



# Opioids: Know the Risk

DEATHS AND SUICIDES IN CHRONIC OPIATE USERS ISN'T JUST  
A PROBLEM FOR HEROIN ADDICTS.

Rebecca Knight, MD | KCIH | January 28, 2018

Please read this document and sign below to attest that you will NOT attempt to lower your doses or taper it without consulting our office. This is of critical importance.

\_\_\_\_\_ Signed \_\_\_\_\_ Date

## Heath Ledger, Prince, Chris Cornell

These men all died due to an opiate overdose. Heath and Chris were also taking benzodiazepines. Prince may have as well, but I didn't catch what his final autopsy showed. I assumed Heath died of a heroin overdose, but he didn't. It was prescription narcotics. These people make big news because they're stars but in the past year, two of my patients died both chronic opiate patients. I suspect suicide was possibly the motivation for one and the other I know even less. However, both patients had chronic pain that had worsened in the past year and for which we weren't able to do much to help. That's why I worried that their deaths were suicides. I'm bringing this to your attention because I don't want to lose anyone else.

The increase in deaths nationwide has brought this issue under scrutiny and insurance companies are already limiting the amount of opiates some patients will be allowed to take. This has happened in the past 12 months to three patients so far (and not the same ones who died.) The first patient this happened to in the practice, we at least had 30 days warning. The second patient received no warning, just a simple denial when she went to refill a prescription. The timing could not have been worse because she was just 10 days from going through surgery. I'm predicting it's going to happen to all the plans very soon. So, we need to discuss it before it happens in case you are also not given any warning. The third was told they had to choose, but they could not fill scripts for both opiates and benzodiazepines anymore.

These changes have already happened for a few plans but I expect will be widespread soon:

- Limits on the # of pills that can be dispensed in a month. (Cigna did this and just set it at an arbitrary #180).
- Limits on daily dosage using Morphine Milligram Equivalent (MME) to move toward doses < 50 MME per day.
- Not allowing prescriptions for benzodiazepines for a patient taking opioids.

### CALCULATING YOUR MME

Choosing to limit a number of pills dispensed is a stupid idea. But that's what Cigna did October 1, 2017 with no warning. One reason it's stupid is because they didn't say anything about dosage. If a patient was taking hydrocodone 5 mg with 325 mg of acetaminophen and was getting #240 pills a month now they could only get #180. It doesn't mean they couldn't buy the remainder with cash either-that was allowed. However, I could also change them to hydrocodone 10 mg/acetaminophen 325 mg which is double the hydrocodone strength and recalculate their prescription so that it is under the cutoff number. New script is #120 with half the Tylenol. Well that's probably better for the liver anyway. But if you're already on the 10-325 there isn't a higher dose, so that means you're

going to have to pay for the rest or have withdrawal symptoms this month. Another reason it's stupid is that they are not giving people a chance to at least taper gradually to avoid withdrawal.

If this happens to you, and you are on the highest dose of that medication, then you at least want to buy the extras if you can afford them and contact us immediately so we can figure out a taper schedule to reduce your risk of withdrawal.

The next limit is going to be on MME or Morphine Milligram equivalent dosing and this makes more sense. If they don't allow a taper period though, it's going to send a lot of people to the hospital or worse. The reason for this approach is based on a national sample of Veterans Health Administration patients with chronic pain on opiates from 2004-2009. Patients who died of opioid overdose were prescribed an average of 98 MME/day, while other patients were prescribed an average of 48 MME/day. Taking higher doses of opiates at a dosage higher than 50 MME/day doubled the risk of those on < 20 MME/day.

What's the MME risk of your daily dose of opioids? Better sit down because it's probably going to shock you. Ten tablets of hydrocodone-acetaminophen 5/325 is equivalent to 50 MME. 33 mg of oxycodone is equivalent to 50 MME. Only takes 12 mg of Methadone to equal 50 MME.

Opioid (doses in mg/day except where noted)	Conversion Factor
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone (I refuse to prescribe this drug)	
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

Let's say, for example, you are currently using the Duragesic patch at 100 mcg/hr, TWO patches every 72 hours. (Some people switch them every 48 hours and I'm sure that won't fly anymore soon.)

Fentanyl 200 mcg/hr x 2.4 conversion factor = 480 MME!!!

Yes, 480 MME and your insurance company may decide you can't have more than 50 MME very soon. I'm not telling you this to cause panic. It's a much bigger panic if you find

this out when you go to refill without any warning. It's happened to three patients so far so I know it's only going to increase. So, we all need to be prepared.

## Other Pain Options

Thank goodness we live in Illinois and some of you can qualify for cannabis. I was a skeptic about cannabis five years ago. I thought there was no way it could possibly do everything they said it could do because then it would be a miracle drug. The reason I mention cannabis before other prescription drugs is that I learned a couple years ago that it lowers opioid tolerance. Yes, it lowers opioid tolerance. That's a good thing when you aren't going to be able to take the same dose anymore. It also helps with pain. So that's a win-win. But it's not approved for chronic pain YET. Hopefully it will be very soon.

Meanwhile it is approved for the following conditions:

To be eligible for a medical cannabis card in Illinois, qualifying patients must be diagnosed with a debilitating condition, as defined in the Compassionate Use of Medical Cannabis Pilot Program Act.

- Agitation of Alzheimer's disease
- HIV/AIDS
- Amyotrophic lateral sclerosis (ALS)
- Arnold-Chiari malformation
- Cancer
- Causalgia
- Chronic inflammatory demyelinating polyneuropathy
- Crohn's disease
- CRPS (complex regional pain syndrome Type II)
- Dystonia
- Fibrous Dysplasia
- Glaucoma
- Hepatitis C
- Hydrocephalus
- Hydromyelia
- Interstitial cystitis
- Lupus
- Multiple Sclerosis
- Muscular Dystrophy
- Myasthenia Gravis
- Myoclonus
- Nail-patella syndrome
- Neurofibromatosis
- Parkinson's disease
- Post-Concussion Syndrome
- Post-Traumatic Stress Disorder (PTSD)
- Reflex sympathetic dystrophy
- Residual limb pain
- Rheumatoid arthritis
- Seizures (including those characteristic of Epilepsy)
- Severe fibromyalgia
- Sjogren's syndrome

- Spinal cord disease (including but not limited to arachnoiditis)
- Spinal cord injury is damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity
- Spinocerebellar ataxia
- Syringomyelia
- Tarlov cysts
- Tourette syndrome
- Traumatic brain injury
- Cachexia/wasting syndrome

*Last updated November 1, 2016*

It's a strange list for sure. Many people suffer from anxiety but if you have: recurring nightmares; avoid going places or doing things that remind you of a traumatic event; are very easily startled; or have developed negative changes in your beliefs and feelings; then you likely have post-traumatic stress disorder.

If you have a terminal illness (which means your life expectancy is less than 6 months) you also qualify and don't have to pay any fees to get the card. Cancer is a broad category and qualifies with reduced fees. Both categories also get expedited with a typical turnaround time of 15 days.

## Other Pain Approaches

The main reason we have chiropractic, physical therapy and massage therapy in our office is to help pain patients to improve their function and decrease their pain. Just because you've been in pain a long time doesn't mean there isn't room for improvement. Both Dr. Miles, our chiropractor, and Dr. Goeken, our physical therapist, offer needling options as well. Manual therapy is also available and sometimes covered by insurance. Unless your insurance requires one you can see Dr. Miles for an evaluation without a referral from me. (Health Alliance requires a referral.) The important thing is that these physical medicine modalities are very low risk and work by restoring normal movement and function, when possible, to your musculoskeletal system. They also reset or retrain the nervous system and increase fluidity and movement to the fascial system. Needling and acupuncture work well by stopping the nerve signaled-muscle spasm. Dr. Miles can also use acupuncture the more traditional way to work on lines of energy. But in 2018, you need to understand that chiropractors don't just adjust people, physical therapists aren't just watching you do exercises, and massage therapists are doing a lot more than Swedish massage. If you tried these disciplines before with poor results that doesn't mean they won't help now. Everyone's hands-on skills are different and different strokes do work for different folks. So, try something new and keep searching.

## Other Prescription Medication Options

### ANTICONVULSANTS

When it comes to pain that's from neuropathy or neuralgia, the opiates don't really work they just make you care less. The better choice is an anti-convulsant or an anti-depressants. The medications that work for pain in this category are Neurontin (gabapentin) and Lyrica (pregabalin) for first-line choices. They are started at a lower dose and titrate up to find a dose that works but is also tolerated well. Gabapentin usually starts at 300 mg a day usually and titrates up to as much as 1800-3600 mg/daily. Most won't need close to that dose. The most common side effects of gabapentin are drowsiness, dizziness, and I felt less sharp. I still could take it for four years during my medical training so it's probably the most tolerable of the bunch. Lyrica is still a brand name drug so it's much more expensive. Its advantage is reaching efficacy faster with less side effects EXCEPT for some it'll cause water retention, edema and weight gain. Other anticonvulsants that work well include Topamax (topiramate) has been well studied for migraine prevention. It might work for other pain and its side effects are weight loss, paresthesias, and drowsiness. Tegretol (carbamazepine), Depakote (valproic acid) and Lamictal (lamotrigine) have been used as well for neuropathic pain but are usually tried after the others were not successful.

### ANTIDEPRESSANTS

Anti-depressants do help pain but doctors often do a poor job of explaining this and anger the patient that thinks this is their way of saying it's all in their head. But that's not the case. Pain signals, like other brain signals, are mediated by neurotransmitters. The drugs that affect neurotransmitters therefore can all affect pain.

Anticonvulsants help epilepsy by slowing down nerve transmission and that helps pain too. Antidepressants increase serotonin and norepinephrine which are involved in pain transmission in the spinal cord and decrease or dampen pain signals. Some may take both groups of medication and they can work together.

The oldest class of antidepressants are Tricyclic Antidepressants (TCAs). They all have similar sounding names, Elavil (amitriptyline), Tofranil (imipramine), Anafranil (clomipramine), and Pamelor (nortriptyline) to name a few. They have successfully been used for neuropathic pain including post-herpetic neuralgia, sciatica, diabetic neuropathy, idiopathic peripheral neuropathy, spinal cord injury, stroke, radiculopathy, trigeminal neuralgia, migraine, and more. They also work for irritable bowel syndrome, tension headache, and interstitial cystitis. They all have similar side effects that are usually not a problem at very low doses and thankfully they usually don't require higher doses like they did to be effective for depression. As you raise the dose they can increase drowsiness,

blurred vision, dry mouth, nausea and constipation so you stick to low doses. But taken at night they improve sleep, which is often a time when pain is at its worst.

Another class of antidepressants are serotonin and norepinephrine reuptake inhibitors. They mediate pain as we already discussed. Now if a side effect is an improvement in mood that's not so bad. But it's not the reason they're prescribed for pain. Cymbalta (duloxetine), Effexor (venlafaxine), Savella (milnacipran) have been used for management of diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain. The most common side effects with this group is nausea and the biggest drawback is the withdrawal symptoms when you stop them if you don't taper off them carefully. They give you the strangest dizziness or "brain zaps" as many describe them. Savella was developed in the US for Fibromyalgia only and was FDA approved and for some of my FMS patients was the only thing that worked. But it's limited by formulary coverage and unlike the other two isn't available as generic yet.

## Tramadol

What is Ultram (tramadol) anyway? Tramadol is a synthetic drug that interacts with three kinds of receptors in the body, norepinephrine, serotonin, and mu (opiate) receptors. I was taught that it was not a narcotic but the fact that it interacts with that receptor means it must be an opioid, albeit a very weak one. By blocking the uptake of serotonin and norepinephrine in the spinal column, it is increasing the signals of pain dampening neurons. But it also interacts with the mu receptors so it's technically an opioid but it's 1/10<sup>th</sup> the strength of morphine. Meaning it takes 500 mg of tramadol to equal the 50 mg of Morphine in strength and the maximum daily recommended dose is 450 mg. I think the thinking was it would hit all three receptors and work to reduce pain in a whole new way. But it also can interact with other medications that increase serotonin and norepinephrine such as SSRIs, SNRIs, triptans and then increase risk for Serotonin Syndrome. Some of the most common symptoms of serotonin syndrome include confusion, irritability, disorientation, muscle spasms and/or rigidity, rapid heartbeat, high blood pressure, nausea, diarrhea, tremors and shivering, anxiety, and dilated pupils. I've only seen that once but I've seen milder cases of confusion that I believe were due to a "mini-serotonin syndrome". Unfortunately, there have also been people that became addicted to tramadol and abused it. We had a patient that took 300 pills in a week one time and clearly had a problem. This was before it was changed to be considered a controlled substance. Now, I wouldn't consider it a safe bet in a patient that had prior addiction issues. It's closest in structure to codeine and like codeine can make people nauseous.

## Muscle Relaxers

Muscle relaxers are often prescribed for acute pain relief but also taken by people with chronic pain involving chronic muscle spasm. Two of the muscle relaxers used are also controlled substances now, Valium (diazepam) is also a benzodiazepine and Soma (carisoprodol) are schedule IV controlled substances because of their potential for abuse and addiction. Muscle relaxers were never my favorite drug to prescribe because I always wondered how do they know which muscle they need to relax? I may have 2 muscles that are spasmed and causing pain but how will this medication know to only go there. I don't want my other muscles to relax. But later I realized they did help one thing very much. Most of them make people very sleepy and when people are in pain they tend to have trouble sleeping. So, I now am more open to prescribing them but I'm only recommending you use them at night and make sure you don't have to drive before they're out of your system. There is one non-sedating muscle relaxer called Skelaxin. I've used it and it felt to me to be like taking an Aleve or ibuprofen. Since I can't take NSAIDs I would consider taking it again if I needed that type of effect. Studies as to their long-term effectiveness or shortening of healing time have been mixed.

## Topical NSAIDs

Various formulations of topical NSAIDs are available, including Voltaren gel, Pennsaid solution, and Flector patch, and are used in the setting of osteoarthritis or musculoskeletal pain. I like this idea because I'm directing the medication then to where I need it. Aside from those three commercially available products there are plenty more that can also be compounded. In clinical practice, these agents are often considered when there is a contraindication to oral NSAID therapy, such as cardiovascular disease, kidney impairment, or history of gastrointestinal bleed, as the systemic absorption of diclofenac with these formulations is low. For example, the amount of diclofenac that is systemically absorbed from Voltaren gel is on average 6% of the systemic exposure from an oral form of diclofenac. Flector patch is dosed as 1 patch to painful area twice daily and is indicated for acute pain due to minor strains, sprains, and contusions. No direct comparison between the various topical diclofenac formulations has been performed and in clinical practice the choice often depends on the area needed to cover and other aspects. One of my patients that found Voltaren gel to be very helpful and then about died at the cost. She was on Medicare and it was close to a thousand dollars and not covered!

She ended up trying CBD oil and claims it's as effective if not moreso. (CBD oil can be from cannabis or hemp.)

## Oral NSAIDs-Ibuprofen, Naprosyn, Diclofenac, Celebrex, Meloxicam, Aspirin

All the above are NSAIDs which stands for non-steroidal anti-inflammatory drugs. Really these drugs are under appreciated because I can't take them and how I miss them. I used to think why does anyone need Vicodin when they can take ibuprofen. They are powerful and really reduce inflammation by a lot. But some people can't take them that have kidney disease, gastrointestinal bleeding from them, cardiovascular disease, or Samter's Triad. I'm in the last category. Samter's triad used to be considered very rare and now they think it may be 40% of asthmatics. The typical person with this condition develops asthma quickly in their early 20's and had nasal polyps and loses their sense of smell. They often have had sinus and nasal surgery for complete nasal obstruction. Turns out it's all caused by taking NSAIDs. If they continue to take NSAIDs they'll continue to have asthma and their nose becomes blocked again and worse one day with no warning they can have anaphylaxis shock from taking a NSAID. The treatment if they really need to take them for other reasons is aspirin desensitization but then they must take 650 mg of aspirin twice a day for the rest of their life. No thank you. Unless I need aspirin, I wouldn't take that because it doesn't keep me from being higher risk for GI bleeding and that's no fun either. Everyone else can take these occasionally but if you take them daily and have high blood pressure you are risking kidney failure later in life. I hope I don't develop arthritis or I may change my mind and go get aspirin desensitization, because I think this class of drugs work better for inflammation than anything else out there. Besides steroids I should say but they have a whole different set of issues and are usually only used for pain by rheumatologists.

I should address which NSAIDs work best? Which are safest? Everyone probably has tried ibuprofen (Advil) and Naprosyn (Aleve). I personally always thought ibuprofen worked better than Naprosyn and most of the other NSAIDs but admittedly Diclofenac is probably the strongest. Actually, Vioxx was the strongest and yet easy on the stomach, but its no longer available. The safest over the counter is Naprosyn as it's the only one that didn't increase risk of heart attack or stroke. The safest prescription NSAID was meloxicam. It does not appear to increase risk of heart attack compared to either no drugs taken or compared to diclofenac. In elderly patients, limited evidence suggested Celebrex (celecoxib) lowered risk of GI, cardiovascular, and renal adverse events compared to diclofenac and ibuprofen. Aspirin is included in this category and the preferred drug for preventing heart attack and should be taken daily by all men over 50 and women with higher risk of heart attack (>10% on the Framingham risk score).

## Tylenol (acetaminophen)

Many say that Tylenol doesn't do anything. But they would be wrong. I agree with them that by itself it doesn't do much besides bring down a fever. But what it does very well is increase how long other medications stay in your system. It does this because most

medications are metabolized by the liver but, it takes more liver power to metabolize Tylenol so that keeps it busy and it can't metabolize the opioid as fast. It makes tramadol immediate release that might last only two hours then last for six hours. I'm amazed at the number of people that come in with pain that's 5-10 out of 10 and when asked what did you try say nothing. Most homes probably have a bottle of Tylenol, aspirin and ibuprofen in them so if you're an adult feel free to try those first because how the pain responds gives me a clue about the cause. Chances are if Tylenol doesn't work but ibuprofen does then that tells me it's an inflammatory type pain. I'm not saying it's going to drop to zero but hopefully it'll lower the pain score some. People taking chronic opiates ideally would not be taking Tylenol or NSAID regularly. Then when they have a flare in pain they could add those to get through the flare.

## If I knew then what I know now....

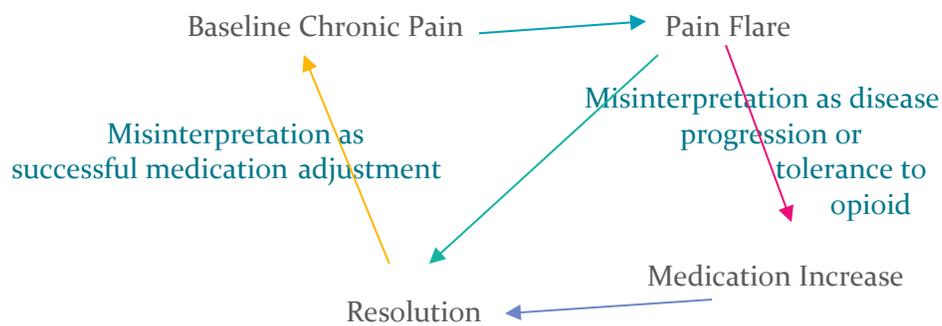
If I could go back in time when you and I sat down and I prescribed you opiates for the first time this is what I would do differently. First, I would do a better job explaining up front how they work and what goes wrong and how we can best avoid that and whatever dose we found worked initially for at least a couple months would be your chronic dose no matter what. I know you're thinking doc that's cruel, but hear me out. This is how it's done when you want to keep the dose low. You don't take any NSAIDs or Tylenol except when you have a flare up. They are very effective at helping a flare. But you must stop them and not take them all the time. This is assuming you can even take these meds. But we're going back in time remember, so your liver and kidneys are still healthy in this scenario and I didn't develop Samter's triad.

Then we would find this magic dose of whatever medicine it is and we keep it at 50 MME or below. To figure out what that equals here's a list of narcotics and their 50 MME dose.

Opioid (doses in mg/day except where noted)	50 MME Dose
Buprenorphine patch	>25 mcg/hr patch
Butorphanol	7
Codeine	333
Fentanyl transdermal (in mcg/hr)	<25 mcg/hr
Hydrocodone	50
Hydromorphone	12.5
Methadone (I refuse to prescribe this drug high risk for overdose)	Variable
Morphine	50
Oxycodone	33
Oxymorphone	17
Tramadol	500

Then when you had a flare in pain I would remind you of this diagram. We would use Tylenol or Ibuprofen to boost your already daily level of opiate with the caveat that you would not stay on those for longer than a week or two. Because the diagram below is what leads us to higher and higher doses and puts you at more and more risk.

### PAIN FLARE-MEDICATION VICIOUS CYCLE



One thing that sucks about being a doctor for sure is that they're always figuring this \*(^% out later and then making us look bad. Had I known most patients would end up on super high doses and then insurance companies would balk at paying for them I'd not have gone there.

Of course, one of my favorite sayings in medicine is: "If you don't like what I'm saying, just wait a year or two and come back and it'll be totally different!"

I also realize that it's doctors that live in the Ivory Towers of Academic Medicine that come up with these ideas of how medicine "should" be working. Later when it's tried by us in the trenches, we realize that most of those doctors see so few patients they have no clue what will really work. But I know that at some point a pain patient usually gets to the dose that their doctor just won't go any higher. What do they do then? They figure out other ways to cope with pain. So, all I'm saying is that we should try to find ways to lower the opiate doses and still manage your pain especially if you're on a very high dose. Be thankful that Illinois has a cannabis program because really, I think it's the answer to this problem. It's one of the few "drugs" out there that you truly cannot over dose on and it has the side effect of making people more mellow. Yeah you can overdo it and get paranoid and it's a horrible feeling but you didn't die and you lived another day. You can still try it



the plant God gave us. This plant is amazing and has so many uses that I can understand it being a part of a religious worship because one of its most endearing qualities is that it gives people empathy. If you have a hard time putting yourself in other people's shoes, as most of us do, then this could be the cure. I'm very empathic, sometimes too much, but I can understand now why people are not empathic feel the way they do, so wrap your head around that one for a while. No one, yes this is true, NO ONE ever died from too much cannabis. You can't say that about alcohol, opioids, or benzodiazepines. You can't even say that about aspirin, ibuprofen and Tylenol.

Is it a gateway drug? Possibly to greater understanding for your neighbor but to harder drugs? No. Your prescription opioid if not kept locked in a safe so your children can't access it is the number #1 gateway drug to heroin use. Yes, this is the truth. Most heroin users started with prescription opiates. If you are between the ages of 15 and 35 and have an injury, you better have broken bones or there isn't going to be any opioids written because this person has a 1 in 10 chance (might be 1 in 4) of becoming addicted to opioids if given a prescription. I broke my wrist when I was 23 years old. It was excruciating and hydrocodone 5mg with 325 mg Tylenol knocked me out for 6 hours. I was pretty much asleep for a week except the night I had to have the first cast cut off because it was too tight and my fingers were black. No pain medication could help that pain and that's a good thing or I'd have lost a hand while knocked out. But I was also a resident in Internal Medicine and didn't have more than a week of sick time so I was back on the wards in a week. The most horrible pain was over and I probably took ibuprofen then as it was before I knew it caused me to grow nasal polyps.

Attention deficit disorder is a risk factor for addiction because of the poor ability of the Prefrontal Cortex in ADD. That's the same area we think is diseased and makes for an addict. So, the real question here is what leads to addiction and what is the difference between addiction and dependence? Two big differences, the addict does not ration their opioid medication but uses it up faster every time because the addict is trying to capture a high they used to get that's is harder and harder to get the longer they use a drug. The addict also must use to feel normal. Once a person has been an addict and especially if it was to opioids they must go through a lengthy rehabilitation program to safely reduce opiate use and can't quit cold turkey. If they quit cold turkey they will never reprogram their brain and will have cravings for the drug that are immense and very difficult to ignore. It is now they often relapse and die because they have lowered their tolerance and forgot that when you first start it suppresses respiration. After you've used for while that no longer happens. But if they stop and start again it happens again and the amount it takes to feel high will likely stop their breathing. This can happen whether you take it by mouth or inject it.

So, it's very important to understand how opiates affected your brain so you understand why you MUST not taper on your own or quit cold turkey. Because even those dependent could make a mistake that is deadly. Speaking of brains, one caveat about cannabis it's

best to avoid the use of products containing THC until after your 18<sup>th</sup> birthday as it may harm the developing brain.

Please read that again and sign below here that you will NOT attempt to lower your doses or taper it without my permission and my guidance. This is of utmost importance.

\_\_\_\_\_ sign \_\_\_\_\_ date (you)

\_\_\_\_\_ sign \_\_\_\_\_ date (witness)

\_\_\_\_\_ sign \_\_\_\_\_ date (me)

## The science of opioids and addiction

I'm going to explain opioid addiction because I have patients that have this problem and I always wondered why it took so long to get out of the methadone program. But I read about it and it gave me a whole new appreciation for how hard it is to get off heroin and other opiates and why it's different than other addictions. Plus, I realized it could still affect those that are dependent (not addicted) when they try to taper down. The whole point is to be healthier. Which reminds me of another reason why this is so important. If you are on a high dose of opioid daily and you require surgery for knee replacement you are going to have some serious pain. You are so opioid tolerant that you will require more pain medication than what the orthopedic doctor or hospitalist are used to writing and chances are they'll be nervous about it so you're not going to get enough. Even I, who's taken an opiate only three or four times in my life now have higher tolerance to hydrocodone. The first time it knocked me out. But I took two Percocet after my hysterectomy and they made me goofy but did nothing for my pain. Or maybe oxycodone just doesn't work for me. I took 30 mg of long acting morphine because it's the equivalent of taking 6 hydrocodone 5mg over a day and that worked perfectly and I never needed another medication. But three days later I dropped a paperclip, yes, a paperclip and it hit my foot and felt like I stabbed it. Why? Because I have Fibromyalgia, and Fibromyalgia people should avoid opiates like the plague because they make our body increase our pain receptors by a lot and make nonpainful stimuli now painful. Luckily if you avoid the opiate it goes back to normal with time.

## The brain and addiction

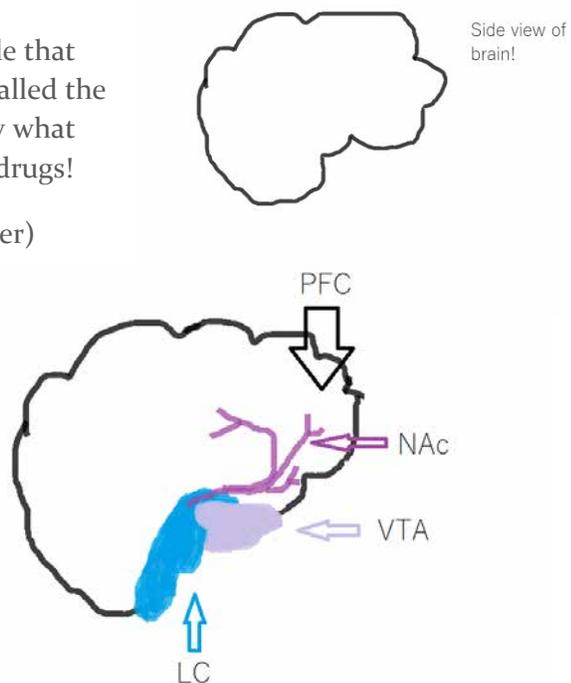
When we eat or have sex and it's pleasurable that pleasure is triggered in a part of the brain called the VTA for Ventral Tegmental Area. You know what this means! I must do this is your brain on drugs!

The Ventral tegmental area or VTA (lavender) causes release of DA (dopamine) in the Nucleus Accumbens (NAc) which causes feelings of pleasure (violet). At first, this also causes sedation due to suppression of release of Noradrenaline (NA) from the LC (Locus ceruleus) by opioids. The LC is turquoise in my drawings.

You take your first Vicodin (Hydrocodone and acetaminophen) for a broken wrist. If you've never broken a bone, the pain is from the muscles trying to put the bone back together by spasming ever 3-4 minutes. It'll make you Lamaze breathe without having attended the class. After taking one Vicodin, the pain stops but you can't keep your eyes open. You sleep. You continue to take these and by the fifth day you can function a little and get up and start cleaning the house. (Maybe you're delirious?)

After the repeated exposure the LC has adjusted and now it's secreting the normal amount of Noradrenaline with the opioids you are taking. I'm not trying to escape the pain of life just the broken arm pain and the cast helps tremendously so I take less and less. But let's say I keep taking it to feel good and I take 2-3 at a time but then I run out! Now the LC without the opiates increases Noradrenaline production to 3 times the normal. That causes anxiety, jitters, muscle cramps and diarrhea. I need to fix that so I look around and let's pretend I find an old prescription in the drug cabinet for Percocet my mom had for surgery. I take them and whew that's better. See how easy it starts?

Over time this kid (not me it didn't make me feel that good) also happens to be ADD and so his or her PFC (prefrontal cortex) doesn't work so well at "delayed gratification". They just think about feeling good now. But now they only feel good when they have some opiate in them. Food doesn't taste as good. Sex isn't as pleasurable. Nothing makes this kid feels as good as it and nothing is as cheap as heroin.



## Opioid Tolerance

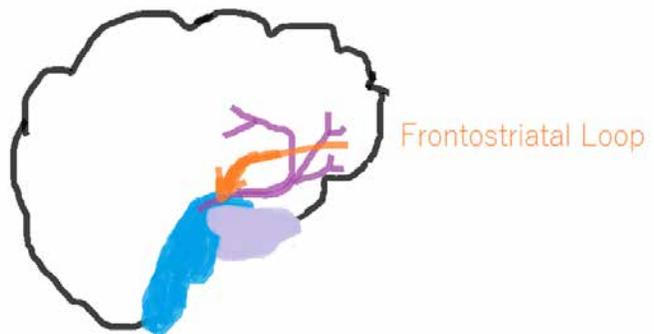
Opioid tolerance happens no matter who is taking it with a working PFC or not. The brain cells that have opioid receptors gradually become less responsive to opioid stimulation. It takes more and more opioid to stimulate the VTA to release the same amount of dopamine (DA). Remember this... **Dope is Mean**. It makes it harder and harder to feel good.

That Noradrenaline secretion is needed to be at a certain level to stay awake, breath, maintain blood pressure and general alertness. NA keeps us alive. They use opioids in surgery as part of sedating us to make us unaware of the surgeon's scalpel and they breathe for us but they must be very careful because our heart still needs to pump and when we wake up we need to breathe for ourselves. Anesthesia is no joke. They take us down under and keep us alive while horrible things are happening. When you're opioid tolerant their job is much, much harder.

Daily use of opioids induces the brain mechanisms of dependence. You must take your opioids frequently enough to not experience the unpleasant symptoms of withdrawal. In addition, they must take a certain amount to even operate normally. Addiction doesn't happen just one way either. That's the

most common way probably but there are other factors that lead to addiction. It's much more likely to happen in a younger brain. The PFC or prefrontal cortex is the "adult" part of the brain that is supposed to signal the mesolimbic system "whoa there, if you wait it will be better". That's called delayed gratification. This is non-existent in the classic addict

model. It can also be broken by abusing Methamphetamine. It's carried out by the fronto-striatal loop shown here in orange. That's not the same as using stimulants for AD/HD in proper dosing but from **abusing** meth. Chronic alcohol abusers also have low GABA. GABA is gamma-amino butyric acid and is the neurochemical the PFC uses to signal the reward system to release the less DA. GABA is important for having patience. I'm convinced that long after the alcoholism is over some still make very little GABA and that's the reason for their "dry drunk" behavior. They have no patience and are always grumpy. Anti-social personality disorder individuals have PFC deficits and are more prone to severe heroin addiction.



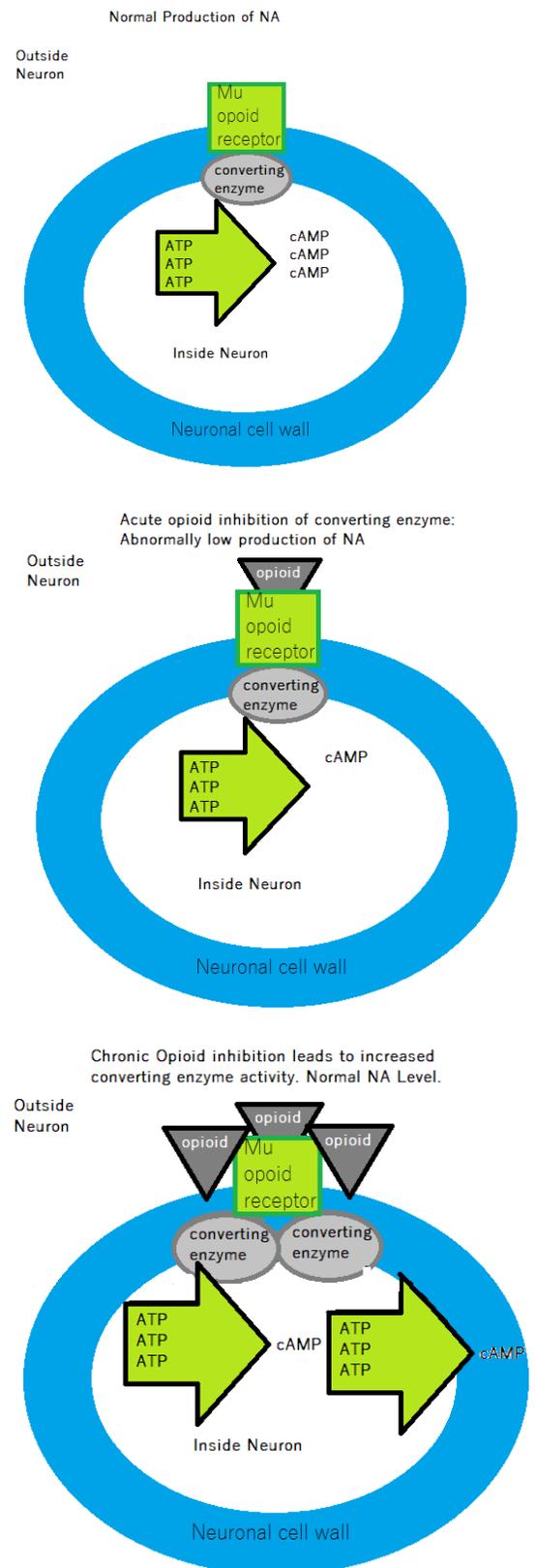
There is still so much to know and I'm sure this is only the tip of the iceberg when it comes to how we understand addiction. But let me explain what is happening in that turquoise area a little more in depth in the next section.

## Neurobiological Basis of Dependence and Withdrawal

To better understand how dependence and withdrawal work they have developed a model. We're going to look at a single neuron this time that lives in that turquoise blue part, the Locus ceruleus (LC). The opioid Mu receptor is the green box in the cell wall and it's linked to this converting enzyme. Normally at baseline this individual is making their normal amount of Noradrenaline to function day to day.

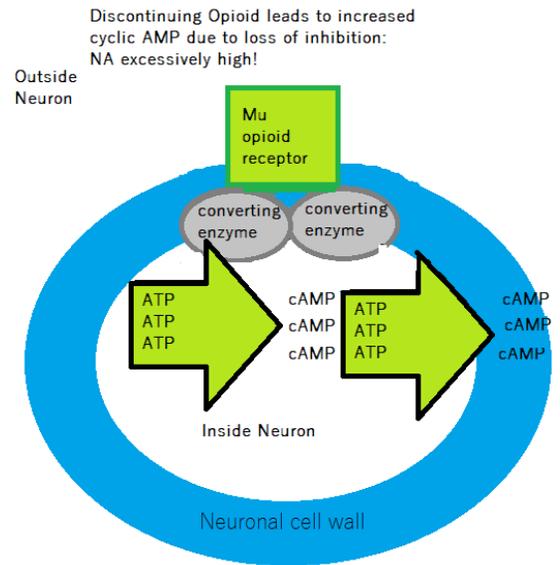
Then they get hurt and take the opioid and it attaches to this green box. The opioid is represented by the black triangle. At first, the opioid inhibits the converting enzyme that converts ATP to cAMP. ATP stands for adenosine triphosphate which is power. ATP is converted to cAMP, cyclic adenosine monophosphate and power is released. But now only one is released for every 3 used. It slows it down. Less Noradrenaline is made. The person is tired, breathing shallower, decreased muscle tone, and not as alert. Therefore, we say don't drive until you see how it affects you but eventually you keep taking it develop tolerance and you can drive again. Why? Because the following happens.

The LC neuron increases its supply of converting enzymes and ATP molecules. Now it can make enough cAMP to offset the effect of the opioids. It will keep doing this so that you can take more and more and it'll keep adjusting to keep you awake, alive, alert and breathing. Then intensity of the opioid is lessened as well so it takes more to be effective.



But now if it were suddenly discontinued the drug's inhibitory effect is lost. But there is more substrate and more converting enzyme now so production of Noradrenaline surges to an all-time high level and the person experiences the symptoms of withdrawal-jitters, anxiety, muscle cramps, diarrhea. If no further drug is taken it will eventually revert to its pre-drug condition in days or weeks.

Meanwhile over in the violet area, it will take longer to adapt to no opioids and may never return to the same release of dopamine from the drug. Now the person is in a very dangerous place. If they take enough opioid to get their rush and feel really good, because the LC is no longer tolerant, then they will not wake up. This is how overdose happens.



## Drug Rehabilitation and Methadone and Suboxone and Rehabilitation

It would seem if this was the whole story addicts would have no hope of getting off heroin or other opiates but that isn't the case. There are medications that can reduce the drug craving that normally occurs as part of withdrawal and can help the addict and still reverse this state of the brain that is most conducive to just worsening the opioid habit. The drugs used the most are Methadone, LAAM (longer acting methadone), Naltrexone and Buprenorphine. Suboxone is a combination tablet with naltrexone and buprenorphine in it. I don't prescribe methadone, LAAM, buprenorphine or suboxone. If someone needs them I would refer them to Dr. George Gilbert. It requires a special DEA license to prescribe suboxone that I don't have and would require I quit my job and work at White Oaks for a while to get enough experience and I'm not interested in this being my full-time work. I also don't prescribe methadone because I had a patient die that was taking it for pain and it was started by her pain doctor. I don't know for sure that she died from over dose of methadone but had I understood more about it then I wouldn't have prescribed it when he asked me to take over. Remember the MME table and it showed methadone had four different conversion factors depending on the overall dose. That's way too hard for me to understand.

Another problem with methadone is it so long acting and that's because it stores in your fat cells and then if you take another medication that interacts with it you can suddenly have it leave the fat cells all at once and overdose you. 25 mg of methadone is fatal if

you've never taken an opiate. Most heroin users start at 200 mg of methadone and work down very slowly. The reason for its use in addiction, is it doesn't produce the euphoric rush that other opiates do. It takes a huge amount of methadone to release any dopamine from the pleasure centers. But take another narcotic or alcohol and it will produce euphoria but it will also quickly kill you when combined with methadone.

Benzodiazepines are often used for opiate withdrawal but it's dangerous because they are also addictive and the combined effect of benzos and opiates is a better high than they are by themselves. You are basically handing the addict the loaded gun. Remember I said earlier that people may have to choose between them, I will tell you now, there is no choice really, opiate withdrawal doesn't kill people but benzodiazepine withdrawal like alcohol withdrawal can kill you so the opiates should go first. We'll worry about the benzo's later. But we also will go with only longer acting ones, temazepam is the shortest I'll write for patients wanting help for sleep that are on opiates from now on and preferably we'll get everyone on both over to valium or clonazepam. I'm certainly not starting anyone on benzos that is already on an opiate if I can help it.

Xanax and Ativan are only good in very small quantities in your sock drawer for the next panic attack because they're too short acting and quickly lead to dependence and then you're taking it every day to keep from having withdrawal but you aren't treating anything else. I wrote that guide first if you haven't read it yet. Ask me for it next time.

I mentioned earlier a veteran's study looking at the difference in overdose rates by how much daily opiate they were taking. Another study of 2,400 veterans that died while taking opioid painkiller prescriptions, 49% were also taking benzodiazepines. It's not an infrequent combination. You have surgery and are given opioid for recovery. You go to a psychiatrist for panic attacks and they put you on a benzodiazepine and neither warns you about using them together. Heck, I haven't warned you properly until now! But we're fixing that. Both drugs now have black box warnings in the package inserts to warn patients. Too bad opiates and benzos don't have commercials so you could hear all their possible side effects including death.

I'm always amazed at the patients that are taking opiates that are worried about a statin hurting their liver. It's hard to not laugh at that question. I recently had a patient at his pain medication refill appointment tell me, I'm not like most people you see, I don't really like taking medications. Had I longer arms? I can imagine what his face would have looked like if I said, "Oh my, my mistake, then you won't be needing these!" And ripped them up before he could say anything. Hello!!!! If you are here to get a refill every 3 months then you are on the most dangerous medications we prescribe and that's why they are controlled substances! You are living dangerously, so don't fool yourself.

Sorry, that's sounding somewhat insensitive. I understand that pain sucks and I've had pain that made me very glad they have drugs like these. But I also know for chronic pain that lasts day to day I'm very glad that I haven't so far ever started to take these

medications every day. I can't walk in your shoes. I don't know what your pain is like. You don't know what my pain is like. I take an amphetamine every day so I'm not casting stones. I'm living dangerously too. Between 1999 and 2006, there was a 250 percent increase in fatal overdoses in the United States due to opioid prescription medications. In 2016, more than 46 patients died every day from overdoses involving prescription opioids. Every day more than 1,000 people are treated in emergency departments for not using their opioids as directed. I was taught that 1 in 10 prescribed an opiate can become an addict but they are saying now it's as many as 1 in 4 when used for noncancer pain. Overdose rates were highest in people aged 25 to 54, higher among non-Hispanic whites and American Indian or Alaskan natives, compared to non-Hispanic blacks and Hispanics. If I asked you to cast someone in a movie to play a drug addict who would you picture. Halle Berry maybe in *Jungle Fever*? Well if you are picturing someone overdosing and maybe you thought they were more likely to be of color, you'd be wrong, they are more likely to be white.

## Naltrexone

Police and EMTs are now carrying naltrexone. I offered a naltrexone pen to one of the patients that died last year before it happened but I haven't been able to find out anything about his or her death. I don't know if it was from opiates but I'm suspicious. I didn't offer it because they were on a high dose. I offered it because this person came to me after being fired from the pain clinic for testing positive for cocaine. We urine tested this person and they passed but I was suspicious that this person could have a history of addiction and therefore felt he or she might want to have Narcan (naltrexone) available in case they ever overdosed.

A patient that was here for a refill on their pain medications was complaining about the cost to taxpayers for first responders to carry Narcan and thought it was a waste of money. That's when I realized I need to do some serious education of my pain patients if they don't get that the Narcan isn't just for saving junkies but for saving them! I'm currently in the business of saving lives so until that changes I will give anyone who's on opiates, a prescription for the Narcan pen for home and one for their car or purse. I wish Prince's people had a Narcan pen. Don't you wish Tom Petty's wife had one? Well my wish for any of you is that you have one if you would ever need it. I don't know what they cost but what is your life worth? Accidents happen. I've accidentally taken two Vyvanse 70 mg. That's the biggest dose they make of this long acting amphetamine. Strangely it made me sleepy. But what if that had been 10 mg of methadone. Not hard to do. Narcan could save the day. You should consider having one and teaching the people you live with how to administer it.

In 2012, 79.9 percent of prescription pain reliever overdoses were UNINTENTIONAL, 13.2 percent were intentional (suicide), 2 percent were considered homicide, and 6.7 percent they couldn't determine.

## Most commonly overdosed prescription opioids

Methadone

Oxycodone

Hydrocodone

## Safest way to taper

Thankfully the state of Washington has put together a whole guide on how to taper down on opiates. They've also put into writing guidelines for what primary care physicians (PCPs) should be comfortable writing and when we should consult a pain specialist. The bad thing about this now being published is that it brings us under scrutiny so I'm going to make sure everyone knows where their daily dose of opioids falls on this scale and then if you are above 60 MME (they use a cut off of 50 MME) we have big decisions to make:

1. If your daily dose is > 60 MME but <120 MME then I'm well within the accepted guidelines to continue to prescribe your pain meds. But I still encourage you to consider tapering to the 60 or lower level. Studies have shown your pain control will not change, your quality of life will improve, and you'll be safer. I want you to consider it but promise to not do anything without my knowledge and assistance.
2. If your daily dose is >120 MME I think we have no choice but to consider planning to taper and I can prepare for that at the next appointment or you can be referred to a pain specialist to continue the medications at this dose level. But if you want to lower them then I can help you do that.
3. If you want to also get a cannabis card that can help but that is also up to you and finding a qualifying condition.
4. I'm willing to write for Narcan for anyone that wants it and encourage you to teach your family members how to use and what to watch for.

If we decide to taper, the schedules available taper down either weekly, every 2 weeks or monthly by 10% of the original dose until you get to 30% of the starting dose. Then start again with that dose as your starting dose and taper down weekly, every 2 weeks or monthly by 10% of that dose until done. So far every 2 weeks tapering has been working the best but that doesn't mean I haven't slowed some of those people down either.

It takes some planning on my part so this isn't something I can figure out in the usual end of the day GO appointment either. I need a heads up if you want to do this ahead of time. The best way to do that is to tell Ian or I a week before your appointment and make the appointment a regular POV not GO appointment (30 minutes). You can email us at [Ian@theknightcenter.com](mailto:Ian@theknightcenter.com) or [drknight@theknightcenter.com](mailto:drknight@theknightcenter.com). Or if you call ask to leave Ian a message. He doesn't get many messages so this is not to be used for other things. He doesn't have time to listen to messages since he's usually running patients so you must get it to him in advance to improve our chances of knowing ahead of time. Or when you make the appointment you must tell Amy or Danielle it needs to be a POV and you want to "taper" down or off your pain meds, so warn Dr. Knight. Use the word TAPER. Just saying I want to talk to Dr. Knight about my medications is something people say all the time and won't get the proper response.

## Resources used in preparing this guide:

Wa State Agency Medical Directors' Group Interagency Guideline on Prescribing Opioids for Pain, 3<sup>rd</sup> Edition, June 2015

Kosten TR, George TP, "The Neurobiology of Opioid Dependence: Implications for Treatment", Science & Practical Perspectives, July 2002.

CDC data found at <https://www.cdc.gov/drugoverdose/data/overdose.html>

"Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy: A Systematic Review" Ann Intern Med. 2017;167(3):181-191.

## Appendix 1

### MME Worksheet

#### Calculating Current MME Dose

Opioid (doses in mg/day except where noted)	Conversion Factor
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone (I refuse to prescribe this drug)	
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

Current Medication 1: \_\_\_\_\_ X Conversion Factor: \_\_\_\_\_ = MME Dose \_\_\_\_\_  
 Average Daily dose \_\_\_\_\_

Current Medication 2: \_\_\_\_\_ X Conversion Factor: \_\_\_\_\_ = MME Dose \_\_\_\_\_  
 Average Daily dose \_\_\_\_\_

Current Medication 3: \_\_\_\_\_ X Conversion Factor: \_\_\_\_\_ = MME Dose \_\_\_\_\_  
 Average Daily dose \_\_\_\_\_

I'm hoping I don't need that third line for anyone. But just in case.  
 Target Dose MME to be less than 98 MME:

Target Dose MME to be less than 50 MME (especially if take BENZO):

Appendix 2: Tapering Plan for Patient with chronic, non-cancer pain according to Washington State Department of Social and Health Services

Short and long acting narcotics should be tapered separately; first taper the short acting agent, then taper the long acting.

Tapering short acting narcotics: As a general rule, if the % of total MED is < 10% of the initial total MED of all the narcotics, taper by 10% of the initial total dose (milligrams) every 3 days. If the % of the total MED is >10% of the initial total MED, taper by 10% of the initial total dose (mg) every week.

Tapering long acting narcotics: As a general rule, taper by 10% of the initial total dose (milligrams) until down to 30% of the initial total dose (milligrams). Then, taper by 10% of the remaining 30% of the initial taper (milligrams).

Symptoms of an abstinence syndrome, such as nausea, diarrhea, muscle pain and myoclonus can be managed with clonidine 0.1 to 0.2 mg orally q 6 hours or Catapres TTS 1 patch/weekly. Sleep problems can be treated with zolpidem and/or low dose tricyclic agents, such as doxepin 10-50 mg q HS. DO NOT TREAT WITHDRAWAL SYMPTOMS WITH ADDITIONAL OPIOIDS OR BENZODIAZEPINES.

Short acting drug:

MME Dose \_\_\_\_\_ equals % of total \_\_\_\_\_

Long acting drug:

MME Dose \_\_\_\_\_

Total daily MME Dose \_\_\_\_\_