Opioids & Chronic Pain
Efficacy and Safety

Safe and Effective Opioid Prescribing for Chronic Pain

October 23, 2010

Daniel P. Alford, MD, MPH, FACP, FASAM
Associate Professor of Medicine
Boston University School of Medicine
Boston Medical Center
Efficacy and Safety

DR. DANIEL ALFORD: Let’s move on. Let’s talk about opioids. What is their efficacy and safety? How good are they? First of all, they come in lots of different flavors,
and I want to impress upon you that they’re not all the same. Some patients respond to one and not another, so they are pharmacologically different in a lot of ways. Where do they come from? They come from morphine and/or codeine. Where does that come from? That comes from opium. Where does that come from, probably Afghanistan. You can take morphine and/or codeine and you can add a couple of CO [phonetic] groups and make heroin or you can add other groups and make hydrocodone, oxycodone, hydromorphone (Dilaudid), and so forth. You can make semi-synthetic opioids from the natural morphine and codeine that came from opium which came from the poppy.

The important thing to remember here, and you’ll hear more about this in the tools talk, is when you do a urine drug test, they are telling you whether or not there is morphine or codeine in it. It might be that one of your semi-synthetics converted back to its original compound, morphine or codeine, and turns it positive, or it might be that the person’s not taking a lot of oxycodone and that it doesn’t turn your urine positive for the opiate. I will tell you that there’s a group of synthetic opioids, like Methadone, meperidine or Demerol, and Fentanyl that are purely synthetic, never came from morphine and codeine, will never convert back to morphine and codeine, will never turn your urine positive for an opiate, but you can test, there are immunoassays for all of these opioids.

You can test specifically for oxycodone. You can test specifically for Methadone. We’re going to talk about using urine drug testings and what their utility is, but you need to understand before you send them what to expect. Then when you get something that you don’t expect, you need to have someone you can call to say, this result doesn’t make sense to me, can you explain it. The bottom line is morphine and codeine are the natural ones. They make up the semi-synthetics. Oftentimes they metabolize back and will turn urine positive for one of these. The synthetics will not.
We also know that there is variability in response to opioids; that is, some people respond and some don’t, some pain responds, some doesn’t. It all happens at the Mu receptor. It’s a G protein-coupled receptor that uses a second messenger system, the cyclic AMP. We know that there are over 100 polymorphisms to the human Mu-opioid receptor gene and that there are Mu-receptor subtypes and that not all patients respond to the same opioid in the same way. Not all pain responds to the same opioid in the same way, and that there’s incomplete cross-tolerance between one opioid to another, so if you have a person on oxycodone and then you want to switch them to morphine and you go to one of those tables, you need to remember that there’s incomplete cross-tolerance when you make those conversions.
When you activate those Mu receptors, they do a lot of stuff. They turn on the descending inhibitory pathway which is here in the periaqueductal gray. That’s an incredibly powerful pain relieving system. They prevent ascending transmission of the pain signal from the periphery. They inhibit even the peripheral terminals, the C-fibers in the spinal cord. They inhibit the nociceptors, those receptors as far peripheral as you can get. They may even inhibit some cells that release inflammatory mediators.

When you give someone an opioid and they activate Mu receptors, they’re doing a whole bunch of stuff. What’s not listed here is that they turn on the reward pathway, a dopamine system, that can cause some people to feel tremendous reward and euphoria and that’s where their addiction potential occurs.
Opioid Choice

- Duration and onset of action
  - “Rate hypothesis” - fast on, fast off – most rewarding – addicting
- Patient’s prior experience
  - M6 polymorphisms – differences in opioid responsiveness
- Route of administration
- Side effects and Cost
- Currently there are NO abuse resistant opioids or opioid formulations

How do you choose opioids? It kind of depends. You can choose based on the duration of action, the onset of action, and there is something called the “rate hypothesis“. That is that the opioids that are most addicting are the ones that get on the receptor really quickly and get off the receptor really quickly. Heroin is one of those that’s really very, very rewarding; thus, why we were told that sustained released opioids were safer because they weren’t giving that rush, that high. We soon found out that patients or people, who subsequently became addicted, knew how to bypass that sustained release mechanism by chewing it and breaking it all up and getting that fast onset of oxycodone or extracting the Fentanyl from a Fentanyl patch and getting a rush because of that.

If you take it as prescribed, if you take sustained release oxycodone or morphine or Fentanyl patch as prescribed, there is less opportunity to feel reward or rush. Also, a patient’s prior experience. I no longer discount the patient who says you know, the opioid that worked for me is x, because now I’m starting to get an understanding that the opioids are somewhat different, that people have different MU receptor systems. If someone tells me they responded to one particular opioid, I put that in the back of my mind in terms of maybe that’s the one that they’ll respond to.

Also the route of administration, so maybe a patient might do better with a patch. Side and effects and cost, we know that the sustained release preparations tend to be more costly, but I will tell you that currently there are no abuse resistant opioids or opioid formulations, so do not select an opioid because you think this is going to be less abuse able, because they can all be abused at some point. We used to think that with the sustained release preparations and we got into trouble because people found ways to abuse them. I will tell you that there is a lot of money and effort going into creating abuse resistant formulations. They likely will be available in the next 5-10 years and they will probably be very expensive, but there is a lot of work being done to do that.
### Opioids

<table>
<thead>
<tr>
<th>Short-acting</th>
<th>Long-acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>Fentanyl transdermal</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Extended release morphine</td>
</tr>
<tr>
<td>Morphine</td>
<td>Extended release oxycodone</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Methadone</td>
</tr>
</tbody>
</table>

There are short-acting opioids; hydrocodone, hydromorphone, morphine, oxycodone, and then there are long-acting ones; long acting, mostly, because of the formulation. Fentanyl is very short acting but in a transdermal preparation it’s long acting. Extended release morphine, extended release oxycodone and I’ve highlighted Methadone because Methadone is long acting because of its pharmacology, but Methadone can be potentially dangerous. We’ll talk about that. Part of the problem is that people started moving away from sustained released oxycodone because of their fear of that issue instead of prescribing Methadone and then we started seeing a rise in Methadone deaths. We’ll talk about that.
Short- vs. Long-Acting Opioids

- Insufficient evidence to determine whether long-acting opioids are more effective or safer than short-acting opioids
- Insufficient evidence to suggest one long-acting opioid is superior to another

Chou R et al. J Pain Symptom Manage 2003

What is the story between short versus long-acting opioids? I’ll tell you that there have been a couple of systematic reviews looking at the literature, and this is one from 2003 that shows that there’s insufficient evidence to determine whether long-acting opioids are more effective or even safer than short-acting opioids. There’s insufficient evidence to suggest that one long-acting is superior to another.
Let’s talk about Methadone. Unfortunately, this is not showing up but I think it’s showing up in your booklet. The number of prescriptions for dispensed Methadone have gone up. I think, again, it’s in response to the whole sustained release oxycodone problem. As I had mentioned, along with this increase in prescribing Methadone has been an increase in the percentage of Methadone as a percentage of all poisoning deaths.
Methadone is Different

1. NMDA receptor antagonist
2. Less euphoria (po)
3. 5HT, NE uptake inhibition
4. No neurotoxic metabolites
5. Inexpensive
6. **Long, variable, unpredictable half-life**
7. QTc prolongation, risk of torsade de points

Why is that? Methadone is different. First of all, it actually has some positive characteristics and that is, unlike the other opioids, it has this unique characteristic of being an NMDA receptor antagonist. It turns out that a lot of neuropathic pain and kind of central sensitization that occurs in the nervous system can be treated with an NMDA receptor antagonist. The problem is we don’t have a very good tolerable NMDA receptor antagonist, but Methadone seems to have that property.

There also tends to be less euphoria because it has that slow onset even if you chew it. It does have some effect on serotonin norepinephrine reuptake inhibition which enhances that periaqueductal gray system. There are no neurotoxic metabolites and it’s incredibly inexpensive compared to all the other long-acting preparations. The problem is that it has a long, variable and unpredictable half-life and you’ve probably heard about the QTc prolongation, the risk of torsades, but probably the most important thing related to the increase in deaths is SIKS [phonetic] that we just didn’t have enough experience with Methadone and we were escalating the dose too high, too quickly.
The problem lies with the following. The dose kinetics are different depending on what you’re trying to treat. So if you’re trying to treat addiction with Methadone and a Methadone maintenance program because we all know that it’s illegal for primary care doctor to use Methadone to treat addiction in a primary care setting, so if using Methadone to treat addiction in a Methadone clinic,
you dose Methadone once a day because you get a 24, even up to 36-hour, relief of craving and withdrawal and so forth.

The problem is that it’s analgesic efficacy or effects only last 6, even up to 8 hours. So patients if you dose them today, they’re only going to get relief for 6-8 hours. Therefore, you need to dose it three times a day, so you can already see what’s going to happen here where if you start to bump up the dose too quickly, you’re going to start increasing CRM [phonetic] levels because it has a very long half-life to toxic levels. If you’re going to use Methadone to treat pain, which I do because it’s cheap and you can use very small doses, I do it t.i.d. and I do not change the dose for at least a week. I give them at least a week to kind of tell me how they’re doing, are they getting sedation, because it they’re getting sedated then I can’t really push the dose.
How Much is Too Much?

- Compared with patients receiving 1-20 mg/d of morphine equivalents, patients receiving 50-99 mg/d had a 3.7-fold increase in overdose risk.
- Patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk with a 1.8% annual overdose rate.
- Morphine equivalent doses over 120 mg/d doubled the risk of alcohol- or drug-related health services utilization encounters (withdrawal, intoxication, overdoses).

Braden JB et al. Arch Intern Med 2010

How much is too much of any opioid? There is some recent literature published in the Annals of Internal Medicine, in the Archives of Internal Medicine, that make us somewhat concerned about high dose opioids, but again, these are observational. These are not prospective randomized trials. What they found at looking at large databases where they compared to patients receiving 1-20 mg per day of morphine equivalents, the patients receiving 50 to 99 mg per day had almost a four-fold increase in overdose risk.

In fact, patients who received 100 mg per day, again of morphine equivalents, or more had almost a nine-fold increase in overdose risk with a 1.8% annual overdose rate. The higher the dose, the more the person is at risk; but again, it depends on, does that mean everyone who’s on 100 mg is going to have an overdose? No, it just means that I, as the prescriber, need to pay very careful attention and make sure the patient is aware of the risks associated with those higher doses.

A more recent study showed that morphine equivalent doses of over 120 mg per day doubled the risk of alcohol or drug related health service utilization encounters; that is, people who were having withdrawal, intoxication, or overdoses. Again, there is probably some risk associated with higher doses but it doesn’t mean that some patients don’t benefit from those higher doses. It just means we need to be careful, they need to be careful.
When are opioids indicated? When pain is moderate to severe, when it has a significant impact on function and quality of life, and that you’ve tried non-pharmacotherapy. You’ve tried non-opioids and they have failed. Most importantly, what I would say to you is that the patient is agreeable to have their opioid use closely monitored; that is, pill counts and urine drug testing, for example, because these are the tools that we have to detect patients who are starting to lose control, use in a compulsive way, continue to use despite harm, those things that I told you about in terms of figuring out who’s addicted or not. If you don’t have these tools, then you’re not going to be able to figure out who’s running into problems.

I’ll tell you the time to have this discussion is on day one, because the patient is a little worried that you’re not going to prescribe these medications because they’ve probably run into docs who don’t and they’re willing to engage in this conversation about it. If you don’t have this conversation and then the patient starts to run into problems, like running out early and so forth, and now you have the discussion, it’s going to be confrontational. The patient’s going to feel judged and they’re going to accuse you of judging them or what have you. It’s better to do it on day One, even if the person comes to you as a transfer from some other doc who left the state and they’re already on opioids; that’s the time to have the discussion and say, I’m going to review your case and if we do opioids, I require the following.
How good are they, really, in terms of chronic pain? I’ll tell you most of the literature is surveys and uncontrolled case series, there are some randomized clinical trials but they’re of short duration, less than four months, with small sample sizes, and they’re mostly pharmaceutical company sponsored. I will tell you that pretty much all the studies show pain relief but it’s modest. It’s not going from 10 to zero, but it’s going from maybe an 8 to a 6. That might be an incredible benefit for some patients, but we need to set their expectations to a realistic goal, and we need to have realistic goals as well.

In terms of functional improvement, some studies showed people improved their function, some didn’t. It wasn’t as consistent as pain relief, the modest pain relief.
Opioid Responsiveness

- Degree of pain relief with
  - Maximum opioid dose
  - In the absence of side effects ie. sedation

- Not all pain is opioid responsive

It’s important to remember that some pain is opioid resistant and some is opioid responsive. We used to think that all neuropathic pain was resistant to opioids. We now know, and there are some good studies, that show that neuropathic pain can respond to opioids, but in those studies, sometimes up to 60%, 50% of people didn’t have any effect. If we’re treating our diabetic patient with neuropathic pain, early on we need to decide are they opioid resistant or are they opioid responsive. We’ll talk about that.
Pseudo-Opioid-Resistance

- Some patients with adequate pain relief believe it is not in their best interest to report pain relief
  - Fear that care would be reduced
  - Fear that physician may decrease efforts to diagnose problem

Evers GC. Support Care Cancer. 1997

Keep in mind that when you’re trying to figure out if this person is responsive or resistant to this opioid, there is something called pseudo-opioid resistance; and that is, that some patients feel that have adequate pain relief with that opioid you’re prescribing do not feel that it’s in their best interests to tell you that, why? One is their fear that as soon as they say my pain is better doc, you’re going to say, okay, I’m going to decrease the dose; meanwhile, this dose is working really well for them, or that you’re going to stop looking for what’s causing their pain. Even though you’ve done 10 MRIs of their head, they’re still convinced there’s a tumor in there that you haven’t found yet and as soon as they say their pain is getting better, you’re going to stop looking. This is something to keep in mind is the patient, do they feel comfortable with you and do they trust that you trust that their pain complaints are real so they can tell you exactly how they’re feeling.
Exploit synergism; I think certainly when I was in medical school and probably everyone in this crowd was taught polypharmacy is bad. In general, polypharmacy is bad except for chronic pain management. This was a study that was reported in the *New England Journal of Medicine* in 2005 where they compared morphine versus Gabapentin versus their combination for neuropathic pain. What did they find? If you look on the left graph first, they found that at baseline the pain scores on a scale of 10 were around 5.7 or so, so that was their neuropathic pain scores. When they got placebo, they got benefit. That’s not uncommon actually in pain studies. It’s not that they were faking their pain. It probably has something to do with endorphins.

We have endogenous endorphins that act on those same MU receptors that I talked about. So if the patient has some level of expectation that they’re going to get benefit, even if it’s a placebo, they get pain relief. Placebo is important to pain relief. Gabapentin did better than placebo. Morphine did better than Gabapentin and look what did the best of all, the combination; Gabapentin plus morphine for treating neuropathic pain, but that’s not even the most interesting part of the story. The most interesting part of the story is in this graph here where when you look at the combination group that got better pain relief, they actually needed lower dose of Gabapentin and lower doses of morphine. They got better pain relief with lower doses of morphine and Gabapentin, so fewer side effects from those medications.
There are risks associated with opioids. It does encourage pain, opioid-centered lifestyle. They can’t get refills. They’re coming in every 30 days. They’re really interacting with the health care system in a way that makes them very kind of opioid centers, so that’s a potential risk. There is a risk of addiction. We talked a little bit about that. There are some side effects and safety issues. In some patients, their pain actually might get worse on opioids due to a couple things. One is the subclinical withdrawal that I’ll talk to you about, and also opioid-induced hyperalgesia. That’s somewhat controversial but some patients develop a hyperalgetic state from being chronically exposed to opioids. 
Opioid Safety

- Allergies are rare
- **Side effects** are common
  - Nausea, sedation, constipation
  - Urinary retention, sweating
- **Organ toxicities** are rare
  - Hypothalamic-pituitary-adrenal axis: ↓ cortisol
  - Hypothalamic-pituitary-gonadal axis: ↑ prolactin, ↓ LH, FSH, testosterone, estrogen, progesterone
- **Overdose** especially at high doses and when combined with other sedatives

Let’s talk about safety. Allergies are incredibly rare. Side effects are common; nausea, sedation, constipation; turns out people become tolerant to the nausea and sedation, not so much for the constipation. Some people develop urinary retention and sweating is very common, this kind of diaphoresis that some patients experience. Organ toxicities are incredibly rare. There is some endocrinologic things you need to worry about like the hypothalamic pituitary adrenal axis that some patients actually have a decreased cortisol response in response to stress, although I don’t know how clinically important that is, but certainly there is also an effect on the gonadal axis.

Some patients become hypogonadal and actually have issues with bone health, so that’s something to think about too. Is their testosterone level low? Do they need bone mineral density scans and so forth? Now, we’ve already talked about the risk of overdose especially at higher doses. We talked about that as well, and especially when combined with other sedatives.
**Can Opioids Worsen Pain?**

- Some patients obtain better pain relief when tapered off opioids
- Animal studies chronic opioid administration results in increased pain sensitivity versus placebo
- Methadone maintenance patients with enhanced pain sensitivity versus controls
- Release of peptides “anti-opioids”, neuroadaptation to chronic opioids
- Opioid withdrawal mediated pain
- Opioid-induced hyperalgesia

Li X et al. Brain Res Mol Brain Res 2001
Doverty M et al. Pain 2001
Angst MS, Clark JD. Anesthesiology 2006

This whole concept of, can opioids worsen pain in some patients? Some patients do obtain better pain relief when they get off these opioids, so that’s kind of a curious phenomenon. There are some animal studies that chronic opioid administration can result in increased pain sensitivity in those animal models. We know from the Methadone maintenance literature where people are on high doses of opioids for long periods of time that some experimental studies show increased pain sensitivity.

What is the mechanism? No one really knows. Is there a release of anti-opioids or some neural adaptation to the chronic opioid exposure causing this hyperalgetic state, or do they have opiate withdrawal mediated pain? Let me tell you what that is.
As I told you before, every single patient on chronic opioids is going to become physically dependent. That means during a certain part of the day, their level might drop to a point where they go through withdrawal, not the kind of withdrawal that you’re used to seeing in the person who’s heroin addicted where they have nausea, vomiting, diarrhea, and they’re curled up in a ball, but they have subtle withdrawal where the first thing they feel when they start to go through withdrawal is worsening of their pain.

They’ve got back pain and they’re feeling fine when they take their oxycodone, as soon as the level drops and they start to go through withdrawal, they feel, oh, my back hurts. They take the oxycodone. They feel better and they say, oh, it’s working for my pain, but really what it’s doing is treating their physical dependence and their withdrawal. So this is what’s happening in this graph and that is, when they take their medication, they’re comfortable. When they drop below a certain level, they go through withdrawal, the subtle withdrawal. They feel their pain. They take their medication so in their mind the medication is working.

The only way you could figure this out is to make people opioid free and see is their pain better or the same or worse. This is an argument for using sustained release preparations to try to prevent people from going up and down, up and down, up and down. Someone’s going to take sustained release preparations the way it’s prescribed; you can avoid this potential problem.
Opioid Rotation

- Switch to another opioid as means of restoring analgesic efficacy or limiting adverse effects
- Based on large intra-individual variation in response to different opioids
- Different variants of mu-opioid receptors
- Based on surveys and anecdotal evidence
- Promising but needs validation

Inturrisi CE. The Clinical J of Pain. 2002

What about rotating people? The person doesn’t respond to oxycodone, should you try morphine? There’s growing literature about this; again, as we start to learn more about the differences between the various opioids and the differences in the MU receptor systems. Switching to another opioid to restore algesic efficacy, it’s based on large intra-individual variation of response to different opioids and the whole MU receptor system we talked about.

I will tell you that the literature is weak. It’s mainly surveys and some anecdotal evidence, and it’s promising but it needs validation. Although it is something to consider clinically if someone isn’t responding to one opioid, you could try another, or they are no longer responding to the one that they were responding to.
Opioid Conversion Tables

- Derived from relative potency ratios using single-dose analgesic studies
- Subjects with limited opioid exposure
- Do not reflect clinical realities of chronic opioid administration
- Therefore dose ratios are guidelines to be used cautiously

Pereira J et al. J Pain Symptom Manage 2001

Just be cautious when you use opioid conversion tables. If you take three opioid conversion tables and you put them side by side, they will have differences. Part of this has to do with the way they’re derived, from relative potency ratios to single dosing algesic studies, the subjects that they study have limited opioid exposure, and they’re opioid naïve. It really doesn’t reflect to the realities of our chronic pain patients who are on long-term opioids. They are guidelines. You’re a whole lot safer cutting that - - algesic equivalent by 25%, 30%, and then titrating it up rather than making the one to one conversion.
In summary, not all pain is opioid responsive. Analgesia and functional improvement may be modest. Not all opioids are equal. Methadone must be used with extreme caution, don’t increase the dose sooner than a week I would say. For all opioids risks include side effects, overdose, addiction, but organ toxicity is low compared to the NSAIDs that we’re delighted to prescribe and the acetaminophen that we’re delighted to prescribe. Opioids are safe from an organ toxicity standpoint.

Addiction risk is similar to the risk of becoming addicted to any of the other substances that people get addicted to and clearly when you take a history and you find that they have a history or they have a family history, you need to be cautious.
Opioid Summary 2

- Conversion tables are just estimates and can vary.
- Start low and go slow.
- Optimal dose determined by careful titration and monitoring.
- Exploit synergism with other treatments.
- Some pain will improve off chronic opioids.

Conversion tables are just estimates and can vary. Start low and go slow. Patients have chronic pain. They’ve been suffering for probably years by the time they come to you, and by the time you’re considering using an opioid, you don’t need to maximize their therapy in a week. Take your time. Do it carefully. Do it slowly. Monitor the patient. Optimal dose determination is done by careful titration and careful monitoring. Exploit synergism with other treatments. Don’t stop the NSAID if you’re going to start an opioid, combine them.

I have plenty of patients who are on t.i.d. oxycodone with t.i.d. ibuprofen with t.i.d. acetaminophen. They take all three tablets three times a day and they get improvement. Some patients will improve off chronic opioids. If the patient isn’t doing well and their pain is still 15 out of 10 all the time and they’re on an opioid, you can start to think well maybe they actually aren’t benefiting from the opioid and maybe they’ll actually do better off the opioid. I’ll get rid of the physical dependence. I’ll get rid of that opioid withdrawal mediate pain.

Maybe they’ve developed opioid-induced hyperalgesia, so I don’t feel bad as the clinician stopping the opioid because; (1) they’re not benefiting; (2) they might do better. So keep that in mind. Thank you.

[Applause]