Rethinking Opioid Tapers, Buprenorphine Induction, and Perioperative Buprenorphine

The BRAVO Protocol:
A Biopsychosocial Approach to Opioid Tapers

Anna Lembke, MD
I have been retained as an expert witness on the plaintiff side in federal and state litigation against opioid manufacturers and other defendants.
Overview

✧ How to taper opioid dependent, chronic pain patients down and/or off of long-term opioids.
✧ How to transition patients from full opioid agonists to buprenorphine using transdermal buprenorphine.
✧ How to manage buprenorphine in the perioperative period.
HOW TO TAPER PATIENTS OFF OF CHRONIC OPIOID THERAPY
ONLINE CME COURSE

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COURSE DETAILS

Original Release Date: 08/02/18
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Tapering – Guidance & Tools
Clinical Update Dec. 2018

Overview

Over the last 20 years, the liberal prescribing of opioids for chronic pain has created a population of patients who been on long term opioid therapy (LTOT) for several years if not decades. Many patients are on doses well above the CDC recommended upper limit of 90 Morphine Equivalent Dose (MED) for new starts. Patients, however, may be reluctant to taper, fearing withdrawal and increased pain. Prescribers are also asking whether or not tapering is necessary if the patient is stable and compliant on their current dose. Yet, overdose rates continue to be high compared to historical standard and it is well established that patients on chronic opioids are at risk for overdose even if they are not dependent.
B=BROACHING THE SUBJECT
At age 18, developed a mysterious pain in her abdomen that spread to her whole body.

All medical work-up negative.

Saw many doctors over time, and was diagnosed with fibromyalgia and rx’d opioids.

By age 30 was taking ~800 MED’s, prescribed by “the most compassionate doctor I ever saw.”

Sherry always took her opioids exactly as prescribed.
Sherry’s story

- Despite meds, pain no better, function worse.
- On high dose opioids, Sherry spent more time in bed.
- Her husband remarked she was “detached from family life.” Sherry was not aware of being more detached.
- Her pain increased over time.
Broaching the subject

Summary points

✧ Suggesting an opioid taper can trigger anxiety.
✧ Identify this feeling for patients, normalize it and express empathy.
✧ Make clear that the opioid taper was carefully considered, not impulsive and not punitive.
Carefully Considered: “Sherry, I scheduled some extra time for us today because I want to discuss a very important topic with you. *I’ve been thinking a lot about your chronic pain* and how to help you with that.”

Gentle Introduction: “I would like to suggest that we taper you down and maybe even off your opioid medication.”

Anticipate Fear: “Now, I know the very thought of an opioid taper is terrifying for you, and you’re not alone in that … it’s totally normal to feel afraid about going down on your dose, especially after you’ve been taking opioids for so long. But, please hear me out, and let me tell you the reasons why I think it’s a good plan for you.”
Medicolegal considerations for the inherited high-dose opioid patient. It’s okay to continue the high dose at first, as long as you:

- Demonstrate and document you are weighing the risks and benefits of a taper, discussing the topic with the patient, and building a therapeutic alliance to optimize the chances of a successful taper.
- Monitoring the patient, including checking the PDMP, urine toxicology, and other screening for opioid use disorder.
- Offering naloxone and overdose prevention education.
Take more time, and get support
Donald Winnicott’s “holding environment”

“I’ve been thinking a lot about your chronic pain …”
R=RISK BENEFIT CALCULATOR
Consider the risks of long term opioid therapy and weigh against the benefits in this patient (PDMP, toxicology, collateral information)

Is MED > 90 mg? Are there medical comorbidities? Are there side effects? Is there a lack of functional improvement? Is there a lack of significant pain relief despite dose increases?

Is there dangerous co-prescribing such as benzodiazepines?
First Do No Harm: “I think we need to get you off opioids because they’re doing more harm than good. Your pain is no better than before you started on opioids, and may even be worse.”

Medicating Withdrawal: “I know you feel like opioids are helping your pain, but they’re most likely medicating withdrawal from your last dose.”

Functionality: “More importantly, you’re less functional than you used to be, spending most of the day in bed. Your husband reports you are detached from family life. Opioids can do that, even when we’re not aware of them doing that.”

Medical Decision-Making: “For all of those reasons, we’re going to work together to slowly taper you off these medications.”
The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop

Roger Chou, MD; Judith A. Turner, PhD; Emily B. Devine, PharmD, PhD, MBA; Ryan N. Hansen, PharmD, PhD; Sean D. Sullivan, PhD; Ian Blazina, MPH; Tracy Dana, MLS; Christina Bougatsos, MPH; and Richard A. Deyo, MD, MPH

**Background:** Increases in prescriptions of opioid medications for chronic pain have been accompanied by increases in opioid overdoses, abuse, and other harms and uncertainty about long-term effectiveness.

**Purpose:** To evaluate evidence on the effectiveness and harms of long-term (>3 months) opioid therapy for chronic pain in adults.

**Data Sources:** MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PsycINFO, and CINAHL (January 2008 through August 2014); relevant studies from a prior review; reference lists; and ClinicalTrials.gov.

**Study Selection:** Randomized trials and observational studies that involved adults with chronic pain who were prescribed long-term opioid therapy and that evaluated opioid therapy versus placebo, no opioid, or nonopioid therapy; different opioid dosing strategies; or risk mitigation strategies.

**Data Extraction:** Dual extraction and quality assessment.

**Data Synthesis:** No study of opioid therapy versus no opioid therapy evaluated long-term (>1 year) outcomes related to pain, function, quality of life, opioid abuse, or addiction. Good- and fair-quality observational studies suggest that opioid therapy for chronic pain is associated with increased risk for overdose, opioid abuse, fractures, myocardial infarction, and markers of sexual dysfunction, although there are few studies for each of these outcomes; for some harms, higher doses are associated with increased risk. Evidence on the effectiveness and harms of different opioid dosing and risk mitigation strategies is limited.

**Limitations:** Non-English-language articles were excluded, meta-analysis could not be done, and publication bias could not be assessed. No placebo-controlled trials met inclusion criteria, evidence was lacking for many comparisons and outcomes, and observational studies were limited in their ability to address potential confounding.

**Conclusion:** Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms.

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For author affiliations, see end of text.

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R=Risk benefit calculator

Weighing the Risks and Benefits of Chronic Opioid Therapy

*American Family Physician*, Lembke, A., 2016 ◆ Volume 93
Involve family in risk assessment

- 2016 Washington Post Kaiser Family Foundation Survey of patients on chronic opioid therapy
- 33% of patients worried about addiction
- >50% of family members worried about addiction
Rx Naloxone and educate about overdose risks (now law in California)

Family Practice
123 Main Street | Anytown, USA

Rx

Naloxone HCl 1mg/mL

2 x 2mL as pre-filled Luer-Lock needleless syringe

2 x Intranasal Mucosal Atomizing Device (MAD 300)

For suspected opioid overdose.
Spray 1mL in each nostril.
Repeat after 3 minutes if no or minimal response.

MD

Signature
Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain
The SPACE Randomized Clinical Trial

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**Importance** Limited evidence is available regarding long-term outcomes of opioids compared with nonopioid medications for chronic pain.

**Objective** To compare opioid vs nonopioid medications over 12 months on pain-related function, pain intensity, and adverse effects.

**Design, Setting, and Participants** Pragmatic, 12-month, randomized trial with masked outcome assessment. Patients were recruited from Veterans Affairs primary care clinics from June 2013 through December 2015; follow-up was completed December 2016. Eligible patients had moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use. Of 265 patients enrolled, 25 withdrew prior to randomization and 240 were randomized.
Why the SPACE trial is the gold standard

- Key finding: **No benefit of opioids** above non-opioids; fewer side effects with non-opioids
- 12 months in duration
- Studied opioid-naïve patients in a primary care setting, including patients with severe depression and post-traumatic stress disorder
- Not sponsored by an opioid manufacturer
Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial

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Abstract: Patients receiving long-term opioid therapy for chronic pain and interested in tapering their opioid dose were randomly assigned to a 22-week taper support intervention (psychiatric consultation, opioid dose tapering, and 18 weekly meetings with a physician assistant to explore motivation for tapering and learn pain self-management skills) or usual care (N = 35). Assessments were conducted at baseline and 22 and 34 weeks after randomization. Using an intention to treat approach, we constructed linear regression models to compare groups at each follow-up. At 22 weeks, adjusted mean daily morphine-equivalent opioid dose in the past week (primary outcome) was lower in the taper support group, but this difference was not statistically significant (adjusted mean difference = −42.9 mg; 95% confidence interval, −92.42 to 6.62; P = .09). Pain severity ratings (0–10 numeric rating scale) decreased in both groups at 22 weeks, with no significant difference between groups (adjusted mean difference = −6.68; 95% confidence interval, −2.01 to .64; P = .30). The taper support group improved significantly more than the usual care group in self-reported pain interference, pain self-efficacy, and prescription opioid problems at 22 weeks (all P-values < .05). This taper support intervention is feasible and shows promise in reducing opioid dose while not increasing pain severity or interference.

Perspective: In a pilot randomized trial comparing a prescription opioid taper support intervention to usual care, lower opioid doses and pain severity ratings were observed at 22 weeks in both groups. The groups did not differ significantly at 22 weeks in opioid dose or pain severity, but the taper support group improved significantly more in pain interference, pain self-efficacy, and perceived opioid problems. These results support the feasibility and promise of this opioid taper support intervention.

© 2016 by the American Pain Society

Key words: Chronic opioid therapy, opioid dose taper, pain intensity, pain interference, pain self-management.
A=ADDITION HAPPENS

Addiction. It can happen to anyone.
I am your ...

https://Bonnie4Salem.us
Facebook & Twitter: @Bonnie4Salem
A=Addiction happens
Summary points

✧ Opioid misuse and addiction in long term opioid therapy is common.
✧ Physical dependence, withdrawal and tolerance by themselves do not define addiction.
✧ Addiction refers to behaviors associated with opioid use. Think of the 4 C’s: Control, Compulsion, Craving, Continued Use (despite Consequences).
✧ Normalize the concept of addiction to medications prescribed for pain and reassure patients that there are effective treatments.
Mea Culpa: “When we [doctors] first started prescribing opioids more liberally for chronic pain in the 1980s, we believed the risk of becoming addicted, as long as we were prescribing them for a medical condition, was very low. Now we know better.”

Pain Patients Get Addicted Too: “Since then, we have learned a lot and now know that even when patients are being prescribed opioids for a legitimate pain condition, and take them as prescribed, they can become addicted to those opioids.”

Anticipation: “So, if in the process of a slow and medically supervised taper, you are unable to come off opioids, it is possible that you too have become addicted. If that’s true for you, you’re not alone. Millions of people have become addicted to prescription opioids through a doctors’ prescription.”
Risk of opioid misuse ~ 25%
Risk of opioid addiction ~ 12%

- Systematic review and meta-analysis from 38 studies. Across most calculations, rates of misuse averaged between 21% and 29% (range, 95% confidence interval [CI]: 13%-38%). Rates of addiction averaged between 8% and 12% (range, 95% CI: 3%-17%).

- Used real world and population based studies.

Using the DSM-V criteria to diagnose “opioid use disorder” in the context of a medically managed opioid taper

- Tolerance and withdrawal: These criteria don’t count when patients taking opioids as prescribed.
- DSM-V Criteria (need at least 2 beyond tolerance and withdrawal)
  - Control
  - Compulsions
  - Craving
  - Consequences
Sherry’s story

- At the start of the taper (800 MED’s), Sherry did not meet DSM-V criteria for opioid use disorder.
- But as we attempted to taper her over 18 months, it became apparent she had developed an opioid use disorder, based on:
  - Her inability to adhere to even minimal dose decrements (Control)
  - Her inability to taper despite ongoing serious medical consequences as a result of opioids, including hypoxemia, somnolence, depression, cognitive dysfunction (Consequences)
Sherry’s story

- We transitioned her to buprenorphine
- She experienced improvements in mood, cognition, activity level, alertness, breathing
- Her pain did not improve, but also did not get worse
Sublingual buprenorphine

- FDA approved treatment for opioid use disorder
- 3 unique properties
  - Long half life
  - High binding affinity
  - Ceiling effect on euphoria and respiratory depression

Typical buprenorphine induction in our outpatient clinic

- 12-48 hours no opioids, then …
- See patient in clinic and assess for opioid withdrawal
- Send patient home with prescription for home induction, typically 2 mg TID prn daily for the first week (for patients on 150 MED or less)
- Follow up by phone during the week prn
- RTC day seven for seven day refill, urine tox screen, PDMP check
Buprenorphine equivalents (courtesy of Dr. Paul Coelho)

<table>
<thead>
<tr>
<th>Morphine</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>250mg</td>
<td>30</td>
<td>8mg</td>
</tr>
<tr>
<td>500mg</td>
<td>40</td>
<td>8-16mg</td>
</tr>
<tr>
<td>750mg</td>
<td>60</td>
<td>8-24mg</td>
</tr>
<tr>
<td>1000mg</td>
<td>80</td>
<td>8-32mg</td>
</tr>
</tbody>
</table>
Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method

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Background: Buprenorphine is a partial μ-opioid receptor agonist used for maintenance treatment of opioid dependence. Because of the partial agonism and high receptor affinity, it may precipitate withdrawal symptoms during induction in persons on full μ-opioid receptor agonists. Therefore, current guidelines and drug labels recommend leaving a sufficient time period since the last full agonist use, waiting for clear and objective withdrawal symptoms, and reducing pre-existing full agonist therapies before administering buprenorphine. However, even with these precautions, for many patients the induction of buprenorphine is a difficult experience, due to withdrawal symptoms. Furthermore, tapering of the full agonist bears the risk of relapse to illicit opioid use.

Cases: We present two cases of successful initiation of buprenorphine treatment with the Bernese method, i.e., gradual induction overlapping with full agonist use. The first patient began buprenorphine with overlapping street heroin use after repeatedly experiencing relapse, withdrawal, and trauma reactivation symptoms during conventional induction. The second patient was maintained on high doses of diacetylmorphine (i.e., pharmaceutical heroin) and methadone during induction. Both patients tolerated the induction procedure well and reported only mild withdrawal symptoms.

Discussion: Overlapping induction of buprenorphine maintenance treatment with full μ-opioid receptor agonist use is feasible and may be associated with better tolerability and acceptability
Butrans patch

Butrans 5 mcg/hour
45 x 45 mm

Butrans 7.5 mcg/hour
45 x 58 mm

Butrans 10 mcg/hour
45 x 68 mm

Butrans 15 mcg/hour
59 x 72 mm

Butrans 20 mcg/hour
72 x 72 mm
A 21-year-old woman with a history of multiple hospital admissions for sepsis secondary to injection heroin use presented to the hospital with a right thigh abscess and dyspnea. Her diagnostic workup revealed pulmonic valve endocarditis, with both abscess and blood cultures growing methicillin-sensitive *Staphylococcus aureus*. The patient developed sepsis with respiratory failure and was intubated. Despite 11 days of treatment with antibiotics, her condition worsened and necessitated pulmonic valve replacement. She improved after surgery and received intravenous antibiotics for 6 weeks. She also received 220 morphine milligram equivalents for postoperative pain. Based on concerns that she would be at high risk to use her peripherally inserted central catheter to inject heroin as an outpatient, the decision was made to keep her hospitalized while completing the course of antibiotics.
Using transdermal buprenorphine to transition patients to sublingual formulations

Raheemullah, A., Lembke, A. Initiating Opioid Agonist Treatment for Opioid Use Disorder in the Inpatient Setting: A Teachable Moment, JAMA Internal Medicine, 2019
**Figure. Buprenorphine Induction With Transdermal Buprenorphine Microdosing**

<table>
<thead>
<tr>
<th>Before Induction</th>
<th>Day 1</th>
<th>Day 2^a</th>
<th>Day 3</th>
<th>After Full Agonist Opioid Discontinuation</th>
</tr>
</thead>
</table>
|                  | Slowly taper full agonist opioids as tolerated until discontinued | Administer transdermal buprenorphine 20 μg/hr microdosing 48 hr bridge | Administer previous day’s total SL buprenorphine dose. If tolerated,^b^ administer 2 to 4 mg every 2 to 4 h as needed.^c^ Limit second day SL buprenorphine dose to 16 mg.^d^ | Discontinue full agonist opioids not yet tapered. Continue established SL buprenorphine daily dose.^

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^a Algorithm would require adjustment for longer-acting opioids such as methadone.

^b Delay extra doses of buprenorphine for adverse effects such as oversedation. Minor withdrawal symptoms can be treated with nonopioid medications such as alpha-2 adrenergic agonists, loperamide for diarrhea, and ondansetron for nausea.

^c Titrated to an effective dose that relieves opioid withdrawal, suppresses cravings, avoids adverse effects such as sedation, and has stable treatment effects for 24 hours.

^d On average, buprenorphine doses after induction and titration should be at least 8 mg/d. The US Food and Drug Administration approves up to 24 mg/d, and there is limited evidence regarding the relative efficacy of higher doses. Sublingual (SL) buprenorphine-naloxone can be used in place of SL buprenorphine.

^e The daily dose can be divided and administered every 6 to 8 hours to take advantage of its analgesic properties. The ratio of buprenorphine to morphine is 10 mg to 1 mg.
Perioperative bup: Reduce bup to 12 mg 2-3 days before surgery, and maintain through the perioperative period

Stanford Perioperative Buprenorphine Protocol

Lembke, A. Ottestad, E., Schmiesing, C. Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period, Pain Medicine, 2018 https://doi.org/10.1093/pm/pny019
V = VELOCITY AND VALIDATE

PLEASE SLOW DOWN
V=Velocity and Validate Summary points

✧ Tapering too fast is the most common mistake physicians make.

✧ It’s ok to take breaks in the taper schedule, but never go backwards during the taper!

✧ Validate the patient’s experience of opioid withdrawal, which may initially increase body pain. Pain from withdrawal will resolve and doesn’t mean any underlying condition is worsening.

✧ Use other medications to mitigate some of the symptoms of withdrawal.
V=Velocity and Validate
How to talk to patients

بيع

(validation)

I know this is scary, but we’ll do this together, and I’ll support you as much as I can.

Autonomy: “Let’s start wherever you feel comfortable. You want to taper your fentanyl patch before your oxycodone? That’s fine.”

Velocity: “You’ll get a say in how fast we taper. If you need to take breaks from going down, we can hang out at one dose for a couple of months, until you’re ready to continue. The important thing is not to go backwards, because you’ll lose all that hard work you put in.”

Expectations: “Every time you decrease your dose, your pain will increase. This isn’t the pain you’ll have to live with. This also isn’t a sign of your underlying pain disorder getting worse. This is opioid-withdrawal-mediated pain. If you can just stick with it, you’ll feel better in 2-4 weeks. If you don’t, we’ll slow down the taper.”

Outcomes: “There’s a chance your pain may actually improve off of opioids. Opioids taken every day for a long period of time can make pain worse, by changing pain perception thresholds.”
Adjunctive meds to treat withdrawal

- Antidepressants to manage irritability, sleep disturbance (e.g., trazodone)
- Hydroxyzine for insomnia and anxiety
- Anti-epileptics for neuropathic pain
- Clonidine for autonomic withdrawal symptoms such as rhinorrhea, diarrhea, sweating, tachycardia, hypertension
- NSAIDS for myalgia (e.g., ibuprofen)
- Anti-diarrheal agents for diarrhea
- Opioid Withdrawal Attenuation Cocktail (Appendix F)
- BE WARY OF BENZOS
OTHER TREATMENTS FOR PAIN
(AND WAYS TO TALK ABOUT PAIN)
Other ways to talk about pain

Summary points

- Non-opioid medications
- Non medication treatments
- Mindfulness
- Opposite action
- Radical acceptance
Other ways to talk about pain

Mindfulness

- Attention without judgement.
- “Acknowledge pain and notice if something in the environment is making it worse at the moment.”
- “Make adjustments.”
Other ways to talk about pain

Opposite action

- Act opposite to the emotional urge in the service of pursing values or goals.
- “Do the opposite of dialing into pain, and instead, engage in activities, within reason, in spite of pain being present.”
- “Hurt does not equal harm.”

PAIN SCALE

No  Mild  Moderate  Severe  Very Severe  Worst Pain
Radical acceptance is accepting reality as it is, not as we wish it would be.

“Your pain may likely never go away, but life can still be worth living even if it includes pain.”
Sherry’s story

✧ Sherry continues on buprenorphine SL 8 mg daily two years later.

✧ Overall pain is slightly improved. Function is significantly improved.
“Morphine is not the answer to chronic pain. Because of the development of tolerance to the analgesic effects of morphine, alleviation of pain becomes inadequate. Under such circumstances the physician, by gradually withdrawing narcotics, does not deprive the patient of any actual benefit but protects him and his family from the possible legal, social, or economic difficulties attendant on opiate addiction. The administration of morphine to a patient with chronic pain is a short-lived type of kindness. Longterm kindness would begin when opiates are withheld or withdrawn in favor of other therapeutic measures.”

More references

BRAVO summarized

**Figure 14-4: Discussing Prescription Opioid Dependence with Patients in the Primary Care Setting**

- **Broaching the Subject**
  - Schedule enough time with your patient to have a discussion on this difficult topic
  - Anticipate the patient’s strong emotional reaction
  - Identify the feelings, normalize those feelings, and express empathy with the concerns the patient may have

- **Risk-Benefit Calculator**
  - When assessing benefits, weigh the patient’s pain relief against their functionality
  - Involve family members for more objective views on a patient’s opioid use
  - Track common risks such as tolerance and opioid-induced hyperalgesia
  - Include all of these factors when discussing reasons for tapering off opioids

- **Addiction Happens**
  - Addiction is defined by the “Four C’s”: out-of-Control use, Compulsive use, Craving, and Continued use despite consequences
  - Dependence happens when the body relies on a drug to function normally
  - Dependence and Addiction are not equivalent

- **Velocity Matters - and So Does Validation**
  - Go slowly, take the necessary time to ease your patients down on their doses
  - Let the patient be involved when deciding how much to decrease and at what time
  - It is OK to take breaks in lowering the dosage
  - Never go backwards; your patient’s tolerance will increase and progress will be lost

- **Other Strategies for Coping with Pain** - teach patients these 3 Dialectical Behavioral Therapy (DBT) practices:
  - STOP: Stop, take a breath, observe internal and external experiences, and proceed mindfully
  - Opposite Action Skills: acting opposite to a negative emotional urge in the service of pursuing values goals
  - Radical Acceptance: accepting reality as it is and not as we wish it to be

http://stan.md/taper-off-opioids