain. For more intense pain, you or your child may need more potent, prescription-only analgesics.

Pain medications to treat acute and chronic pain are often divided into three groups:

1. *Non-opioids*, including acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs).
2. *Opioids* (narcotics), including hydrocodone and morphine.
3. *Adjuvant analgesics*, a loose term for many medications, including some antidepressants and anticonvulsants, originally used to treat conditions other than pain.

## Non-Opioids for Acute Pain

Non-opioids are the drugs of choice for mild to moderate acute pain.

Acetaminophen is the analgesic most often recommended for people with hemophilia because it doesn't affect the blood's clotting ability, as do most NSAIDs. Brand names of acetaminophen include Tylenol® and FeverAll®. Although acetaminophen is relatively safe when used as directed, it's sometimes called the most dangerous of OTC analgesics, because the maximum dose and the toxic dose are relatively close. High doses and long-term use of acetaminophen may cause severe liver damage—an especially serious concern for people infected with hepatitis C. Acetaminophen overdose accounts for 56,000 emergency department visits, 26,000 hospitalizations, and over 450 deaths annually in the US—and most of these overdoses are accidental.

Accidental overdose on acetaminophen often happens when people take more than one drug without carefully reading the labels. Acetaminophen is a component of more than 600 drugs, including many OTC drugs sold for purposes other than pain relief (for example, some cold medications), but this may not be clearly shown on the label.<sup>1</sup> Acetaminophen may also be combined with other painkillers (for example, opioids) and sold under a brand name, such as Vicodin® and Darvocet®. Accidental overdose can happen if you take acetaminophen plus another



1. Common medicines containing acetaminophen: [www.knowyourdose.org/common-medicines](http://www.knowyourdose.org/common-medicines)

drug that you don't realize also contains acetaminophen. To prevent overdosing with acetaminophen, carefully read the label of any drugs you are taking, and consult your physician or pharmacist for the correct dosage.<sup>2</sup> And remember, when it comes to acetaminophen dosing, *more is not better*.

NSAIDs are a large group of analgesics that include common OTC pain medications, such as aspirin, ibuprofen (Motrin®, Advil®), naproxen (Aleve®, Naprosyn®), and ketoprofen (Orovail®). Many other NSAIDs, such as meloxicam (Mobic®), are available by prescription only. No two NSAIDs work in exactly the same way. Each has slightly different side effects and effectiveness, and each lasts for a different length of time. Unlike opioids (see Managing Chronic Pain section), all NSAIDs and acetaminophen have a *dose ceiling*: the maximum safe or effective dose of a drug. Taking doses above the ceiling dose offers no additional therapeutic benefits, but significantly increases the risk of serious or life-threatening side effects, including kidney failure, liver failure, and gastrointestinal bleeding.

NSAIDs reduce pain, but unlike acetaminophen, they also have an anti-inflammatory effect. This means they help reduce swelling and inflammation in joints, often providing more relief than acetaminophen. But NSAIDs have drawbacks for people with bleeding disorders:

1. Almost all NSAIDs reduce the blood's ability to clot, by inhibiting platelet *aggregation* (when platelets stick together to form a platelet plug). This results in prolonged bleeding.<sup>3</sup>
2. NSAIDs can cause gastrointestinal (GI) bleeding and ulcers.
3. When used long-term at high doses, NSAIDs can harm the kidneys and, to a lesser degree, the liver.

Physicians don't often prescribe high-dose NSAIDs for people with hemophilia. If used, NSAIDs should be taken at the lowest effective dose, for a limited time, and in limited circumstances. Never give your child with hemophilia NSAIDs without consulting your hemophilia treatment center (HTC) staff!

Some NSAIDs are simply dangerous for people with bleeding disorders, and should not be used under any conditions. Aspirin (acetylsalicylic acid or ASA) deserves a special warning: *Aspirin should never be used by anyone with hemophilia* because it forms an irreversible chemical bond with COX-1, an enzyme in the blood involved in the clotting process. The bond with ASA, or aspirin, prevents platelets from aggregating to form a platelet plug—the first step in the blood-clotting process. This effect on platelets is irreversible and lasts for the life of the platelet, about 7 to 10 days. A person with hemophilia who takes aspirin risks



GI bleeds and uncontrolled spontaneous bleeding. Aspirin is found in several dozen OTC medications, including many (like Pepto-Bismol™) not indicated for pain relief. Carefully check all OTC medications for the presence of aspirin, acetylsalicylic acid, or ASA—and if you see any of these on a label, don't use the product!

Another dangerous product is ketorolac (prescription-only, brand name Toradol®). It's more likely than other NSAIDs to cause GI bleeding. The risk of GI bleeding can be reduced (but not eliminated) by using OTC topical NSAIDs, such as diclofenac (Pennsaid®, Voltaren®), which are almost as effective as oral NSAIDs, with a lower risk of side effects. But keep in mind that these drugs are absorbed systemically; the risk of side effects is similar to the oral form, though lower. Check with your hematologist about the tendency of any NSAID to cause GI bleeding, and its effect on clotting.

Low-dose OTC ibuprofen (Advil®, Motrin®) is an NSAID commonly used to treat pain and inflammation. Ibuprofen also slows platelet aggregation, but much less so than aspirin; and the effect is temporary, lasting only about four hours. While taking ibuprofen, you may have no excessive bleeding problems, but do *not* take it when a bleed is in progress, because it can increase or prolong bleeding. High-dose ibuprofen (600 mg or 800 mg tablets) is a prescription-only medication with a greater risk of GI bleeding; use only under a doctor's direct supervision.

Selective COX-2 inhibitors (*coxibs*) are a different class of NSAIDs, developed specifically to reduce the risk of gastrointestinal bleeding and ulcers for people taking the drug for an extended time. By targeting only COX-2 (not COX-1 and COX-2, as other NSAIDs do), these drugs have less effect on platelet aggregation. But National Hemophilia Foundation's (NHF) Medical and Surgical Advisory Council (MASAC) reports some incidences of bleeding, and recommends using coxibs at the lowest effective dose, for a short time.<sup>4</sup> Currently,

2. Historically, the maximum daily adult dose of acetaminophen was 4 g. In response to overdose deaths, in 2012 the FDA suggested, but did not mandate, a maximum daily dose for adults of 3 g, with no more than 650 mg every 6 hours, as needed. 3. Although most aspirin-related compounds containing salicylic acid also affect platelet aggregation, two do not: salsalate (Disalcid®) and choline magnesium trisalicylate (Trilisate®). These drugs are sometime prescribed for children with hemophilia. 4. MASAC recommendation 162, "Use of COX-2 Inhibitors in Persons with Bleeding Disorders," [www.hemophilia.org](http://www.hemophilia.org).

only one coxib, celecoxib (Celebrex<sup>®</sup>), is available in the US. Although NHF recommends this drug for short-term use, many people with hemophilia use it long term to treat mild to moderate chronic joint pain. *Always consult your HTC about NSAID use.*

Treating mild to moderate acute pain is almost always manageable with OTC or prescription-strength acetaminophen or NSAIDs. To treat severe acute pain, you may need to use an opioid for a few days, or a combination analgesic containing an opioid plus an NSAID or acetaminophen. For example, the combination prescription analgesics Darvocet, Percocet<sup>®</sup>, and Vicodin all contain both an opioid and acetaminophen. (Note: Percodan<sup>®</sup>, another combination analgesic, contains both an opioid and aspirin, and should not be taken by people with hemophilia.)

As part of an overall pain management plan, your physician may also prescribe adjuvant analgesics, drugs with no direct pain-relieving properties. Medications to treat insomnia, anxiety, depression, and muscle spasms can significantly help some patients. Combination analgesics, opioids, and adjuvant analgesics are usually reserved for severe acute pain and chronic pain.

## Managing Chronic Pain

Unlike acute pain, chronic pain may be underappreciated and undertreated by many healthcare providers. Chronic pain often creeps up slowly, over time. In people with hemophilia, it's usually first apparent as recurring joint pain that tends to be more severe in the morning, then decreases as the day wears on. Parents should suspect their child may be having chronic pain if the child has had repeated bleeds into a joint (a target joint). And young people should be taught to distinguish between acute and chronic pain—not always easy to do. Often, when young people with hemophilia first experience chronic pain, they may believe the pain is due to a bleed, so they treat with factor—which doesn't reduce chronic pain.

Chronic pain is managed differently than acute pain. It has a major psychological component, and can even cause physical changes in the brain. Chronic pain and depression are closely related, and can create a vicious cycle: the pain makes the depression worse, and the depression makes the pain worse. Some common symptoms of depression and chronic pain:

1. Emotional symptoms: irritability, anxiety, excessive worry, crying, depressive style of thinking, and obsessions;
2. Somatic symptoms: sleep and appetite disorders, reduced psychomotor efficiency (decreased coordination or dexterity) and life energy, impairment of concentration and attention;

3. Feelings of guilt, sadness, loss of interest, and suicidal tendencies.

A good pain management plan for chronic pain must be personalized. It should use a *multimodal* or multidisciplinary approach. Along with using an effective analgesic, this multimodal approach should

1. Address the psychological component of chronic pain, by treating depression and reducing anxiety and stress;
2. Use adjuvant therapies, including antidepressants and anticonvulsants;
3. Include an exercise and/or a physical therapy component;
4. Use *complementary and alternative medicine* (CAM). (See YOU, p. 6, on CAM and its benefits.)

A multimodal approach will allow you to manage moderate to severe chronic pain with the lowest possible dose of analgesic.

This brings us to analgesics for chronic pain. Unlike acute pain, severe chronic pain often doesn't respond to OTC analgesics. Even high-dose, prescription-only NSAIDs may not reduce the pain enough; and when used for extended periods, high-dose non-opioid analgesics pose a significant risk of bleeding complications and other serious side effects. So for moderate to severe chronic pain, stronger analgesics—opioids (narcotics such as morphine and codeine)—are the drugs of choice. Unlike NSAIDs, opioids have no ceiling dose. They don't damage the kidneys or liver, don't cause gastrointestinal bleeding, don't increase the risk of heart attack, and don't interfere with clotting by inhibiting platelet aggregation. Note that the long-term use of opioids for chronic pain management in children and adolescents is disputed, because opioids may harm their developing brains, and possibly may predispose them to later drug abuse.

But opioids do have multiple side effects: the most common is constipation, affecting 40% to 95% of people on opioids.<sup>5</sup> Other possible side effects include nausea, dizziness, drowsiness,



5. O. B. Woodward, S. Naraen, and A. Naraen, "Opioid-Induced Myoclonus and Hyperalgesia Following a Short Course of Low-Dose Oral Morphine," *British Journal of Pain* 11, no. 1 (2017): 32-35.

twitching, urinary retention, bladder spasm, sleep disturbances, itching, and respiratory depression (slow breathing rate). Some of these side effects may go away in a few days, and many people using opioids for long periods report becoming *tolerized* to these side effects—that is, the side effects disappear. The number and strength of the side effects you may experience are also related to the dose: the higher the dose, the more likely you'll experience side effects or more serious side effects. Some side effects that don't go away, such as constipation, can be treated with various medications. Constipation may require a change in diet and the use of stool softeners and stimulant laxatives.

## Respiratory Depression

The most serious—and potentially fatal—side effect of high-dose opioids is respiratory depression, sometimes to the point where breathing stops. The risk of severe respiratory depression is greater in the elderly and young children. That's one reason opioids are rarely prescribed for young children. Death from respiratory depression due to opioid overdose often happens accidentally:

- An elderly person forgets they already took their opioid medication and takes another.
- Someone's long-acting opioid doesn't seem to be working, so they take another.
- After previously taking a gabapentinoid medication (such as Neurontin<sup>®</sup>, Gralise<sup>®</sup>, Lyrica<sup>®</sup>) for pain or another indication, a patient decides to take an opioid drug during a spike in pain.
- While also taking an opioid, someone takes a cold or sleep medication.
- Someone takes an old high-dose opioid medication to which they were previously tolerized and have lost tolerance.
- A patient takes someone else's opioid, which may be a high dose to which they are not tolerized.
- Someone decides to “self-medicate” with alcohol while taking an opioid.

All of these actions strongly increase the risk of severe respiratory depression, and possibly death.<sup>6</sup> And all these examples are considered instances of opioid abuse. According to the National Institute on Drug Abuse (NIDA), more than 30% of overdoses involving opioids also involve benzodiazepines, a type of prescription sedative commonly prescribed for anxiety or insomnia.<sup>7</sup> Benzodiazepines (or “benzos”) like diazepam (Valium<sup>®</sup>), alprazolam (Xanax<sup>®</sup>), and clonazepam (Klonopin<sup>®</sup>) work to calm or sedate a person. But using these benzos in combination



with opioids increases the risk of severe respiratory depression. In 2016, the US Centers for Disease Control and Prevention (CDC) issued new guidelines for prescribing opioids, recommending that whenever possible, clinicians should avoid prescribing benzodiazepines together with opioids.<sup>8</sup>

Remember: *No one has to die from an opioid overdose.* Respiratory depression caused by an opioid can be reversed in minutes with a drug called *naloxone*. Naloxone is an opioid antagonist: it binds to the same nerve receptors as the opioid, displacing the opioid and temporarily undoing its harmful effects. Naloxone is available as OTC Narcan<sup>®</sup> Nasal Spray (the preferred form compared to the injected form) or as prescription-only naloxone auto-injector (Evzio<sup>®</sup>). *Anyone on opioids, no matter the dose, should also receive a script for naloxone auto-injector or have Narcan on hand!* Friends and family should be aware that you are taking an opioid, be taught the signs of severe respiratory depression, know where your naloxone is kept, and be trained in how to use it in an emergency.<sup>9</sup> Note: Naloxone is only meant to be a first line of defense during an overdose, giving you time to get to a medical facility for treatment, because its antidote effect will wear off in 20 to 90 minutes. Both Narcan and Evzio come in two-packs, in case a single dose doesn't work, or the person relapses on the way to the hospital.

Accidental death from respiratory depression by overdose of prescription opioids is easily preventable. Most of these deaths are the result of ignorance about the dangers of combining multiple drugs. And death from overdose in chronic pain patients is extremely rare. In one study of more than 2,182,374 patients prescribed opioids, the death rate from respiratory suppression was 0.022% per year.<sup>10</sup>

You may still worry about the risk of addiction or death from opioids. But remember, prescription opioids are safe and effective for treating moderate to severe chronic pain, when patients are pre-screened for addiction risks and the drugs are taken as directed.

6. The CDC and NHF suggest that physicians prescribe short-acting/immediate-release opioids instead of long-acting/extended-release opioids. MASAC recommendation 260, "Management of Chronic Pain in Persons with Bleeding Disorders: Guidance for Practical Application of the Centers for Disease Control's Opioid Prescribing Guidelines," [www.hemophilia.org](http://www.hemophilia.org) (search: 260\_pain). 7. "The Science of Drug Use and Addiction: The Basics," [www.drugabuse.gov](http://www.drugabuse.gov). 8. Deborah Dowell, Tamara Haegerich, and Roger Chou, "CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016," *Morbidity and Mortality Weekly Report Recommendations and Reports* 65, no. RR-1 (2016): 1–49. 9. Many people using prescription opioids believe that an overdose will never happen to them—but it can happen accidentally to anyone. The word "overdose" can sound negative. If you're concerned about others making judgements, try using a term like "opioid emergency" instead of overdose. And wear a medical ID. 10. N. Dasgupta, et al., "Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality," *Pain Medicine* 17, no. 1 (2016): 85–98.

## Addiction, Tolerance, Dependency: What's the Difference?

Most physicians have no worries about prescribing necessary pain meds for acute pain. But opioids are a different matter—they carry the stigma of addiction. Everyone has seen the portrayal of narcotics abuse in movies or on television. But most people don't know that many of these media portrayals are inaccurate. In fact, misinformation about opioids abounds in the media and even medical journals. Both you and your physician might have fears, or outdated and incorrect information, about the risk of addiction.

Misunderstanding about opioids often centers on misunderstanding three terms:

- Tolerance
- Physical dependence
- Addiction

### Tolerance

Tolerance is a normal adaptive response to repeated exposure to a drug. The same dose of a drug becomes less effective over time; in other words, your body becomes desensitized to the drug's effects. Tolerance can be both “good” and “bad.” If you become tolerized to some side effects of a drug, that's good. If you become tolerized to the analgesic effects of a drug, that's bad. Tolerance also develops at different rates for different effects of a drug. And the tolerance for a specific drug may vary between people; with other drugs someone is taking; and with underlying medical conditions. When a drug is stopped, tolerance decreases over days to months.<sup>11</sup>

Normally, opioids are first prescribed at the lowest possible effective dose. Then, if you become tolerized and the drug becomes less effective at reducing pain, the dose is increased to maintain effectiveness. This can be done several times, because unlike NSAIDs and acetaminophen, opioids have no ceiling dose. But if you continue developing tolerance to higher and higher doses, then your physician will need to switch you to another opioid.<sup>12</sup> Why? Because high levels of opioids increase the risk of serious side effects like respiratory depression, and other side effects including drowsiness and tremors.

Note: A patient who is tolerized to an opioid may be taking a high dose that could be lethal to someone who is new to the drug. *Never take another person's prescription pain medication, and never give your prescription pain medication to anyone else!* Always properly dispose of opioids you no longer need. This prevents *diversion*—stealing a drug for illicit use—and accidental overdose, which

can happen if you were taking a high-dose opioid, stopped taking the drug and lost tolerance, then started taking the drug again.

Opioids can and should be used when needed.<sup>13</sup> When taken as directed under good medical supervision, they can be effective, with limited addiction issues. Developing a tolerance to the narcotic is normal and does *not* indicate addiction.

### Physical Dependence

Physical dependence is an “adaptive state” that develops from repeated drug use: your body has adapted to the drug, and now needs it to maintain normal function. So you have withdrawal symptoms when you stop taking the drug. For opioids, you may have withdrawal symptoms if you suddenly stop the drug, or if the dose is lowered too quickly. Symptoms of withdrawal may include sweating, rapid heart rate, nausea, diarrhea, and anxiety. Dependence and withdrawal symptoms are more pronounced the longer you're on an opioid, and especially the higher the dose.<sup>14</sup>

Physical dependence is often confused with addiction, and in the media, the two terms may be used interchangeably. But *dependence is not addiction*. Physical dependence is considered a normal reaction to opioids and to many other drugs. For example, heavy coffee drinkers often become tolerized to the effects of caffeine, and become physically dependent. If they abruptly stop drinking coffee, they may have withdrawal symptoms for several days: headache, fatigue, low energy, irritability, anxiety, poor concentration, depressed mood, and tremors. Indeed, anyone on opioids for more than several days is usually considered dependent to some degree.

To minimize or avoid withdrawal symptoms, especially with a high dose, the dosage must be decreased slowly over time (days to months); this process is called *tapering*. The higher the dose and the longer you've taken opioids, the longer the tapering period needed. Never stop taking an opioid suddenly, and without medical advice. Going “cold turkey”—suddenly stopping a drug that causes dependency—may be life-threatening. Always consult your healthcare professional before stopping any opioid.

### Addiction

According to NIDA, addiction is a “chronic, relapsing disorder characterized by compulsive drug seeking, continued use despite harmful consequences, and long-lasting changes in the brain. It is considered both a complex brain disorder and a mental illness. Addiction is the most severe form of a full spectrum of substance use disorders, and is a medical illness caused by repeated misuse of a substance or substances.”<sup>15</sup>

11. “Former Opioid Users Are at a Greater Risk of Overdosing Than the Newly Addicted,” blog post, Jackson Laboratory, [www.jax.org](http://www.jax.org). 12. Opioids affect one or more of three major nerve receptors; switching to an opioid that uses a different receptor will allow you to use a lower dose. 13. Special precautions are needed for children and adolescents, and if opioids are necessary, they should be used at the lowest effective dose for a short time only (a few days). The brains of children and adolescents are still developing, and are more “plastic” than those of adults, making young people more susceptible to permanent changes as a result of taking an opioid. 14. Morphine milligram equivalents (MME) is an opioid dosage's equivalency (potency) as compared to morphine. The MME/day metric is often used to gauge the overdose potential of the amount of opioid given at a particular time. Before the 2016 CDC opioid guideline, a “high dose” was defined as greater than 120 MME/day. It's now usually defined as greater than 90 MME/day. 15. [www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drug-misuse-addiction](http://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drug-misuse-addiction).

Addiction is not a moral failing or character flaw, but a chronic illness that harms quality of life. Addiction often leads to weakening of interpersonal relationships, as well as withdrawal from work, family, or community. People may eventually appear to be in a state of persistent sedation or intoxication because they are overusing the drug. The addicted patient may also show psychological symptoms of addiction: increased irritability, anxiety, depression, and apathy. Addicts take drugs in spite of these consequences. Addiction is a long-lasting mental disorder, and an addict may relapse even after decades of being sober.

Overall, the risk of addiction to opioids is low for chronic pain patients, but it isn't low for all patients: some patients are at higher risk of addiction. Before receiving a script for opioids, you should be screened by a healthcare professional, using an opioid risk tool, for depression, anxiety, and stress. You should also be screened for addictive tendencies (family or personal history of substance abuse, including alcohol, depression, sexual abuse, ADD, or OCD).<sup>16</sup> Researchers believe there's a strong hereditary component to addiction risk. If you're at high risk for opioid abuse, you'll probably be required to agree to close monitoring by your healthcare provider as part of your pain management plan. This may include regular urine drug tests, to identify and prevent drug abuse in its early stages.

Sometimes, what seems to be addiction may not be addiction. When pain is undertreated, a patient may show "drug-seeking" behaviors that look like signs of addiction. He may groan and moan, watch the clock, or ask repeatedly for medication before the prescribed dose is due. His complaints may seem excessive, given the cause of the pain. This behavior is called *pseudoaddiction*.

How can you tell the difference between pseudoaddiction and true addiction? In pseudoaddiction, the behavior disappears when the pain is adequately treated. But for people who are truly addicted to opioids, the behavior *worsens* when the drugs are administered. The "treatment" for pseudoaddiction is simple: treat the pain effectively. This means (1) assessing if the pain normally responds to opioids (some types of pain, such as neurogenic pain caused by nerve damage, don't respond to analgesics); (2) checking the appropriateness of the opioid, dose, scheduling, and administration route (people with certain genetic mutations can't metabolize some opioids to create the active compounds that give pain relief, so certain opioids won't work for them); (3) if the pain responds to opioids, escalating the dose aggressively until the pain is relieved. These actions should eliminate pseudoaddictive behavior.

Good news is on the horizon. Researchers have identified several molecules with analgesic properties: they're more power-

ful than morphine, and most important, they don't have the side effects or addiction risk of opioids. These molecules include Astraera Therapeutics' AT-121, already in testing with primates; Centrexion's CNTX-0290; and Tulane's ZH853.

Because most people with hemophilia will have to manage chronic pain later in life, it's essential to understand the difference between tolerance, physical dependence, and addiction. *Dependence and tolerance are not addiction!* Opioid use does not automatically lead to addiction. Don't let misinformation or fear prevent you from getting adequate pain treatment. Studies show that opioid addiction is uncommon among chronic pain sufferers, averaging around 8%. With proper screening for addiction risks and monitoring by your medical team, this risk can be lowered.<sup>17,18</sup> Remember, good pain management is the key to taking any medication safely.

## Managing Chronic Pain: The Multimodal Approach

Chronic pain management is an ongoing process that needs to be monitored and adjusted over time. Chronic pain is best managed by a combination of medication and non-medication treatments, with close attention to mental health. This multimodal approach allows you to manage pain with less medication.

You'll need the expertise of specialists in pain management. If you're lucky, your HTC will have a pain clinic with physicians who specialize in chronic pain management and can help you develop a personalized pain management plan.<sup>19</sup> If not, you



16. "NIDA Screening and Assessment Tools Chart," [www.drugabuse.gov](http://www.drugabuse.gov). 17. N. D. Volkow and A. T. McLellan, "Opioid Abuse in Chronic Pain—Misconceptions and Mitigation Strategies," *New England Journal of Medicine* 374, no. 13 (2016): 1253–63. 18. David A. Fishbain, Cole Brandly, et al., "What Percentage of Chronic Nonmalignant Pain Patients Exposed to Chronic Opioid Analgesic Therapy Develop Abuse/Addiction and/or Aberrant Drug-Related Behaviors? A Structured Evidence-Based Review," *Pain Medicine* 9, no. 4 (May–June 2008): 444–59. 19. In a study of more than 1,000 people with hemophilia, only 7% were seen by a pain clinic for pain management. Michelle Witkop, Angela Lambing, et al., "A National Study of Pain in the Bleeding Disorders Community: A Description of Haemophilia Pain," *Haemophilia* 18 (2011).

can request a referral to a pain clinic at a nearby teaching hospital. Unfortunately, many non-medication therapies for pain management are still not covered by all health plans. And many Americans—more than 28 million—don't have health insurance and can't meet with health professionals who can counsel them. Without health insurance, these people are left to self-medicate, and may turn to dangerous illicit drugs, contributing to the US opioid epidemic.

In the past few years, many pain patients have also met roadblocks because of the CDC's "Guideline for Prescribing Opioids for Chronic Pain" (2016). Many health plans misinterpreted this guideline, and forced almost half of their high-dose opioid patients into withdrawal by suddenly cutting them off from their medication—sending many to emergency rooms.<sup>20</sup> It took the US Food and Drug Administration (FDA) almost three years after the release of the CDC guideline to issue a warning that suddenly stopping opioids can be risky for patients. Disturbingly, studies showed that the risk of death from opioids tripled after pain patients were denied their opioids, possibly because they sought relief from dangerous illicit opioids.<sup>21</sup> In response to these studies, in 2019 the CDC issued a statement against misapplying its guideline.<sup>22</sup>

As mentioned earlier, a good plan for managing chronic pain must be personalized, and should use a multimodal approach to help manage moderate to severe chronic pain with the lowest possible dose of analgesic. Along with using an effective analgesic, a multimodal plan should

1. Address the psychological component of chronic pain by treating depression and reducing anxiety and stress, for example through stress management training.
2. Use adjuvant therapies.
3. Include exercise and/or physical therapy.
4. Use CAM techniques including therapies, biofeedback training, and behavior modification.

## The US Opioid Epidemic

A quote attributed to Mark Twain, "There are three kinds of lies: lies, damn lies, and statistics," applies to data in the media about opioid deaths. Data on opioid deaths is sensationalized—even by government agencies. Problems with data are common. For example, any death involving someone with opioids in their system, no matter how little, is listed in the National Vital Statistics System (NVSS) as being an "opioid overdose." But this is an association, not a causation (see Insights), and the death may have had nothing to do with opioids.

The number of deaths in the NVSS is also exaggerated because deaths are listed by type of opioid; so people with more than one opioid in their system are listed as dying multiple times—once for each opioid! For example, NIDA listed about 63,000 deaths involving opioids in 2017, when the actual number of deaths was about 49,000.

For users of prescription opioids, the risk of opioid overdose is also inflated because deaths from *illicit* opioids and *prescription* opioids are not separated; this makes using prescription opioids for chronic pain therapy seem much riskier than it really is. For example, all deaths involving fentanyl (a very potent opioid often named in overdose deaths) were listed in NVSS as being caused by prescription opioids. But in fact, most of these deaths were from illicit heroin and fentanyl, not from pharmaceutically manufactured fentanyl used in prescriptions. Of the 45,495 opioid-related deaths in 2016, 17,029 were related to prescription opioids. There is also no breakdown of the data on what percentage of prescription opioids were diverted—stolen and used illicitly by someone other than the prescribed person. In other words, deaths of illicit drug users using diverted opioids are lumped together with those of chronic pain patients, inflating the risk to chronic pain patients.

Death from opioid overdose is a US national health problem—but it's significantly smaller than what's portrayed in the media and by some government agencies. It's mainly a problem of illicit drug users, not people responsibly using prescription opioids for chronic pain. While deaths from using prescription opioids continue to decrease each year, deaths from illicit opioids continue to increase. One model projects that, of the opioid deaths in 2025, as much as 86% will be caused by illicit opioids.<sup>23</sup>

Unfortunately, in recent years, many of the efforts to reduce opioid deaths have focused on chronic pain patients, rather than on users of illicit drugs. Federal and state laws and guidelines have moved to restrict access to opioids for people in need. Many pain patients, misled by sensational news on the opioid epidemic, are afraid to use opioids, fearing they'll automatically become addicted. And doctors—under great pressure by health plans and state or federal authorities to reduce opioid use—may be overly cautious or afraid to prescribe opioids. Left to suffer are people with chronic pain, who are often stigmatized, not only by the general public, but sometimes by the healthcare professionals who should provide help and relief from pain.

You don't have to suffer pain every day. If pain affects your quality of life, causes depression, prevents you from sleeping through the night, or stops you from daily activities, then consult with a pain specialist to develop a plan to get your pain under control and your life back on track. ☺

20. T. L. Mark and W. Parish, "Opioid Medication Discontinuation and Risk of Adverse Opioid-Related Health Care Events," *Journal of Substance Abuse Treatment* 103 (2019): 58–63. 21. J. R. James, J. M. Scott, J. W. Klein, et al., "Mortality After Discontinuation of Primary Care-Based Chronic Opioid Therapy for Pain: A Retrospective Cohort Study," *Journal of General Internal Medicine* 34 (2019): 2749–55. 22. "CDC Advises Against Misapplication of the Guideline for Prescribing Opioids for Chronic Pain," [www.cdc.gov](http://www.cdc.gov). 23. Michael Devitt, "Research Shows Nation's Opioid Epidemic Is Far from Over More Comprehensive Approach Is Needed to Reduce Opioid Use, Deaths," *American Family Physician* Feb. 20, 2019, [www.aafp.org](http://www.aafp.org).

## — MANUFACTURER —

### Welcome Esperoct

Novo Nordisk has launched Esperoct, a PEGylated recombinant extended half-life factor VIII replacement therapy for adults and children with hemophilia A. Indications include routine prophylaxis to prevent or reduce the number of bleeding episodes; treatment and control of bleeding episodes; management of bleeding during surgery in people with hemophilia A. **Why this matters:** Esperoct's half-life is extended 1.6 times in adults and adolescents, and 1.9 times in children, compared to standard half-life factor VIII products.

*For info:* novonordisk-us.com

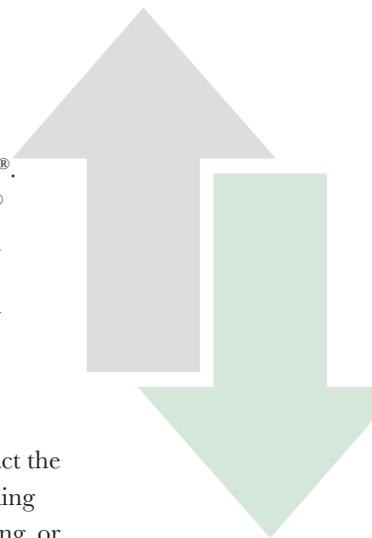


### Shift in Share

In the first quarter of 2020, about 23% of US hemophilia A patients used Genentech/Roche's Hemlibra®. For hemophilia B, Pfizer's BeneFix® (recombinant factor IX) maintained its market leadership, but dropped below 50% of patients in the survey sample, as more patients switch to extended half-life products.

**Why this matters:** Changing market shares of products can impact the community in different ways, including increased or reduced charitable giving, or sales and acquisitions of products.

*For info:* marketingresearchbureau.com



### Another Injectable Being Studied

Catalyst Biosciences completed dosing and a 30-day follow-up for its open-label phase IIIb trial of subcutaneous dalcinonacog alfa (DalcA) in six adult male subjects with severe hemophilia B. DalcA is an investigational recombinant factor IX variant. After 28 days of daily sub-Q dosing, factor IX levels above 12% were achieved. No antibodies were

detected; no serious adverse events reported. **Why this matters:** This is the first sub-Q factor IX product to reach effective factor levels.

*For info:* catalystbiosciences.com

### Recall: Stimate®

CSL Behring and Ferring Pharmaceuticals are recalling some lots of Stimate Nasal Spray (DDAVP, desmopressin) distributed after January 10, 2018. Stimate is owned and manufactured by Ferring Pharmaceuticals Inc., and is distributed and sold in the US by CSL Behring. It's being recalled because the potency of some lots is higher than specified. Contact your pharmacy to learn if your vials are involved, or visit National Hemophilia Foundation's (NHF) website, to see MASAC Advisories 426 and 427. **Why this matters:** High levels of DDAVP may lower levels of sodium in the blood, potentially causing seizure, coma, and death.

*For info:* call CSL's Medical Information line, 800-504-5434

## — SCIENCE —

The US Food and Drug Administration (FDA) denied approval of BioMarin's factor VIII gene therapy product, Roctavian (previously branded as Valrox, BMN 270), for this year. In a letter to BioMarin, the FDA stated that it needs more time to consider the clinical data. The FDA is requesting complete results from two years of follow-up on the 134 patients in the company's phase III GENER8-1 trial, which investigates the safety and effectiveness of a single infusion of Roctavian in adults with severe factor VIII deficiency. **Why this matters:** Although hopes were high for an approval for the first gene therapy this year, it will now be another year or more before gene therapy will be commercially available.

*For info:* biomarin.com



## — GLOBAL —



### Year of Growth

Save One Life's 2019 Annual Report shows growth in programs for child sponsorship, college scholarships, and micro-enterprise grants for patients with bleeding disorders in developing countries. One-to-one sponsorships, the flagship program, boasts \$432,962

donated to 1,455 children and young adults in direct financial assistance. Project SHARE donated over 7 million IU of factor to 30 developing countries. **Why this matters:** Save One Life offers immediate aid and relief directly to patients, and allows families in developed countries to directly impact another family or patient.

For info: [saveonelife.net](http://saveonelife.net)

## — PROGRAMS —

### Hemophilia on iTunes!

The documentary *Bombardier Blood* is now on iTunes and other streaming platforms! The extraordinary story of mountaineer Chris Bombardier, who has hemophilia B, and his quest to conquer the Seven Summits is available for \$12.99. The movie explores

Chris's motivation for undertaking these death-defying climbs, and follows his journey to Nepal to summit Mt. Everest.

**Why this matters:** Part of the proceeds from the sale and rental of the film will go

to support Save One Life's programs in developing countries.

For info: [bombardierblood.com](http://bombardierblood.com)

## — SOUNDBITES —

- Takeda's Advate (recombinant factor VIII) held its US **market leadership** position with 35% of the hemophilia A market. (Marketing Research Bureau)
- The 2019 US plasma proteins market, including recombinant products and nonfactor therapies, totaled just over **\$17.2 billion**, up 6.6% from a year earlier. (Marketing Research Bureau)
- The US FDA approved **Pfizer's** supplemental Biologics License Application (BLA) request for BeneFIX to include an indication for routine prophylaxis in adults and children with hemophilia B.
- The third edition of the **World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia** offers practical recommendations on diagnosing and managing hemophilia.
- **BioMarin Pharmaceutical** estimates that its hemophilia A gene therapy, Roctavian (formerly Valrox), could cost as much as \$3 million per patient, making it the most expensive drug ever approved.
- **Sobi** and **Sanofi Genzyme** announced a donation of up to 500 million IU of clotting factor therapy in support of WFH's Humanitarian Aid Program, and are recognized by WFH as visionary founders of the program.
- CSL Behring has acquired exclusive global rights from **uniQure** to commercialize AMT-061, a potential gene therapy for hemophilia B, now in a pivotal phase III clinical trial.
- Novo Nordisk and Genentech have warned healthcare professionals that their respective hemophilia treatments, Rebinyn<sup>®</sup> and Hemlibra, can interfere with some common lab tests that measure blood coagulation; this is a medical concern in patients with **COVID-19** who experience blood clotting. The two companies recommend using alternative blood tests.

Sadly, many people with bleeding disorders have been offered pain medications as the only solution to their pain. Too much reliance on pain meds may be nothing more than a *deception* that obscures the true problem(s). While effective over the short term in tamping down pain signals (the effects), pain meds also disguise the complex set of underlying factors (the causes). If we don't address the true causes of pain, and instead focus solely on the effects with pain medication, the condition or behaviors at the root of pain will get worse, not better.

So, is pain your enemy, or is it your collaborator? If you want to live a long and healthy life, pain can't be reduced to your tormentor. Don't let your pain be in vain by seeking

remedy only through pain medications. You can't arrive at the underlying causes of your pain when you are literally numb to them. Our pain is not what ruins life; it is what prolongs life, but only if we listen and learn from it. @

*Corey Pierce is a PhD candidate in public health at Oregon State University. He is currently completing his PhD dissertation, which explores how pain attitudes are connected to the experience of pain and use of pain medication. Corey has severe hemophilia A. He is active in the bleeding disorder community as an advocate and teacher of yoga, and he serves on the board of Pacific Northwest Bleeding Disorders.*

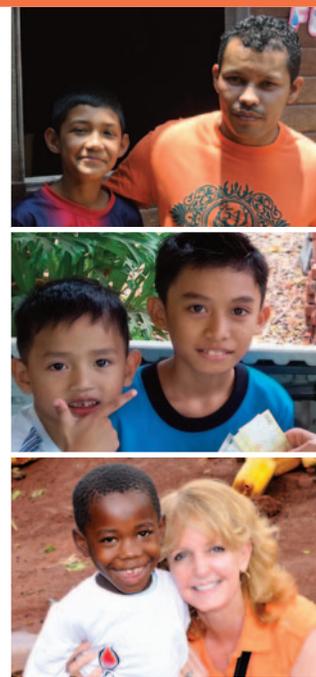


## PROJECT SHARE is now part of

**Save One Life!**

*Do you have factor to donate?*

**Contact: [info@saveonelife.net](mailto:info@saveonelife.net)**



### *Inhibitor Insights... from page 4*

through June 2020, 26 Hemlibra patients died worldwide, 9 of them in the US, as reported in FAERS.<sup>4</sup> During the same period, 95 patients died worldwide when on recombinant activated factor VII (rFVIIa, including NovoSeven<sup>®</sup> RT, a bypassing agent sometimes used by people with inhibitors), including 3 in the US. Worldwide, 88 patients died while on FEIBA (anti-inhibitor coagulant complex, a bypassing agent sometimes used by people with inhibitors), 13 in the US. And a total of 34 patients died worldwide while on the factor VIII concentrates Advate<sup>®</sup> and Elocatate<sup>®</sup>; 11 were in the US.

Do the deaths mean that all of these drugs are dangerous? No. Does the fact that these fatalities were reported to FAERS mean that the drugs caused the patient deaths? Again, the answer is no.

### **Association versus Causation**

Why are these deaths listed in FAERS if the drugs didn't cause them? First, we need to understand a key word in the FDA definition of an adverse event: *association*. An association (or correlation) is a statistical relationship between two variables; in this case, death and being on Hemlibra. People may be frightened by the FAERS data or data in Genentech's fatality report, because they often misinterpret an association to mean *causation*. They assume that a variable (like being on Hemlibra) *directly caused* a health outcome (like death). But most associations are random, coincidental relationships between variables; one thing doesn't necessarily cause the other.

4. FAERS doesn't allow users to filter data down to individual months.

It's not surprising that we may confuse association with causation. We're bombarded daily by media making this mistake, especially sensationalist journalism, where associations are intentionally written as causations to create eye-catching (but false) headlines. For example, the headline "Credit Cards Make You Fat and Dumb!" states a cause-and-effect relationship. The actual research shows that compared to people who pay cash, people with credit cards tend to (1) spend more, (2) purchase more unhealthy things, and (3) pay less attention to their finances. All three of these statements are associations, but none is an example of causation; having a credit card does not make you "fat and dumb."

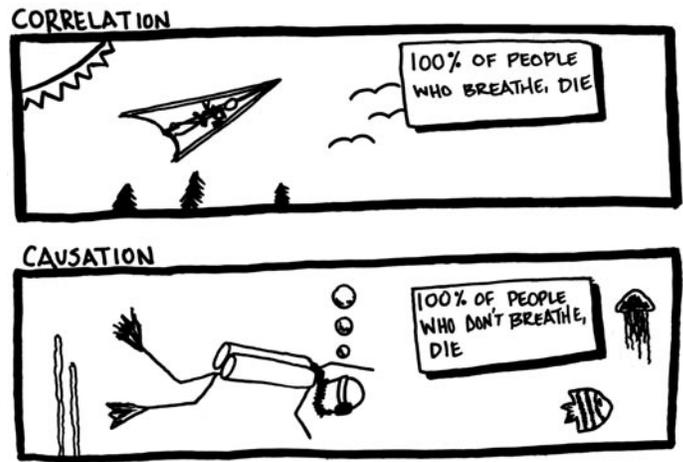
Be careful not to jump to conclusions about an association between variables. Don't assume that causation—a cause-and-effect relationship—exists.

## The Real Cause of Death

How did some of the people on Hemlibra die? And how do we know that Hemlibra wasn't the cause?

Of the people in the Genentech fatalities report, 16 had inhibitors. Having an inhibitor increases the chance of death by as much as 70% compared to having no inhibitor, *regardless of type of treatment*.<sup>5</sup> Of the people who died, nine had acquired hemophilia A (this is an *off-label* use of Hemlibra, not FDA-approved). Acquired hemophilia A is a very rare autoimmune disease, usually affecting the elderly and involving massive bleeding under the skin and into muscles. It's often associated with another underlying medical condition, such as cancer. Acquired hemophilia is a medical emergency, but because it's so rare, an accurate diagnosis is often delayed, so there's a high mortality rate: between 28% and 42%.<sup>6</sup>

Other patients in the Genentech report died of cirrhosis of the liver (hepatitis C infection, contracted through contaminated blood products, is the most common cause of cirrhosis for older people with hemophilia). Others died of cancer and causes not related to taking Hemlibra. An analysis of the cause of death between different classes of hemophilia therapies showed no significant differences; in other words, people were dying of the same causes at similar rates, both before and after the drug was introduced.<sup>7</sup> (Significant differences in the cause of death—provided the sample size is large enough—might indicate a problem with a product.) The same goes for deaths of people being treated with FEIBA and NovoSeven: the drugs are not the cause of the deaths; and although NovoSeven has a significantly higher death rate than FEIBA, that's largely



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because NovoSeven is used more often off-label, especially in heart surgery.<sup>8</sup>

Also, remember that the information in the FAERS database is not "clean." The FDA cautions users of FAERS that the data alone does not indicate the safety profile of a drug or biologic, and the database has other limitations, too. Here's why there may be discrepancies between the FAERS database and adverse events reports from manufacturers like Genentech:

- Duplicate and incomplete reports are in the system. Doctors, patients, and pharma companies may all report the *same* single incident, possibly inflating the number of cases of an adverse event. This also means that rates of occurrence can't be established from these reports.
- Existence of a report *does not establish causation*.
- Information in reports has not been verified. Submission of a report doesn't mean it has been medically confirmed, or that the drug caused or contributed to the event.

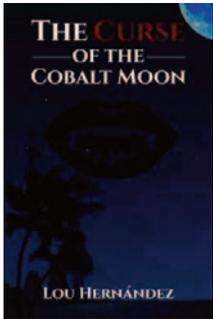
## The Bottom Line

For reliable information, visit websites of National Hemophilia Foundation (NHF), Hemophilia Federation of America (HFA), and World Federation of Hemophilia (WFA). When on social media, take online posts with a grain of salt: distinguishing between *causation* and *association* is sometimes tricky, and people posting may not know the difference.

If you're unsure about something, speak with the person who can give you firsthand information—your hematologist! Make your hemophilia treatment center (HTC) your first stop for information. And don't spread fear or contribute to the problem by repeating misinformation on social media. ☺

5. C. E. Walsh, J. M. Soucie, and C. H. Miller, "United States Hemophilia Treatment Center Network: Impact of Inhibitors on Hemophilia A Mortality in the United States," *American Journal of Hematology* 90, no. 5 (2015): 400–405. 6. A. Tiede, R. Klamroth, R. E. Scharf, et al., "Prognostic Factors for Remission of and Survival in Acquired Hemophilia A (AHA): Results from the GTH-AH 01/2010 Study," *Blood* 125, no. 7 (2015): 1091–97. 7. NHF 2020 poster of analysis of fatalities in people with hemophilia: [medically.gene.com/global/en/unrestricted/haematology/diseases/hemophilia-a/materials/an-analysis-of-fatalities-in-persons-with-congenital-he.html](https://medically.gene.com/global/en/unrestricted/haematology/diseases/hemophilia-a/materials/an-analysis-of-fatalities-in-persons-with-congenital-he.html) 8. If rFVIIa and FEIBA have higher death counts, why is Hemlibra being singled out on social media? It's likely that Genentech's reported fatalities bring attention, and most people aren't aware of deaths of people using other hemophilia products.

cuts with coconut butter. Budi fears internal bleeds. He gets in trouble with the local slumlord, who wants to steal a shipment of football boots and use the shipping container for human trafficking. During the botched crime, and in the aftermath of an earthquake, both the slumlord and Budi's uncle are killed. Yet Budi ends up with all the trafficking money, which he unselfishly gives to a friend. Budi's bleeding disorder is never identified, but a poorly educated boy in a developing country who can't afford healthcare may not be correctly diagnosed and treated.



### **The Curse of the Cobalt Moon**

*Lou Hernandez*

Austin Macauley Publishers, 2019

Rodolfo Josue Puig, who goes by “Joshua” to fit in, is a high school junior living in South Miami. Born in Cuba, Joshua was only nine when he was specially airlifted with other Cuban children to America in 1960. With no

family members to help him, Joshua lives in a foster home. He loves playing on the varsity baseball team. Like his grandfather, Joshua has hemophilia that he treats with a daily injection of

fibrinogen. After a fight with a teammate, Joshua is suspended from the school baseball team for his hemophilia, not because of the altercation. From a classmate, also from Cuba, Joshua learns that he is a docile half-vampire because his human mother married a vampire. On the hunt night of the cobalt moon, hostile half-vampires (having a human father and vampire mother) drain the blood from docile half-vampires to become full vampires. Joshua and his classmates (some are also docile half-vampires) make many fatal errors of judgment while fleeing for their lives, but they eventually escape. Apparently, being a docile half-vampire improves baseball skills and reduces the bleeding due to hemophilia. The treatment of hemophilia seems inappropriate for the 1960s, and the genetics of vampires is never fully explained.

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Based on these fictional characters, the future of our community seems promising. All the young protagonists with bleeding disorders who are depicted in these novels share a trait: they have a passion for what they do, whether it's sports or science. And there is tension or conflict that the fictional characters overcome. That explains each story's drama. Explaining vampirism is more difficult. ☺

your breathing patterns to induce relaxation. Guided imagery is a conscious meditation technique of relaxation followed by visualization of a soothing mental image, like walking on a beach at sunset. Barbara Forss, who has factor VII deficiency, recalls, “As a child, I developed a way to go to a ‘lovely place’ in my head during episodes of pain. I suppose it would be considered a form of guided imagery. While not taking the pain away, it helps me to manage it. As an adult, my lovely place is much the same as when I was a child. Just bigger...and with more animals!”

*Biofeedback Training.* You can learn how to recognize and change your biological reactions to stress and pain by using electronic equipment to monitor your physical responses: brain activity, blood pressure, muscle tension, and heart rate.

*Behavior Modification.* Some people with severe chronic pain may become anxious, depressed, homebound, dependent, or bedridden. Behavior modification helps you create a step-by-step approach to confronting challenges by changing your behavior and shifting your attitude. Matt Barkdull, a man with hemophilia B who is also a licensed mental health specialist, says, “Behavior modification and stress management are my go-to interventions. I resist the urge to curse my bad luck, attack my self-identity, or become bitter (for that which we harbor

is that which we attract). I believe pain is there to teach me a lesson, to remind me to appreciate better days ahead. When I meditate upon these things, I become more grateful for the important things in my life, and make better decisions. These interventions seem to work best when pain is dull but constant and for bleeds that are relatively minor but have caused some mobility problems that will require a little time to heal. Spiking and blinding pain (deep muscle bleeds from injury) often requires me to reach out and share my struggles, perhaps take a pain pill or two, and seek some relief. It's hard to be mindful while battling the sting of acute pain. However, I find if I deliberately engage in deep-breathing exercises and stay connected while avoiding allowing my mind to wander and unhinging from false perceptions, the pain is much better controlled.”

*Stress Management Training.* If your pain level is high, your stress levels probably are, too. This training helps you maintain a routine schedule for activity, rest, and medication. It incorporates exercise or physical therapy into your daily routine, and trains you to keep a positive outlook.

*Hypnotherapy.* Therapeutic or medical hypnosis directs your focus inward to help you relax and reduce pain and anxiety.

You can learn self-hypnosis from a trained hypnotherapist.

*Counseling.* Individual, family, or group counseling with a professional trained in pain management can provide emotional support and guidance. Tina Battillo, mother of two young children with hemophilia A, notes that anxiety is a type of pain: “Most of my boys’ pain is anxiety-related. It causes discomfort. I feel my children are more anxious than non-hemophilic kids because they associate injury with the added step of factor.” Matt Rollins adds, “Speaking with a mental health professional and learning meditation helped me the most. I can’t tell you how at peace I became when my mind accepted the fact that pain is part of my life and I can turn it into power and motivation to help others.”

*Acupuncture.* Many patients report pain relief from this ancient Chinese technique of inserting and manipulating thin needles into specific points on the body known to control pain pathways.<sup>2</sup>

Dozens of other therapies, including acupressure, massage, and chiropractic manipulation, may help control pain. Transcutaneous electrical nerve stimulators (TENS) deliver electrical impulses to interfere with pain transmission. Ultrasound therapy warms joints internally to provide pain relief, and laser treatments may provide relief in a similar way.

A good management plan for chronic pain must be personalized. It should use a multimodal approach, which addresses the psychological component of chronic pain by treating depression and reducing anxiety and stress. A multimodal approach includes *adjuvant* therapies (antidepressants and anticonvulsants); an exercise and/or physical therapy component; and some form of CAM, which allows the person to manage moderate to severe chronic pain with the lowest possible dose of painkillers.

Here’s how Maxwell Feinstein, a person with hemophilia A, sums up personalized pain: “I’ve had to learn to understand my pain in ways that were perhaps discouraged at an earlier age. Pain is a friend; it’s part of me. I’m learning from it every day and learning to live with it makes it less of a burden.” ☺

2. Acupuncture is safe for people on prophylaxis. National Hemophilia Foundation (NHF) advises that if you’re considering acupuncture, first talk to your hematologist or the staff at your HTC.

# inbox

## “Meet Your Child’s Joint!”

(PEN, May 2020)

ONE OF THE GREATEST LIFE-CHANGING quips states, “Doctor, it hurts when I do this.” “Well, don’t do that!” the doctor replies. How simple, but difficult to master. Planning, organizing, and follow-through are essential in life as we mature. At an early age, hopefully, there is someone who will guide us in our decisions and life choices. Think before acting: “What are the possible outcomes of my next move?” Just a moment of clear thought, resisting the impulse to jump, will make our lives, and the lives of those who love and care for us, better. Just think of your last bleed. Today, make a strong commitment to stop, look, and think.

Stephen Choate Place  
Massachusetts

## “Being Better at Life”

(PEN, August 2020)

I AM A FAN OF BUBBA. His ability to address his challenges mirrors that of many in our community. His father Derek Markley recognizes how Bubba’s hemophilia has taught the rest of the family how to handle life’s curve balls. My boys always joke about my dismissal of their cuts and road rash with my standard “Don’t worry, you’ll clot” retort. I have friends who are worse off than me, so I don’t have much time for complaining. Bubba should give classes.

Randy Curtis  
California

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